Development and evaluation of educational intervention to promote informed decision making regarding embryo transfer in IVF patients

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To ‘GOD’ for the blessings

To my children, Pravi and Vipresh, just want to tell you both how blessed and proud I feel because of you. I don’t have words to describe my love for you two.
“Love you both and will always be there for you.”

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To my parents, brothers and sisters for their love and support

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Publications

2006	Presented at the International conference on "Controversies in Reproductive Medicine" 2006 Development and preliminary validation of the Attitudes to Twin IVF Pregnancies scale
2007	Abstract accepted as Poster in Society for Reproductive and Infant Psychology (SRIP) Conference 2007 St Anne's College, Oxford-Validation of the Attitudes to Twin IVF Pregnancies scale in a patient population
2008	Presented at infertility conference at Middlesex university, UK 2008, Validation of the shorter Attitudes to Twin IVF Pregnancies scale in patient and IVF specialist groups
2008	Abstract published in Journal of Reproductive and Infant Psychology
2011	Paper published in the Journal of Assisted Reproduction and Genetics

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ABSTRACT

Increasing the uptake of elective single embryo transfer is necessary to achieve the 10% HFEA limit for multiple IVF births in 2011. This thesis aims to explore patients' and clinicians' attitudes to eSET and to promote effective decision making regarding embryo transfer. .

Study1compared neurobehavioural outcomes between twins and singletons in a prospective study of infants born very preterm (n=233). Despite having older (p=0.025) and higher social class (p=0.023) mothers, twins had the same risk of cognitive impairment at 2 years as singletons.

In study 2, a 44 item Attitudes to Twin Pregnancy scale (ATIPS) was developed and administered to a sample of clinicians, medical students and conference delegates (n=411). Item analysis reduced ATIPS to 2 short subscales. A-Twin (12 items) assessed perceptions of risks and benefits associated with a twin birth (α=0.7). A-SET (8 items) assessed attitudes to eSET (α=0.53).

Study 3 explored the reliability and validity of ATIPS-R in IVF patients. Exclusion of 2 A-SET items increased alpha to 0.8. Female patients (n=100) had more positive attitudes to a twin birth than clinicians (p=<0.001). Less than a third of patients felt that a twin birth was risky for infants and over 80% of doctors agreed that a twin birth was worth any risks to infants. First cycle IVF patients were more positive about eSET (p=<0.001) than women undergoing repeat cycles.

Study-4 developed a decision aid and evaluated its impact in a pilot randomised controlled trial (n=8). Lower decisional conflict in patients at embryo transfer was associated with more positive attitudes to twins at

baseline (p=0.024) and less positive attitudes to eSET, (p=0.04). Although the attitudes of patients receiving the DA did not change, partners became more positive towards eSET (p=0.024).

Conclusion: Patients and clinicians underestimate the risk of a twin birth for infants and would benefit from educational interventions to promote eSET. The ATIPS-R is a useful measure for assessing the effectiveness of such interventions.

Abbreviations: SET- single embryo transfer; HFEA- Human fertility and embryology authority; IVF- In vitro fertilisation; A-Twin- attitude to risks and benefits of twins; ATIP- attitude to twin IVF pregnancy; A-SET attitude to single embryo transfer; eSET- elective single embryo transfer; DET- double embryo transfer; RCT – randomised control trial; DA- decision aid

ARE IN VITRO FERTILISATION (IVF) TWINS AT GREATER RISK OF POOR PERINATAL AND NEO-NATAL OUTCOMES COMPARED TO IVF SINGLETONS?

1.1 Introduction

There have been many advances in the field of infertility treatment in the last 30 years. These advances have brought hope to couples struggling to conceive but they have also brought their own stresses including the need for medical tests and procedures and their own ethical dilemmas, including embryo selection and funding of treatment. One established consequence of IVF treatment for many couples in the UK is an increased likelihood of a multiple birth. Some countries have used legislation to limit the risk of a multiple birth by enforcing single embryo transfer (SET). In UK the approach has been to rely on clinical management and patient choice to guide decisions to limit the risk of a twin birth. As a clinician involved in IVF treatment I am interested in exploring the effectiveness of SET, the attitudes of doctors and patients to IVF twin births and SET and how couples undergoing IVF treatment can be supported to make decisions about embryo transfer.

According to the National Institute for Health and Clinical Excellence (NICE), infertility is defined as an inability to conceive after 2 years of unprotected healthy sexual life. Currently, 1 in 6 couples experience problems with conception which approximately accounts for 3.5 million people in UK alone (HFEA, 2009). Between 85-90% of couples conceive spontaneously within the first eighteen months and another 5% in the next 6 months. However, approximately 5-6% of couples diagnosed with infertility need specialist treatment (HFEA, 2009).

It is psychologically very traumatic and stressful for a childless couple. Infertile patients have high anxiety and depression levels (Kentenich

1989). This high anxiety level can partly be due to the length of time spent on just reaching a diagnosis, which is on average nearly 4.9 years (HFEA, 2009) and also, to some extent, due to the uncertainty of the success of the treatment options available. Over the years, there has been a better understanding of the causes of infertility which can be grouped into female and male related factors. Female factors include anovulation, ovarian underdevelopment, structural problems such as fallopian tube blockage or unicornate uterus and pelvic inflammatory diseases such as endometritis. Male factors may include structural problems such as blockage in the pathway of semen transportation and abnormalities of the sperm. Sometimes both partners can have medically identified causes for infertility with clear indication for either medical or surgical intervention, however sometimes the problem could be unexplained.

Various treatments are now available for treating subfertility. As the causes are varied there is no single treatment that would be suitable for all. Different drug regimens are available for stimulation of the ovaries to produce ova which is often needed in patients with problems of ovulation. Gonadotrophins are one such group of drugs that are used extensively for infertility treatment (Levi Setti, 2006). Most frequent use of these groups of drugs is during artificial reproductive procedures, which has become very common.

Assisted reproductive treatment (ART), is collectively all those procedures that help artificially in the process of fertilisation. The first use of ART was way back in 1785 by John Hunter. During early twentieth century American scientists, Samuel Crowe, Harvey Cushing and John Homans were able to separate and recognise fertility related hormones in the pituitary gland, ovary and testis which are an integral part of infertility treatment. The first scientific article about donor artificial insemination, which is an ART technique in which donor sperms are transferred in an infertile women's uterus for fertilisation in the hope that the patient will

conceive, was published in the British Medical Journal (BMJ) in 1945. However, it only came into standard treatment practice for infertility in 1970. With the birth of Louise Brown in 1978, the world saw the biggest achievement and revolution in the treatment of infertility. All the previous milestones culminated in the successful discovery of a new ART called *In Vitro Fertilisation* (**IVF**) which revolutionised the concept and treatment of infertility.

1.2 An overview of infertility and its treatment

In vitro fertilisation (IVF) is the process of fertilisation of the ovum by the sperm, outside the female body. It is one of the most successful techniques of ART for infertility. Since its first success in 1978, it has evolved in all its aspects, including the method of ovum pick up, the way in which ovulation is stimulated, preparation of the egg for fertilisation and implantation. IVF, which was initially developed in order to treat woman with blocked or absent fallopian tubes, is now more widely used for treating other causes of infertility also. IVF is a complex but well controlled and synchronised process where the ovaries are stimulated by exogenous gonadotrophins such as Follicle stimulating hormone (FSH) to produce more than one follicle which are later matured by Human Chorionic Gonadotrophins (HCG). These follicles are then collected by ultrasound guided technique. The eggs are then placed with motile sperms for fertilisation in an incubator. Great care is taken to maintain the culture environment to ensure normal development during the period of incubation. Fertilised oocytes are carefully inspected at regular intervals for proper growth, and when suitable are inserted into the uterus transvaginally approximately 2-3 days after fertilisation. This is called embryo transfer. Embryos with four or five blastomeres on day 2 and 7 or more cells on day 3, with no more than 20% fragmentation and with the absence of multinucleated blastomeres during the whole observation period are considered to have higher implantation rate than others (Van

Royen et al., 1999). These days, most clinics in the UK are routinely practising day five transfer of more mature embryos, also called blastocyst transfer. This has better implantation rate than day two transfers (Styer et al, 2008). More than one ovum is available for fertilisation due to the controlled super stimulation and therefore a patient undergoing IVF treatment mostly has more than one embryo available for embryo transfer.

To overcome the problem of surplus embryos, extra embryos are often cryopreserved. Australian scientists achieved successful implantation of frozen embryo in 1984 which gave more treatment choices for IVF patients. Since then good quality unused embryos are frozen and used at a later treatment cycle. Many clinics carry out both fresh and frozen embryo transfers. However, it has been found that frozen embryos do not have the same implantation rate as the fresh embryo cycles (Neuborg et al 2002). The traditional way of freezing embryos is by slow freezing, however, with the demand for better success rates for IVF treatments, researchers have found that vitrification has better success rate in terms of implantation for both cleavage stage embryos and blastocysts, than the usual slow freezing (Kader et al, 2009). Better fertilisation techniques such as Intra Cytoplasmic Sperm Insemination (ICSI) give a very high fertilisation rate even in low quality semen samples. Often, because of higher rates of fertilisation, more than one embryo is available for transfer. With fertilisation the rate of implantation has also increased. Consequently more and more couples are conceiving through IVF. The success rate of IVF treatment has increased steadily and latest figures show an implantation rate increase from 23.1% (HFEA 2006) to 29.9% (HFEA 2009) in the UK. IVF treatment is available not only to married couples but single parents and same sex partners can be given IVF treatment too. The number of single mothers receiving IVF has increased 2.5 times and same sex couples 4 times in the last 5 years. It is encouraging to visualise the achievements made in the treatment of

infertility, but it is the need of the time that we analyse the impact it is having on our social structure and the health sector.

1.3 Rates of multiple births associated with IVF treatment

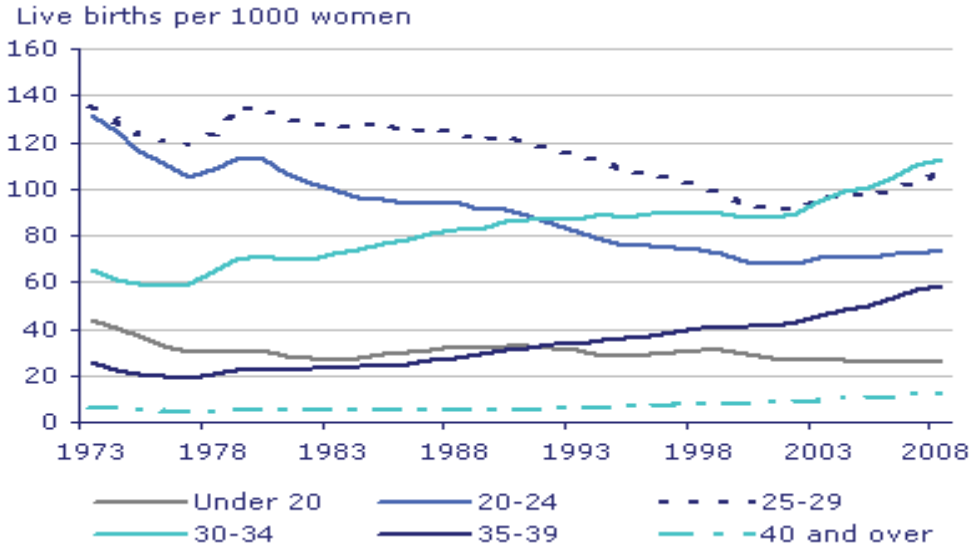
Stimulation of the ovaries by exogenous hormones produces multiple ova which are often of good quality, resulting in good quality embryos. It has been found that the risk of multiple pregnancy (twins) after just gonadotrophin use is considerably higher, in the order of 15-45% and for triplets 5-6%. Quite early in 1990, a Medical Research Council (MRC) report on IVF pregnancies in 3 centres in the UK indicated that 80% of all multiple pregnancies occurred after IVF and other ART (MRC, 1990). The same report showed that the take home baby rate for each patient was in the order of 10-15% with an IVF cycle whereas the rate of multiple births was 22% of IVF deliveries (MRC, 1990; Australian IVF group, 1988). For more than 30 years the rate of multiple deliveries had been on constant rise only recently levelling. The higher rates are a combination of naturally occurring and iatrogenic multiple pregnancies which are a result of liberal ART use for treating infertility patients. Data presented by the Belgian population-based East Flanders prospective twin study suggests that within the obstetric population, 30% of triplets were the result of ART treatment such as IVF, 52% were due to ovulation induction and only 18% were conceived spontaneously (Derom & Derom, 2005).

In a report published by the HFEA in 1998, the number of multiple births from IVF treatment increased from 80 births in 1985 to 1691 births in 1997. This was a huge rise in just a decade. These figures also portray how the use of IVF had soared over a time span of 10 years. Whereas in 1985, 3717 patients underwent IVF treatment, the number of patients in 1996-1997 was 25,563 and this rose to 36,861 women in 2007 which was 46,829 cycles in a year, an increase of 5.8% from the previous year. The number of live births was 364 in 1985 and 22% of the 364 were multiple

births. This figure rose to 5601 live births in 1996-1997 and 30.2% of it was multiple births, which was a rise of 8.2% in a span of 10 years.

The Total Fertility Rate (TFR) in the UK is 1.96 children per woman in 2008 and is the highest level since 1973. In the last three decades the fertility of UK women in their thirties and forties has shown upward trends. Women aged 30-34 have experienced the greatest absolute increase in fertility over this period, with rates rising from 64.1 births per 1,000 women in 1978 to 113.1 in 2008. As a consequence, women aged 30-34 have had the highest fertility rate of any age group since 2004. This is reflective of the latest HFEA report in which under 35's contributed to nearly half (40.3%) of all patients treated for infertility in 2008 (HFEA, 2009). The latest figure shows that the mean age for giving birth in the UK was 29.3 years in 2008, while in 1978 the mean age was (26.7 years) almost three years lower (Fig-1.1).

Fig-1.1 Rise in UK fertility (Office of National Statistics)



In the figures released by the National Statistics office, year 2004 showed that the likelihood of women having multiple births was higher at every age group in 2004 than 10 years previously. Women aged 40 years and over

experienced the highest multiple maternity rate at 21.6 per 1000. This certainly deserved attention and the HFEA since January 2009 has focused initially on the management of IVF treatment to reduce the rate of multiple births from the 2005 national average of 24 per cent or 1 in 4 of all IVF births to 10 per cent over three years. In the first year all clinics were expected not to exceed the 24 percent maximum (HFEA, 2007) but the latest figures have not yet been released. All these measures are to control the soaring rates of multiple births which are mostly twins. IVF came out predominantly as the main reason for increased rates of twins in patients over 40 years of age and in women over 44 years 28.1% of all IVF live births were multiples (HFEA 2010). This is because although these women may not have a good reserve of potent oocytes they do have a greater chance of multiple births with high quality oocytes from younger donors.

A study in England and Wales showed a steady increase in twin births from 9.95 to 14.47 per 1000 live births during the period of 1982 to 2002. The triplet birth rate increased by 400% from 0.12 to 0.48 per 1000 births until 1998 (Lawrence et al, 2001*)*. Rates declined when in 1999 the rate of triple births decreased by 37.5% and further years showed another decline in the births of triplets from 0.48 to 0.3 per 1000 births. This was due to the fact that restrictions on the number of embryo transfer were brought in which helped in restriction of higher order pregnancies. The English and Wales data for 2002 showed a 250% higher rate than that of 1980. This could be attributed to the misuse of the guidance for 3 embryos transfer and to some extent the complications of transferring more than one embryo (Lawrence et al, 2001*)*. The graph in figure 1.2 shows the increasing rate of twins since the year 1978, whereas figure 1.3 shows that the rate of triplets and higher order pregnancies has decreased for all age groups after the year 1998, when the HFEA introduced regulation on embryo transfer. However, the graph shows that the rates of higher order

pregnancies have decreased for all age groups except for those over 35 years of age.

Fig-1.2 Increasing rate of twin pregnancy, BJOG Aug'04

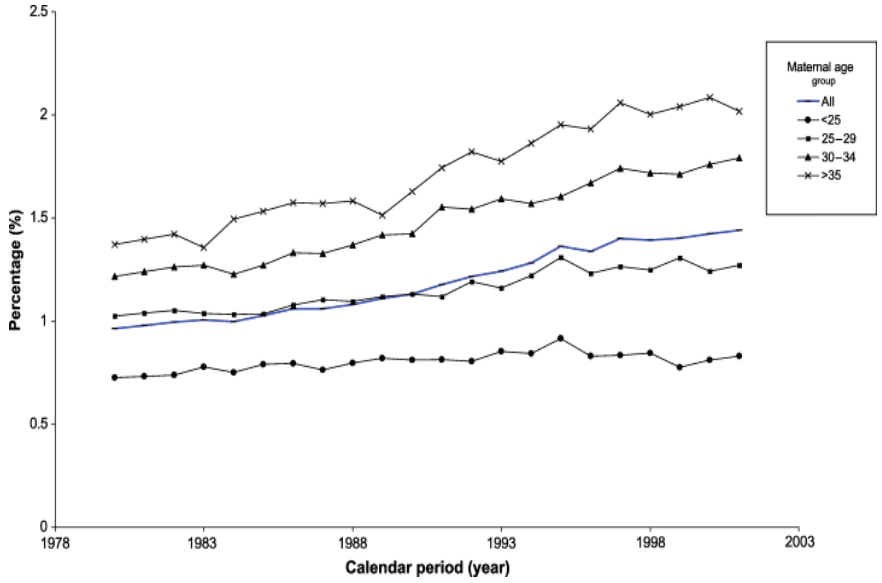
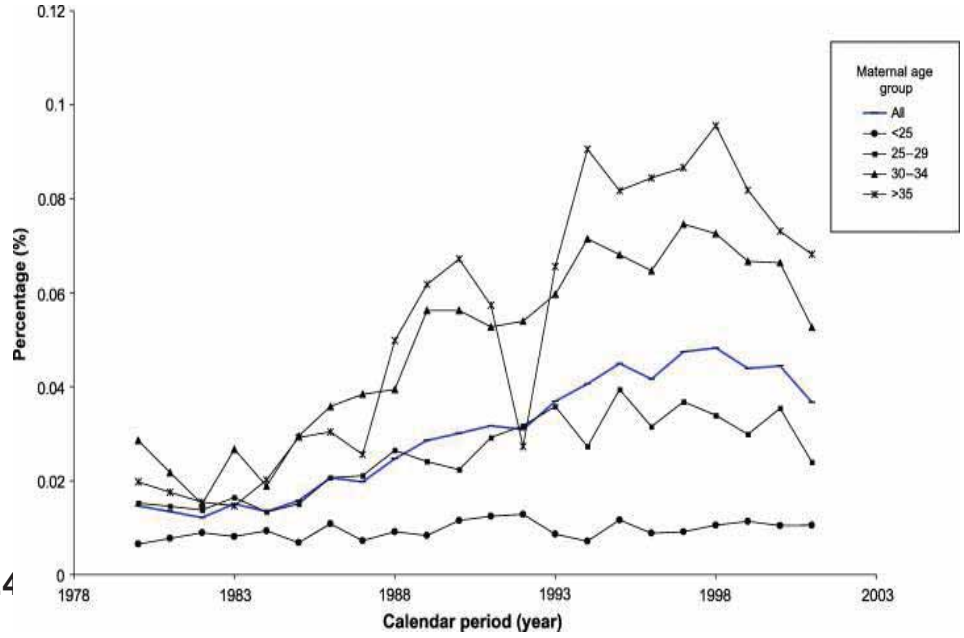


Fig-1.3 Decreasing rate of higher order pregnancies after 1997, BJOG Aug'04



1.4

1.4 Patho-physiology of twin births

Multiple births refer to the delivery of twins, triplets, quadruplets and other higher order multiples. However, the scope of this research focuses on the rising rates of twins. There are two types of twin pregnancies: dizygotic and monozygotic. Dizygotic twins develop when two ovum are fertilised. Dizygotic twins have separate amnions, chorions, and placentas. On the other hand, monozygotic twins develop when a single fertilised ovum splits after implantation. This splitting can be at anytime. An early splitting usually occurs within 2 days after fertilisation and these are monozygotic twins with separate chorions and amnions. Approximately 30% of all monozygotic twins have dichorionic/diamniotic placentas. Splitting at a later stage between day 3 to 8 after fertilisation results in monochorionic/diamniotic placentation and approximately 70% of monozygotic twins are monochorionic/diamniotic. Occasionally splitting can occur between days 9 to 12 after fertilisation. When this happens, monochorionic/monoamniotic placentation occurs and only 1% of monozygotic twins have this form of placentation. Monochorionic /monoamniotic twins have a common placenta, with vascular communications between the two circulations. These twin pregnancies can be complicated with conditions like twin-to-twin transfusion syndrome. If splitting occurs at a much later stage such as more than 12 days after fertilization, then the monozygotic fertilised ovum splits partially, resulting in conjoined twins (Qiu et al, 2008).

1.5 Factors influencing the increase rates of twin birth

Better neonatal care

Many factors have contributed to the increase in multiple pregnancies, and one such factor is better neonatal care in our hospitals. Twin infants are more likely to be born premature and thus at greater risk of neonatal death. However, with better training of the neonatal team and the

accessibility of the latest advanced technology in our neonatal department, survival of more and more babies is becoming a reality. Now babies of <24 weeks gestation can be saved and also those with <2500gm of birth weight (James & James 2001) For example of the 1892 infants in the UK who were born between 23 and 25 weeks gestation, 312 survived to discharge (Bodeau-Livinec et al, 2008*)*. This rise in survival is contributing to the rise in multiple infant rates in society. There are other factors which also contribute to this surge.

Age of mother

The trends that have become more significant are the increasing age of women. With the greater use of ART and a more open and prosperous society, more and more women are having their first child at a much later age. This deliberate choice of late motherhood is decreasing the rates of natural conception in these women who have to resort to ART, and especially treatment, for increasing their family line. The older the mother, the more the chances of having a multiple birth.

Over the years studies have shown that there is an increased chance of multiple births in women of older age whether they conceive naturally or through fertility treatment (Chia et al, 2004). There is also an association between increased parity and risk of twins. Some evidence suggests better outcomes associated with twin birth in older mothers (Delbaere et al, 2008). Regardless of zygosity, mode of conception and socioeconomic status, the outcome of a twin pregnancy in first time mothers of twins over 35 is better than first time mothers in the women in the 25 to 29 age group, although this not true for singleton births. The reasons for this are unclear although it has been suggested that it reflects an evolutionary strategy to ensure increase in fertility prior to menopause (Helle, 2008).

Higher rates of perinatal mortality and morbidity, low birth weight and birth asphyxia are some of the most common obstetrics complications found in

older women after 40 years (Cleary-Goldman et al, 2005, Simchen et al, 2006). As these women tend to have infants with low birth weight who are at a greater risk of perinatal mortality and neurodevelopment complications and this could increase the cost of care (Whitaker et al, 2006).

A cohort study was conducted at Songklanagarind hospital in Thailand between 1997 and December 2006 to examine pregnancy outcomes in women aged 40 or older and to determine the effect of maternal age on low birth weight. The other inclusion criteria was gestational age at delivery to be 28 weeks or greater or a birth weight of 1000g or greater. Total of 789 women aged 40 years or above were compared to 20,852 women aged 20-34 years, which acted as the control. The multivariate, logistic regression analysis found that maternal age was an independent risk factor for low birth weight. During analysis of the result it was found that women in the study group had more medical and obstetric complications (diabetes mellitus, chronic hypertension, malpresentation, pregnancy-induced hypertension, placenta praevia, multiple pregnancies, pre-term labour, foetal distress, retained placenta, postpartum haemorrhage and endometritis) and more poor foetal outcomes (low birth weight, low Apgar scores and congenital anomalies) and a higher caesarean section rate (Tabcharoen, et al 2009).

A retrospective cohort study on twin pregnancies was conducted at Hippokration General Hospital in Thessaloniki in Greece, between 1988 and 2003. Women in the study group were ≥ 35 years (n=57) old whereas women in the comparison group were < 35 years old (n=181). The control group had significantly ($p<0.001$) higher rates of spontaneous conception of twins (90%) compared to the study group (54%), In the older age group 40% of women had conceived following IVF compared to only 6.5% in the younger age group ($p<0.001$). Mean gestational age at delivery and birth weight were similar for both groups. It was found that very low birth weight

(VLBW <1500g) rate was significantly more common in the study group. Although there also were more antenatal, intrapartum and perinatal complications in the study group, these differences were not significant. The study concluded that although higher maternal age with twin pregnancy did not significantly increase complications during pregnancy, VLBW was a serious and significant perinatal complication with increasing maternal age (Prapas et al 2006). This shows the effect that IVF has on twin birth rates in older women and suggests that outcomes may be poorer for infants in these groups of women.

Against the trend of more twin births at older age groups, a study carried out in a London Hospital (Lawrence et al, 2001) shows that the multiple births in IVF patients showed a rise in the age group 30-34 years and a decline on both sides of this range. The study also shows that the risk of multiple births is 35% in younger women having three embryos transferred as compared to 27% in women over 35 years. This study was based at the London Women's Clinic and included 7700 cycles representing 4417 total patients which is quite a good sample size. As it is a single centre study it cannot give the general picture of the country. The other significant drawback in the study is the non-inclusion of patients with hormonal problems such as Polycystic Ovarian disease (PCOD), anovulatory cycles as they are one of the major causes of infertility and a major proportion of IVF patients. Including these category of patients would have certainly accommodated more of the >35 years age group. These groups of patients are the ones going for oocytes and embryo donation. These women benefit from using better quality of donated oocytes and embryos which certainly increases the implantation rate. If these groups of patients were included in the study, the trend of the result might have been different. This study also found that the average age of women coming for the first time for ART treatment in the UK had changed from <35 years to that mostly in between 35-39 years.

Drugs

As mentioned above one of the most important factors in ART practise that may contribute to higher order pregnancies is the use of superovulation inducing drugs. Various drugs such as Clomiphene citrate and Tamoxifen are used for ovulation induction in patients with anovulatory cycles and those undergoing IUI treatments. This makes the probability of a multiple birth much higher than in an un-stimulated cycle. The use of other drugs like gonadotrophins also hold prominent place with regards to the risk of multiple gestation in ART treatment. These drugs have the potency to mature more than one follicle at one time and it is this ability of these drugs that make them so useful and important for IVF patients but also carries the risk of multiple pregnancies.

Procedures

Whether it is artificial insemination, (Gamete Intra-Fallopian Transfer) GIFT, IVF or the more recent ICSI, all carry high risks of multiple births and this has been studied and reported in many studies, as mentioned above. Pison & D' Addato (2006) have reported that the reason for the increase in multiple pregnancies in the developed world is undoubtedly the rapid expansion and use of ART techniques. ICSI, which has changed the treatment of male infertility by increasing the fertilisation rate compared to traditional IVF treatment, also carries a higher risk of embryo splitting and monozygotic twins.

Other factors

Various other recognisable factors contributing to the rise in twin births are family history or hereditary; parity or having more than one previous pregnancies, especially a multiple pregnancy, increases the chance of having a multiple pregnancy; season; race- Afro-Caribbean mothers are at a greater risk of twin pregnancies than others and also the introduction of family planning or delayed childbearing is another factor for rise in twin

births. Nutrition of mothers also played some role as consumption of Vitamin A or Beta-carotene at the time of conceiving produced higher rates of multiple pregnancies, although this needs further research. Mothers smoking just before and at the time of conceiving have also been looked as a risk factor for dizygotic twinning (Kállën 1999). The above mentioned factors seem to have an effect on the rates of multiple births as reported by various studies. It would be significant here to analyse the various specific problems a multiple birth can have and comparing with a singleton pregnancy. What, if any, implications it had on the health of the mother, infant, and our health system and on our society as a whole.

1.6 Are twins a risk factor for preterm and prematurity?

The incidence of twin pregnancies has increased because of more frequent use of assisted reproduction technologies and most adverse outcomes in children conceived with IVF treatment are related to multiple gestations (Schieve et al 2002; Helmerhorst et al 2004). Between 40% and 70% of these twins are born preterm (Steer, 2007) and a high proportion of these preterm twins are premature, as a result the perinatal mortality rate in twins is eight to tenfold higher than in singletons (Steer, 2007).

With the rise rates of infertility rate, more and more couples need IVF treatment. Approximately more than 125,000 IVF cycles are carried out in a year in Europe (Nygren & Anderson, 2002) which is ever increasing and so also are the risks of twin births and related preterm birth and prematurity in these infants. Assisted reproductive treatment cycles result in higher rates of multiple gestation pregnancy rates because of the desire to achieve higher pregnancy rates (ESHRE, 2000).

Higher rates of preterm deliveries, intra-uterine growth retardation and low birth weight are some of the complications of ART treatment identified even in singletons (Tan et al, 1992; Wang et al, 1994) and twins (Moise et

al, 1998). Some other studies at quite an early stage of IVF development and use (MRC, 1990; AIFCG, 1988) also found that IVF singletons were at higher risk of prematurity than natural singletons (Malcolm, 1991). More recent studies that have also looked into ART treatment effects have found similar results. A meta analysis of two studies have shown that singleton pregnancies resulting from in vitro fertilisation (IVF) had increased rates of preterm birth at <33 weeks of gestation (OR 2.99; 95% CI 1.54-5.80), and at <37 weeks of gestation (OR 1.93; 95% CI 1.36-2.74) and a relative risk of 1.98 (95% CI 1.77-2.22) for preterm birth when compared with naturally conceived singleton pregnancies. They found that both IVF twins and singletons have risk of prematurity related to preterm birth (Blickstein, 2006). Data from the East Flanders Prospective Twin Study reflected the change in the proportion of spontaneously conceived twins compared to iatrogenic twins, which has changed from 25:1 to 1:1 over the last twenty years since the vigorous use of new ART techniques (Derom & Derom, 2005). This is of concern since a multiple birth is an additional risk factor in infant wellbeing in IVF treatment. Data from the very low birth weight (VLBW) Infant Database of the Israel Neonatal Network showed that 10% of very low birth weight (VLBW) singletons were a result of assisted reproduction compared with 60% of the VLBW twins (Blickstein, 2006). It is an alarmingly high figure and which is ever increasing with more frequent use of IVF treatment.

Table1.1- Figures of IVF birth (HFEA Fertility Facts & Figures 2008)

Number of births by age	Singleton Births	Multiple Births	Proportion of live births which were multiples %
Under 35	4,555	1,694	27.1
35-37	2,509	681	21.3
38-39	1,259	255	16.8
40-42	813	136	14.3
43-44	143	31	17.8
Over 44	97	38	28.1

It is not only IVF treatment but even less invasive ART treatments such as controlled ovarian stimulation with and without artificial Insemination (AI) which was also associated with an increased incidence of prematurity (<32 weeks and 37 weeks), low birth weight, transfer to NICU in ART singletons than spontaneous singletons (Ombelet et al, 2006). Twins as a result of the subfertility treatment had higher mortality rate and more infants had respiratory distress and needed artificial ventilation compared to natural twins (Ombelet, et al, 2006). When these ART singletons were compared with ART twins, the ART singletons showed significantly higher ($p<0.001$) (mean 39 weeks) gestation age at delivery compared to ART twins (mean 35.6 weeks). Also the mean birth weight in these singletons (2348 gm) was significantly ($p<0.001$) higher than in twins (3315 gm). Other measures, such as preterm birth at <32 or <37 weeks, birth weight <1500gm or <2500gm, perinatal death, transfer to NICU, neonatal death all showed significantly ($p<0.001$) worse outcome for ART twins compared to ART singletons (Ombelet et al, 2006). This study is a retrospective cohort study comparing perinatal outcomes of non-IVF ART with natural pregnancies. It looked into the data of 12,021 singleton and 3108 twin births for ten years and it has found that even just controlled ovarian

stimulation can have poor effects on infants; Mushayandabvu et al (1998) also had similar findings.

A systematic review and meta-analysis was carried out at McMaster University, Canada (McDonald et al, 2010) to determine the risks of preterm birth (PTB) and low birth weight (LBW) in twins conceived through in vitro fertilization (IVF) or IVF/intracytoplasmic sperm injection (ICSI) compared to spontaneously-conceived twins after matching or controlling for at least maternal age. In total 4385 twins from IVF and 11,793 spontaneously conceived twins were included and compared in the 12 studies that were included for the review. All the 12 studies included were retrospective, cohort studies. The inclusion criteria were studies which examined preterm birth or low birth weight (LBW), comparing IVF twins with spontaneously conceived twins. The primary outcomes were PTB (<37 weeks gestation) and LBW (<2500grams). The review found that when the studies were controlled for maternal age, IVF twins had higher relative risk rates of PTB (1.23, 95% CI 1.09, 1.41) and LBW (<2500gm, 1.14,95% CI 1.06,1.22). They also had lower mean birth weight (-105gm, 95% CI -204 gm. -3gm) and higher probability of moderate PTB (<32-33 weeks) (RR 1.63, 95% CI 1.17, 2.27). However, there were no significant differences between IVF and spontaneous twins for factors such as duration of gestation (-0.5 weeks, 95% CI-1.2 weeks, 0.2 weeks); inter-uterine growth restriction IUGR (RR 1.06, 95% CI 0.72, 1.55), risk of late PTB (32-36 weeks, RR 1.12, 95% CI 0.85, 1.47); VLBW (RR 1.28, 95% CI 0.73, 2.24), ELBW (RR 0.88, 0.04, 19.40) were considered. The confidence intervals for these non-significant comparisons are wide and probably reflect the smaller sample sizes available. The review and the analysis of the studies found that IVF twins had increased risk of PTB and LBW compared to spontaneously conceived twins and therefore a higher risk of mortality and morbidity. The study has also conducted quality assessments and looked into biases that could influence the findings in

the studies included. The review found that at least two studies showed high and one had medium selection bias; this could be due to the fact that the spontaneously conceived twins and IVF twins were from different populations. Analytic bias was high in at least 5 of the included studies. Differences in sample size and differences in analytical methods used were the reasons attributed to this bias. The above review is exhaustive and has looked into almost all aspects of bias, but including IVF only and IVF/ICSI in the same group can affect the true picture of the study and the result (McDonald et al, 2010).

A different population based cohort study was conducted within a Network of 19 maternity centres in East Flanders, Belgium (East Flanders twin survey) that looked into the gestational length and prevalence of preterm birth. The study looked into spontaneous twins (n= 2915 pairs), twins born after ovarian stimulation (n=710 pairs) and twins born after IVF or ICSI (n=743) (Verstraelen et al 2005). Women on infertility treatment were significantly older ($p<0.001$) and had significantly lower chance of having had a child before ($p<0.001$) than women who had conceived naturally. It found that twins from assisted treatment for fertility had shorter gestational age at birth (mean difference 4.0 days, 95% CI 2.7 to 5.2) odds ratio 1.6 (1.4 to 1.8) for mild preterm birth (34-36 weeks), a 60% increased risk. Twins after fertility treatment had more chances of both spontaneous preterm birth (odds ratio 1.6, CIs 1.4 to 1.8) and delivery by caesarean section (odds ratio 1.5, CIs 1.2 to 1.9). These twins also, had slightly higher risk of low birth weight (odds ratio 1.2, CIs 1.1 to 1.4) compared to spontaneously conceived twins. However, when controlled for birth year, maternal age and parity, the adjusted odds ratio was 1.3 (1.1 to 1.5) for preterm birth after infertility treatment. The odds ratio was 1.6 (1.3 to 1.8) for preterm when further control for foetal sex, caesarean section, zygosity and chorionicity was done.

The above study also found that the ratio of dizygotic to monozygotic twins in patients with fertility treatment was 95.2:4.8 compared to 53.8:46.2 in spontaneous twins ($p<0.001$). Therefore it was found that although there was an increased risk of preterm birth among twins resulting from subfertility treatment, this risk was mainly caused by a 'first birth effect' in the infertile couples but the impact of prematurity was reduced by the protective effect of dizygosity which is more common in IVF twins and associated with better outcomes. This study also recorded an increase preterm birth rate of 11.7% for ART twins compared to naturally conceived twins, which is nearly double the increased risk rate previously reported in IVF singletons compared to naturally occurring singletons. The difference in rates of prematurity was even greater between naturally conceived twins and IVF/ICSI twins (45.1 vs. 59.4) (Verstraelen et al, 2005).

Another study looking into aspects of behavioural patterns, mental and psychomotor development, as well as maternal and gestational age, foetal presentation, birth weight, sex, apgar scores, perinatal complications, delivery route, and admission to Neonatal Intensive Care Unit (NICU) between naturally conceived twins (n=305) with twins conceived by assisted reproductive techniques (n=119), found that the mean gestational age and birth weight of assisted twins were significantly less than those of spontaneous twins even though the participant mothers were older than that of the naturally conceived twins. Caesarean section rate and the delivery rate of male foetuses were significantly higher in assisted twins, even though there was not much difference between the groups in terms of presentation, perinatal complications, Apgar scores and admission to NICU (Kanat-Pektas et al, 2008).During the first year of infant life, there was more marked retardation in both mental and psychomotor development in assisted twins. Behavioural problems along with difficulties in parent-child interactions were also more frequent in twins from ART treatment (Kanat-Pektas et al, 2008).

In contrast other studies have shown that neither singleton nor twin IVF pregnancies carry any increased risk of low birth weight, prematurity nor any other maternal or foetal complications (Reubinoff, et al 1997; Fitzsimmons et al, 1998) and some have argued that ART singletons are indeed at a greater risk than spontaneous singletons but ART twins on the other hand were at an advantage to spontaneous twins because by virtue of their dizygocity.

A systemic review of 25 studies published between 1985 and 2002 and looking into perinatal outcomes of singletons and twins conceived by ART treatment compared to naturally conceived twins and singletons, found that perinatal mortality in twin pregnancies was 40% lower after assisted conception than those from natural conception. Twins conceived by assisted conception were more likely to be preterm (50% vs. 45.6%; RR 1.07 (CI = 1.02 to 1.13) compared to naturally occurring twins. They reported that factors which influenced gestational age at birth also influenced gestational weight and assisted conception may belong to the factors that influence both foetal weight and length of gestation (Helmerhorst et al, 2004).

A population-based cohort study in Finland evaluated prenatal outcome and costs resulting from prenatal and neonatal care in children born after invitro fertilization (IVF) between 1990–1995, in comparison to those born from natural conception. This study reported that the IVF mothers carried a higher risk of vaginal bleeding, threatened preterm birth and intrahepatic cholestasis of pregnancy than control mothers, and they used more specialised antenatal care than others and because of which the prenatal outcome was not encouraging for these children which meant high cost of care both during neonatal period and antenatal period (Koivurova et al 2002).

When IVF singleton pregnancy was compared to spontaneous singleton pregnancy, it has been identified that even maternal complications like pregnancy induced hypertension and vaginal bleeding are significantly more common in IVF mothers with singletons than in mothers with spontaneously conceived singletons. The same study found that the rate of caesarean section, vaginal bleeding and preterm labour was more common in mothers conceiving twins after IVF treatment than in mothers with spontaneous twins but this difference was not significant (Koudstaal et al, 2000).

Helmerhorst et al (2004) and Dhont et al (1999) found that most medically aided pregnancies, even singletons, resulted from multiple conceptions and therefore, pregnancies that continue as twin pregnancies may have an advantage of survival as a similar picture is evident for natural twin pregnancies also, where, only one in eight fetuses originating as a twin are actually born as a twin (Hall, 2003).

It can be argued that although 1 in 8 natural twin pregnancies actually deliver as twins the ratio of natural and ART conceived twin pregnancies are different in terms of zygocity and this argument may not be appropriate for dizygotic twins who are more frequent from an IVF birth. Most studies mentioned above comparing ART deliveries with spontaneous deliveries have indeed found that both ART singletons and twins carry higher risk of prematurity, preterm birth and low birth along with risk to the mother.

1.7 Evidence for negative effects of twin births for child and mother in IVF studies and in studies comparing naturally conceived twins and singletons

Perinatal mortality rate (PMR) is defined as the number of still births plus early neonatal deaths, per 1000 live and still births. A still birth is defined as a baby born dead after 24 weeks of gestation. Perinatal mortality rate is

considered the measure of development of a society. Countries with lower mortality rates are considered more developed than those with higher rates. PMR in the UK decreased drastically from 21.0/1000 in 1973 to 8.3/1000 in 2000 but since then it has been constant at 8.2/1000, even with the best antenatal and neonatal healthcare. Like other developed nations, the perinatal mortality is 8/1000 for single pregnancy which increases to 37.5/1000 for twins and 73/1000 for triplets. Perinatal mortality rates are fourfold higher for twins and six fold higher for triplets than for singletons (ESHRE, 2000).

This rising figure is enough to draw attention to the complications of multiple pregnancies. The national statistics shows that over the last 3 decades the multiple birth rate per 1000 maternities have risen from 14.95 in 1980 to 15.48 in 2008 and more so after liberal use of IVF treatment. This indeed is an avoidable complication of this treatment that results in a high incidence of perinatal mortality and morbidity (Petterson et al, 1993). A multiple birth can not only increase the risk of perinatal, neonatal and even infant mortality; it can have ominous effect on both the mother and the child which can be traumatic for the whole family as a whole. In a multiple pregnancy, risks to both the mother and the child increase (Crosignani & Rubin, 2000; Elster, 2000). A more detailed evaluation into the complications to both the mother and the child is necessary to understand the exact and true picture of the problem.

Impact of a twin birth on maternal physical health

All patients conceiving after infertility treatment are considered to be at a greater obstetric risk than normally conceiving women (Basso & Baird, 2003). It is estimated that the incidence of first trimester abortion after natural conception is 10-20%, the true incidence might be higher because many early abortions go unrecognised (Tummers et al. 2003). In comparison, spontaneous abortion rate after IVF is slightly elevated

(Schenker & Ezra 1994), varying generally between 10-30% by different techniques (Schröder et al 2002). Higher rates of abortions after IVF can be due to advanced maternal age carrying a higher risk for chromosomal aberrations, higher rate of multiple pregnancies with increased pregnancy loss, and the early recognition of IVF pregnancies and abortions due to close monitoring (Schenker & Ezra 1994). An association between subclinical endometrial infection or inflammation and spontaneous abortion after IVF has recently been suggested (Romero et al. 2004).

In general, higher rates of medical complications like pre-eclampsia and gestational diabetes have been found in IVF mothers, irrespective of the zygocity (Nassar et al 2003, OchsenkÜhn et al, 2003). With ever increasing use of ART and especially IVF treatment, there are increased chances of some maternal complications such as pregnancy induced hypertension (PIH), gestational diabetes and higher rates of elective Caesarean section even in women with singletons (Maman, et al, 1998) and vaginal bleeding with increased rates of elective caesarean section in twins (Koudstaal et al, 2000). As mentioned earlier, it takes a long time to diagnose infertility problems and these days' women tend to start their family quite late and this could be further complicated by other age related medical ailments which can further prove to be a risk for the health of the mother. These are mostly related to chronic illnesses such as diabetes and hypertension (Cleary-Goldman et al, 2005, Simchen et al, 2006, Ziadeh & Yahaya 2001). Mothers with multiple pregnancies also had four times higher chances of a caesarean section when compared with single IVF pregnancy (Glazebrook et al 2004).

Generally, in mothers with multiple pregnancies, pre-eclampsia, a medical complication occurring only during pregnancy and the postpartum period, is very common. This condition can affect both the mother and the unborn foetus. Prevalence of pre-eclampsia is 5-8% of all pregnancies. Its symptoms are fast rising high blood pressure and the presence of protein

in the urine. Usually it occurs after 20 weeks gestation but it can present earlier as well. The risk of pre-eclampsia increases 20 folds, from 10% in singleton pregnancy to 30% in twin pregnancy. It can lead to other more serious conditions like premature birth, foetal distress and sometimes can be more fatal and would terminate as foetal death. When not controlled, mothers can have convulsions which sometimes might lead to death of the mother as well. Multiple pregnancies can carry other medical complications for the mother too. The chances of antepartum haemorrhage (APH) increases from 4.7% in singleton to 6% in twin pregnancy (Wright et al, 2007). APH can have fatal effect on both foetus and the mother at the last stage of pregnancy. During labour, the chances of postpartum haemorrhage (PPH) in twins increase to 10% from 4-6% in singletons. Other conditions like rupture of Vasa Praevia, increased cord prolapse, cord entanglement and premature placental separation are some of the dangerous complications which occur more frequently in multiple pregnancies. Multiple pregnancies also carry increased risk of maternal morbidity during late preterm period (34-37 weeks' gestation) due to increased rate of hypertensive disorders (Wright et al, 2007).

The medically related physical risk on these mothers can increase the stress level of a patient as mentioned earlier who already has increased stress level due to her infertility problem and can be psychologically unhealthy during a treatment as important and complicated as IVF.

Impact of a twin birth on maternal mental health

There is evidence that a multiple birth can have a negative impact on maternal mental health. A prospective follow-up study from delivery was done at 2 years and 4 years to assess the mental health of mothers of triplets and the mother- child relationship. Assessment was done by a psychologist, using semi structured interviews at a maternity hospital in Paris, France (n=11), between October 1988 and February 1990. Almost

all (99%) were conceived after infertility treatment. Evaluation of the mothers' emotional well-being and level of depression was measured using CES-D Scale (Centre for Epidemiologic Studies-Depression Scale). The study showed shocking results because all participant mothers reported emotional distress at 4 years and this was mainly fatigue and stress. Four of the 11 women had high scores for depression indicating clinical disorder and used psychotropic medication. The psychological consequences of bringing up triplets both at 2 years and 4 years after birth, on the mother were considered to be too stressful (Garel et al, 1997). Kentenich (1989), Mori et al in (1997) found that the stress increase in IVF patients is higher than the level of stress an infertile patient has. This could be further increased with the birth of a twin which is proved in the study done by Thorpe, et al. (1991). Thorpe, et al. (1991) has shown that the mental health of mother with twins even during a spontaneous pregnancy is weaker than singleton mothers. A cohort study of 13,135 children born between 4 April and 11 April 1970 was done in the UK to establish whether the obvious additional and exceptional stresses associated with bearing and parenting twins affect the emotional wellbeing of mothers when the child was 5 years of age. In all 139 mothers of twins (122 pairs of twins and 17 twins whose co-twin had died) and 12,573 controls, who were mothers of singletons, were included in the study. Participant mothers were asked to complete a questionnaire, which included the 24 item Rutter malaise scale when their child/children were 5 years of age. The scale is based on the 196 item Cornell medical index of health questionnaire which indicate the presence or absence of several symptoms of mood and psychosomatic disorder. This scale has been found to be a satisfactory predictor of emotional disturbance in adults.

On the malaise scale a score of ≥7 is predictive of clinical depression. The study used a cut off point of >6. The maximum possible score was 24 and the minimum zero. The malaise scores of mothers of twins were

compared with singletons mothers and then with mothers categorised by the age spacing of their children (only one child, widely spaced, or closely spaced), taking into account maternal age, social class, and whether the study child had a disability. The study found that 34.4% mothers of twins were likely to be depressed (score >6) compared to 23.9% mothers of singletons. Still higher (52.9%) was the proportion of mothers with twins who had lost one of the twins who were above the threshold level and indicative of depression (Thorpe, et al. 1991).

Maternal youth and social class were also independently found to predict high maternal malaise score (>6) or indirectly, depression. Independent of all other variables such as maternal youth, social class (particularly being an unsupported mother), number of children in the household, and disability in the study child, caring for a twin on its own was predictive of causing depression (OR 1.6; 95% CI 1.1 to 2.3) and this depression score was three times more (OR 3.0; 95% CI 1.1-8.1) aggravated in mothers who had lost one of the twins compared to singleton mothers. Both mothers of twin pairs and mothers of singletons closely spaced in age were at significantly higher risk of experiencing depression than mothers of children widely spaced in age or mothers of only one child ($p > 0.0001$). The study indicated that the risk of depression in mothers of twins compared to singleton mothers (OR 1.8; 95% CI 1.3 to 2.0) was even higher than that in mothers of closely spaced singletons (OR1.4; 95% CI 1.2 to 1.6). The strengths of this study were that it was large scale and prospective with mothers recruited at delivery. Many twin studies are unrepresentative of twins in the general population, for example if they are recruited through self-help groups or if there is a poor response rate due to the pressures of parenting twins.

A study carried out by Haigh & Wilkinson, (1989) comparing the maternal care of 84 sets of twins in their own homes with randomly selected, matched singleton controls found that the stress experienced by parents

was more related to the number of children to be cared for rather than the fact of twinning. The study also revealed that twin babies received more health visitor care and less GP care than singleton babies.

Despite the fact that IVF mothers tend to be advantaged in terms of social class and likely to be well supported and very positive about parenthood, mothers of IVF twins may also be at increased risk of psychological morbidity. First time mothers who conceived twins by IVF had higher parenting stress than those with previous siblings or twins conceived naturally (Colpin et al, 1999). Furthermore within mothers conceiving through IVF treatment, a twin birth may be an additional risk factor. A prospective study by Glazebrook et al (2004) found that mothers with multiple IVF pregnancies showed 22% of mothers with a multiple birth had high levels of parenting stress compared to only 5% in the singleton group, a five fold increase.

Another study found that higher parenting stress was reported by mothers with twins. In this study of 344 mothers of twins aged 2 to 5 conceived by IVF or ICSI and a matched group of 344 mothers of singletons, only 12% of mothers with twins reported having no problem with parenting compared to 33% of mothers with singletons. Mothers of twins had significantly higher levels of parenting stress and depression. Only 32% of mothers with twins showed desire to have more children compared to 48% of singleton mothers. When asked about pleasure from their children, 76% of mothers with twin experienced colossal pleasure from their children compared to 89% of singleton mothers (Olivennes et al 2005).

Poor psychological health may have a negative effect on infant wellbeing. A study carried out at Osaka University, Japan, looked into the effects of parenting anxiety on a child's mental development in both twin and singleton groups used during the JCFRI Child Rearing Support Questionnaire for measurement of parenting anxiety and the Tsumori-

Inage Infant Developmental Scale. The study found that twins' mothers showed significantly higher scores for parenting anxiety, including general confusion regarding parenting and negative feelings toward their children compared to singleton mothers at all assessment times, that is at birth, after 1 year and at 2 years. It was also found that at 2 years after birth the high parenting anxiety in mothers of twins reflected a negative feeling toward their children and this resulted and showed up as a delay in the child's mental development (Nishihara et al, 2006).

Sheard et al (2007) in a study which used a composite analysis of qualitative and quantitative data provided further support for the negative impact of a multiple birth on psychological wellbeing in first time mothers conceiving through IVF treatment. Interviews at 6-weeks postpartum found that mothers of multiples (twins or triplets) were less likely to describe themselves as euphorically happy unlike mothers of singletons who expressed terms like, 'feeling wonderful', which was a reflection on their pleasure of parenthood ($P<0.05$). This same study found mothers of multiples had significantly higher chance of expressing negative attitudes such as 'tiredness' ($P<0.01$), 'feelings of stress/depression' ($P<0.05$) and 'questioning parenthood' ($P<0.05$). They also found that mothers with a multiple birth had an increased risk of depression as measured by the EPDS.

Recent research suggests that the risk of poor mental health associated with twins may not be confined to mothers. A prospective study, the first of its kind, was conducted using a longitudinal design, looking into symptoms of depression, anxiety, sleeping difficulties and social dysfunction among ART parents of 91 pairs of twins and of 367 singletons and on control parents of 20 pairs of twins and of 379 singletons in the 2nd trimester of pregnancy, and when the children were 2 months and 1-year old (Vilska et al, 2009). ART mothers of twins showed fewer symptoms of depression than control mothers of twins ($P < 0.05$) during

the second trimester of pregnancy, however, this was not the trend with the fathers where all fathers had similar mental health. Both ART and control mothers of twins had more symptoms of depression and anxiety than all mothers of singletons ($F = 5.20$, $P < 0.05$ and $F = 3.93$, $P < 0.05$, respectively) at 2 months post delivery and similarly both ART and control fathers of twins had more symptoms of depression ($F = 4.15$, $P < 0.05$) and social dysfunction compared to fathers of singletons. Again, the study found that both ART and control mothers of twins had more symptoms of depression even at 1 year after delivery ($F = 10.01$, $P < 0.01$), but there was a difference in anxiety symptoms only in the control group. The findings of fathers group showed that both ART and control fathers of twins had more symptoms of depression ($F = 4.29$, $P < 0.05$) and anxiety ($F = 5.40$, $P < 0.05$) than fathers of singletons. Control fathers of twins had more sleeping difficulties than fathers of singletons ($F = 6.66$, $P < 0.01$). Although prematurity did not have any affect on the maternal mental health, it did have a negative impact on control fathers' social dysfunction ($F = 3.34$, $P < 0.05$) (Vilska et al, 2009).The study found that at 2 months postpartum, it is the twin parenthood that had negative impact on the mental health of parents during the transition to parenthood. The study found that ART parents' mental health was not affected either by parity or children's health-related factors. This constant stressful situation in the home environment can put a strain on the relationship of the partners and could lead to neglect of the children. This strenuous relationship can even, in extreme conditions, break a happy family.

The psychological state, not only of the mothers but also of fathers of twins certainly doesn’t reflect a healthy picture in terms of pleasure in raising their infants or desire to have more children. This echoes all the studies mentioned above which can have an unhealthy effect on the upbringing of the infants even at their own home which is supposed to be the safest and warmest place for the development of a child. If this stress

is not managed, infants could be at potential risk affecting growth and care and indirectly, sometimes in extreme conditions, even the survival. This supported evidence of negative social consequences associated with a twin birth. A recent report for the Twin and Multiple Births Association (TAMBA) concluded that parents were more likely to divorce. Analysis of data from the Millennium Cohort Study which has followed up a cohort of a group of 18,500 children born in between 2000 and 2001 showed that married couples with twins or triplets had increased divorce rates compared to those with the same number of children but who were not multiples.

The impact of twin birth on the infant's physical health

For twins, the mean gestational age decreases from 40 weeks to 37 weeks and in triplets it further decreases to 33 weeks. Most adverse outcomes in children conceived with IVF are related to multiple gestations (Schieve et al 2002; Helmerhorst et al 2004). For the foetus the main problem is pre maturity which leads to various other complications. Multiple births due to IVF and other ART procedures are associated with high proportion of stillbirths and infant deaths than naturally occurring multiple births (Oakley & Doyle, 2006). The rate of neurological malformations such as cerebral palsy is five times higher in twins and nearly 18 times in triplets (HFEA 2006). Monozygotic twins have a special problem of intermingling of their blood supply, because of which one of the twins suffers from jaundice and the other is anaemic. Glazebrook et al (2004) in a prospective study comparing outcomes in multiple IVF infants with IVF singletons found that there was a threefold increase in medical complications in the infant, with a tenfold increase in admission to special care baby unit compared to singletons.

The stress of infertility and IVF treatment compounded with the medically and psychologically challenging twin pregnancies can in itself have very

poor outcome for the unborn child. The added effects of premature, preterm birth can be very daunting for the parents. Conditions like cerebral palsy which has higher rates in elderly mothers and in twin pregnancies can later on in life have ill effects on the cognitive development of the child. IVF infants had poorer outcome in terms of gestational age, birth weight, morbidity and intensive care treatment. Congenital heart malformations (septal defects) were fourfold in IVF children compared to naturally conceived infants (Koivurova et al 2002) and therefore with multiple births which are more common in IVF, the implications could be worse.

A retrospective study looking into 588,967 children born in Denmark from 1995 to 2003 comparing cerebral palsy (CP) in children born by assisted conception (IVF/ICSI and ovulation induction) with natural conception found that the increased risk of CP in children born after assisted conception, and especially IVF, was strongly associated with the high proportion of multiplicity and preterm delivery in these pregnancies (Hvidtjørn et al, 2010). It found that children born after assisted conception had an increased risk of a CP diagnosis, crude hazard rate ratio (HRR) 1.90 (95% CI: 1.57-2.31) compared to naturally conceived children. IVF children had higher risk HRR 2.34 (95% CI: 1.81-3.01) of cerebral palsy compared to other assisted technique (ovulation induction) 1.55 (95% CI: 1.17-2.06) which was included in the study, compared to natural conception. However, the subtypes of cerebral palsy and the co-morbidities did not differ between the ART and normal conception group (Hvidtjørn et al, 2010).

The impact of a twin birth on the infant's cognitive development

The psychological consequences on the child are immense (Garel et al, 1997). The potential for adverse effects increases with the rise in plurality of the foetus. (Isaac et al, 2005). Apart from other behavioural problems,

children born as multiples show difficulty in interaction with their parents. They also show slow cognitive and motor development and their language and speech is also delayed as compared to singletons (Sutcliffe & Derom, 2006). Spontaneous twins have shown development delay in language development compared to spontaneous singletons (Rutter 2003). Studies have found delayed cognitive development in IVF/ICSI twins compared to IVF/ICSI singletons (Olivennes et al, 2005; Bonduelle et al, 2003). Olivennes et al, (2005) used the Denver Development Questionnaire to measure cognitive functioning found significant difference between IVF/ICSI twins and IVF/ICSI singletons ($F = 5.20$, $p<0.05$), with twins getting lower scores than singletons. A detailed analysis found that the twin group got lower scores for motor and cognitive items such as 'combining words' ($F= 4.49$, $P< 0.05$), 'speech half understandable' ($F= 8.39$, $P< 0.01$); 'names four pictures' ($F= 9.67$, $P<0.01$); 'counts one' ($F= 4.09$, $P<0.05$); 'imitates vertical line ($F= 4.06$, $P<0.05$); 'wiggles thumb' ($F= 4.13$, $p<0.05$); 'names friend' ($F= 16.10$, $p<0.001$). The study did not find any evidence that natural twins were more at risk of emotional or behavioural problems than singletons unlike delayed cognitive development of IVF twins compared to IVF singletons. This seems to be a good study because it had a big sample size and was the first study to report on the consequences of children's psychological development. As the sample size was large the study did not administer the children's development directly and used a measure designed for completion by mothers. Probably direct testing of the children would have given a more different result.

Twin studies have indicated that during early childhood, shared environment has influence on cognitive abilities (Koeppen-Schomerus et al, 2003). This means that infants are disadvantaged because they have to compete with each other in their environment for attention and interaction. Moreover it has been found that this shared environmental

influence is seen more in twins than in two non-twin siblings. A sample of more than 1800 MZ and 1800 same-sex DZ pairs from the Twins Early Development Study (TEDS), a study of twins born in England and Wales in 1994 and 1995, was compared with more than 130 same-sex younger siblings of the twins. Both groups i.e. twins and their younger siblings were assessed for language, cognitive abilities and behaviour problems by their parents at 2 and 3 years of age. Analysis of the study found that the influence of shared environment on language and cognitive scores at both 2 and 3 years was more than twice as large for twins as compared to non-twin siblings. However, behaviour problems did not echo this pattern. The study suggested that the cognitive-relevant experience shared by twins that was not shared by siblings was because of the proximity in their age (Koeppen-Schomerus et al, 2003). A three year follow-up showed delayed growth and increased morbidity for IVF children in general, but their psychomotor development was similar to that of the naturally conceived children (Koivurova et al, 2002).

Financial implications

Even though Koivurova, (2007) found that the healthcare costs was 1.3 fold for IVF singletons in comparison to natural singletons and the healthcare cost for IVF twins was equal to that of natural twins it did find that financial implication was greater in twins compared to singletons and there were many others with similar opinion. The financial impact on families and also the National Health Service increased considerably in case of twins (Gerris et al 2005). Glazebrook et al, (2004) found that, at 1 year postpartum whereas 73% mothers with singletons were working outside the home only 44% mothers with multiple IVF birth had returned to work. Wright (2007) also identified in his recent report that parents of twins experienced more financial difficulties compared to parents of children born at intervals because of the difficulty in resuming work. Their analysis

found that mothers of twins were 20% less likely to have returned to work at follow-up.

With availability of IVF treatment, both under the NHS and more easily privately and sometimes even overseas, and with better success rates than ever before it would be right to look into ways to decrease these unwanted health complications for the child and the mother without decreasing their chances of success and a lower financial costs both for the family and the National Health Service (NHS).

1.8 Is eSET effective in reducing multiple pregnancy rates?

Min et al (2004) suggested reporting IVF outcomes based on live birth. They emphasized that the best successful singleton at term (BESST) should be the ultimate goal of ART. Higher-order pregnancies were recognised as a serious side effect of infertility treatment way back in the late 80s. At that time two steps were considered as a measure- 1) MFPR- Multi-foetal pregnancy reduction (Evans et al, 2004) and 2) decreasing the number of transferred embryos in IVF treatment cycles. MFPR is mostly used to reduce higher order multiple pregnancies such as triplets and above, as multiple pregnancies have higher chances of being born premature and therefore carry high risk of prenatal mortality and morbidity along with risk of neurodevelopmental complications in those infants who survive. There is an indirect risk to the mother also (Sentilhes, et al 2008). These have been mentioned earlier. Multi-foetal reduction is an outpatient procedure that is most successful when performed between 10 and 12 weeks of gestation. It involves ultrasound guided trans-abdominal needle insertion to inject potassium chloride into one or more of the foetuses which needs removal. Multifetal reduction can sometimes be performed earlier in the pregnancy (between 6 and 8 weeks) using a transvaginal approach and embryo aspiration. This procedure is more invasive than the transabdominal route and requires general anaesthesia. It carries a risk for

infection (Sentilhes, et al 2008). MFPR not only holds much higher ethical issues but as a surgical process it also carries risks both for the mother and the foetus.

A rather less invasive procedure which could be beneficial both for the mother and the infant is successfully being practised in many countries around the world. Elective single embryo transfer (eSET) involves transferring one embryo during IVF treatment instead of double or triple embryos even when more embryos are available. It can be selective eSET for patient having better chance than others or it can be for all patients as a rule and some patients can even choose to have SET. Single embryo transfer is becoming more and more acceptable around the world (Table 1.5). Elective single embryo transfer was first done in Sweden and Belgium. However, the two countries have a very different approach to eSET. Whereas in Sweden SET was introduced first in 2002 only for state funded patients, in 2003 their National board of Health and Welfare made it compulsory for all IVF patients, except in exceptional circumstances for patients with bad prognosis (Saldeen & Sundstrom, 2005). The Belgian approach is more flexible. Since July 2003, Belgium introduced the legislation to promote eSET which allowed patients to be reimbursed for six cycles in a life time per patient under the condition that at the time of the first cycle patients' age was 36 years and only one embryo was transferred, irrespective of the availability of a good-quality embryo. It not only considers the age of the patient but also the number of cycles. Patients with failures have more embryos transferred. This gives the patients a better chance. Scientists from both these countries have published studies supporting the effectiveness of eSET (van Peperstraten et al, 2008).

Some have strict regulations while others take patients choice into consideration. However, UK still doesn't have any firm decision to make SET compulsory for all IVF patients. It will be appropriate to understand

the impact of SET on take 'home baby rate' and other parameters which would be a right measure of the success of IVF treatment. Many studies have reported that elective single embryo transfer (eSET) prevents multiple pregnancies (Pandian et al., 2009; Lukassen et al., 2005; Pandian et al., 2005; Thurin et al., 2004; Gerris et al., 2002) and many others have further claimed that there is no compromise in the pregnancy rates (Neubourg et al, 2002; Bergh, 2005; Ombelet et al., 2005; Saldeen & Sundstrom, 2005) along with the added benefit of decreased multiple birth rates.

A literature review was carried out to understand the impact of single embryo transfer on conception rates and live birth rate compared with double embryo transfer (DET). We set out to do literature review on RCTs comparing single embryo transfer with double embryo transfer. The details are explained below.

Method

Criteria for selection of studies

For the study material, Pubmed, Embase and Medline and clinical trial registration data base were the main search portals. Search terms were single embryo transfer, blastocyst, cleavage stage transfer, embryo cryopreservation, IVF, multiple births, IVF multiple births. Both retrospective and prospective studies, meta-analysis and large systematic reviews comparing SET vs. DET were considered and some studies which fell out of the review parameter were also considered for at least reporting their data and these were not critically analysed. Abstracts where studies were not in English language were also examined. The Cochrane library was also searched.

All randomised controlled trials that compared SET with DET were included in the literature review. We also separately looked into studies which were not randomised control trials. The eligibility criteria were

studies comparing clinical pregnancy, live birth rate, rates of twins/multiple births between SET and DET, transfer of fresh embryos, transfer of frozen/thawed embryo, and cleavage stage embryos and blastocysts. Only studies published in English language were considered for the review. The main focus of study selection was from countries where SET, had been in practise for some time and countries where there were proper marked regulations for IVF treatment and embryo transfer. Those studies that provided data that directly linked the number of embryos transferred with the specific set outcomes and publication between 1997- 2006 were eligible for inclusion in the review.

Outcomes: Comparison of following parameters of the studies

1-Clinical pregnancy: A clinical pregnancy is a pregnancy that is confirmed by both high levels of β HCG and where an ultrasound scan has shown at least one fetal heartbeat (HFEA 2006).

2-Live birth: The number of live births achieved from every treatment cycles commenced.

3-Twin/multiple birth: birth of two or more babies.

4-Preterm: < 37 weeks gestational age

5-Low birth weight: < 2500gm

6-Miscarriage: The loss of a pregnancy before the foetus is 24 weeks old.

7-Cumulative live birth rate- add this in the table

Identification of randomised trials and methodological quality

In all 6 randomised control trials met the inclusion criteria and were selected for review. At the time of the review one trial which was started in 2005 in UK, was stopped in 2007 because of poor recruitment. Trial number: ISRCTN86466058- Efficacy and Cost Effectiveness of Selective Single Embryo transfer: a multi-centre randomised controlled trial. Another

trial was identified during correction but could not be included because it had just started in August 2011 and there was no available data. It is called: Single Embryo Transfer of a Euploid Embryo versus Double Embryo Transfer: A Randomised Controlled Trial-NCT01408433, based in USA.

Description of Individual studies included in the literature review

Gerris et al (1999) aimed to prospectively study data on the implantation rate and the (multiple) pregnancy rate following randomisation to single or double embryo transfer. The researchers first did retrospective analysis because there was not much prospective data available to support the aim of the study. They reviewed retrospectively a continuous series of 400 IVF/ICSI cycles immediately prior to the start of the prospective study (Van Royen et al., 1999). Retrospectively they also identified that certain group of patients such as, who have had several unsuccessful treatment cycles, patients who smoke, who show predominantly poor quality embryos (Magli et al., 1998) are at risk of lower implantation rate.

The prospective study was a RCT conducted between November 1997 to May 1999, when a total of 327 patients completed a total of 545 IVF/ICSI cycles. The mean age of the participant women was 31.9 (range: 22–44) years with an average duration of infertility of 3.5 (range: 1–11) years. The study included only women less than 34 years of age, having their first IVF cycle and who had at least two top quality embryos. Before randomisation, the patients had extensive counseling regarding the risks of multiple pregnancies. Randomisation took place at the time of embryo transfer using external concealment. Patients were told that all extra embryos would be frozen and that the study was limited to the first treatment cycle only. Patients who declined to participate and patients who had agreed but who failed to produce two top quality embryos were given the two best quality embryos (standard treatment) except if only one embryo was available. Due to the counseling, some patients elected to have a single

embryo transfer (elective single embryo transfer) of a top quality embryo in all cases.

Out of the 327 patients, 194 (35.6%) were first treatment cycles in women <34 years of age and were therefore eligible for the study. Of these women, 110 agreed to the study protocol and were therefore recruited. Of those agreeing to participate in the study, 53 fulfilled the study inclusion criteria, i.e. they produced at least two top quality embryos. The rest 57 did not produce two top quality embryos and the other 84 patients either requested an elective single embryo transfer (n = 17) or did not agree to participate (n = 67).

In total 6 groups of patients were created: Group A (n = 26): patients (and cycles) randomised to single embryo transfer; Group B (n = 27): patients (and cycles) randomised to double embryo transfer these were the randomised groups and we would only consider these groups for our literature review.

The other groups which we are not going to consider outcomes for were, Group C (n = 57): patients (and cycles) complying with the inclusion criteria but who failed to produce two top quality embryos; Group D (n = 17): patients (and cycles) requesting elective single embryo transfer (11 received one top quality embryo single embryo transfer, six did not); Group E (n = 67): patients (and cycles) not wanting to participate in the study and who received standard treatment; and Group F (n = 133): patients not eligible to participate in the study (all other IVF/ICSI cycles).

We set out outcome measures for the studies in our literature review and the details are in Table 1.2. The study reported a similar implantation rate (IR) for the single embryo transfer and double embryo transfer groups [42.3 and 48.1% respectively; relative risk (RR) = 0.88, 95% CI = 0.52–1.49]. The ongoing pregnancy rate (OPR) was higher in the double embryo transfer group than in the single embryo transfer group (74.1

versus 38.5% respectively; RR = 1.75; 95% CI = 1.06–2.89). The study concluded that the OPR in the single embryo transfer group was still equal to or higher than the generally accepted monthly fecundity rate of a couple with normal fertility. There was only one monozygotic twin in the single embryo transfer group (A) versus 6/20 = 30% (dizygotic) twins in the double embryo transfer group (B).

These results from the study showed that it was possible to detect embryos with a very high clinical and ongoing implantation potential (±45 and ±40% respectively). They argued that although the ongoing pregnancy rate after double embryo transfer of two top embryos was high, this was at a price of high rates of twins.

It was interesting to see that 67/194 (34.5%) of the patients who met with the clinical inclusion criteria (<34 years of age, first IVF cycle) did not agree to participate in the study. Such high number drop out reflects the attitude of these patients. For them, conceiving seemed the most important priority and some of these patients believed that they would jeopardize their chance of obtaining success by transferring only one embryo. The effect of targeted counselling was also reflected in another group of patients (n=17) who felt that if they participated in the RCT they could get DET and therefore out of fear of a twin pregnancy they went for elective single embryo transfer (eSET). These patients, due to the targeted counselling, elected to have a single embryo transfer (elective single embryo transfer) of a top quality embryo in all cases i.e. even if they had declined for their participation in the study. This shows that researchers were able to influence the attitude of patients even if they did not participate in the study and also shows that providing targeted information about the risks of twins and the benefit of the SET worked in this group of patients. The number of patients included in the study was lower than the number recruited, which was lower than the potentially eligible target group, which was by itself much smaller than the whole

population. The strengths of Gerris et al's (1999) study were the randomised design with concealed allocation although details of randomisation and concealment were not provided. It is not clear if the participants were blind to study allocation. Also the study has not carried out a power calculation and the small final sample size suggests that the study may not have had enough participants in each group to detect small differences in implantation rates. The large number of exclusions which included women with previous miscarriage means it would be difficult to generalise the results to a general population of IVF patients. The study did not analyse data using intention to treat and has not even mentioned about the number of dropouts.

Gardner et al (2004) set up a prospective RCT for single blastocyst transfer after doing a prospective RCT of blastocyst culture and transferring in *in vitro.* In that trial they found that blastocyst achieved higher pregnancy rate (71% vs. 66%) and also found that on an average, there were fewer number of blastocysts (2.2) required, compared to cleavage stage (3.7) (Gardner et al 1999).

The study included only those patients using their own oocytes for their IVF treatment and who met the previously described criteria of the Colorado centre for Reproductive medicine for blastocyst stage embryo transfer as found in their prospective RCT on blastocyst implantation rate. The criteria included a day 3 FSH ≤ 10 mIU/ml, E_2 < 80 pg/ml, hysteroscopically normal endometrial cavity, and at least 10 follicles > 12 mm in diameter on day of HCG administration. Randomisation was done by computer generated table to either group1 (SBT) or group 2 (DBT), for blastocyst (day 5) transfer. In all, 48 patients were enrolled after getting their consent with 23 patients in SBT group, compared to 25 patients in DBT group. The age range of the participants was from 26 years to 43 years for SBT compared with 29-41 years in the DBT group. The study reported that patients with higher number of oocyte collection (group 1-

21.4 ± 1.1 vs. group 2-27.7 ± 1.5; < 0.05) had lower rates of conversion of their embryos to blastocysts (day 5 (blastocysts- group1- 56.3 % vs. group 2- 42.0%; p< 0.05)) and therefore the number of blastocysts available for transfer and cryopreservation (83 % vs. 96%; not statistically significant) between the groups was similar for all participants. The biochemical pregnancy only rate, which is a very early pregnancy were statistically similar (12.5% in the SBT group vs. 5% in the DBT group), as were implantation rates (60.9 % vs. 56.0 %) and pregnancy rates (60.9 % vs. 76.0% in the DBT group). The rate of twin births were very high in the DBT group ((47.4% vs 0% in SBT) but the study did not report if it was statistically significant. The study also looked into the cost effect of twins on community. They found that on day 3 transfer SET was more cost effective than DET. Even though more cycles with SET were required the overall 'cost per child born' was similar or lower than with DET because of higher costs due to twins.

Gardner et al (2004) only measured blastocyst transfers. They used computer generated randomisation table but there was no power calculation reported in the study. The study does not mention about concealment method or blinding. There is detailed description of good blastocysts suitable for transfer but there was no mention of patient dropouts.

Lukassen et al (2005) This study only included patients undergoing their first IVF/ICSI cycle ever or the first cycle after a successful treatment. The age of the women had to be <35 years (at the time of ET) with a basal FSH level <10 IU/l. At least two embryos, with one excellent (grade 4) or one good (grade 3) quality embryo, had to be available for transfer on day 3 after oocytes retrieval: grade 4 = no blastomere fragmentation; grade 3=<10% fragmentation. A total of 107 patients were randomized into the SET (*n* = 54) or DET group (*n* = 53). The ongoing pregnancy rate was

25.9% in the SET group and 35.8% in the DET group. More detail is in Table 1.2.

Lukassen et al (2005): had acceptable allocation concealment and their analysis was based on the intent-to-treat principle. They performed a power calculation assuming 50% live birth rate with DET and 30% with SET and therefore minimum number required was 52 in each group. This would not have allowed detection of small differences in conception rate. There was not enough blinding of both the physicians and the patients and also the morphology of embryos selected for transfer was not described adequately.

Martikainen et al (2001): This study carried out a prospective randomised multicentre study to compare the effectiveness of one and two embryo transfers in a good prognosis group of patients. The main outcome measure was the cumulative pregnancy rate after fresh and frozen embryo transfers. In all four centres involved, there were at least four good quality embryos. According to this study, a good quality embryo was defined as having even-sized blastomeres and <20% fragmentation on day 2. There wasn't a uniformity between the patient recruitment centres for patient selection, for in one of the centres Oulu (*n* = 101), the age of the woman was not taken into account and the first two cycles were regarded as eligible. In the other two units in Helsinki (*n* = 43), only women younger than 36 years who were undergoing their first treatment cycle were included.

Out of a total of 1301 couples fulfilling the inclusion criteria, only 144 agreed to participate in the randomised study. The age range was < 38 years for SET (22-38 years) and <40 years for DET (21-40 years). In all, 187 chose elective one embryo transfer and 970 two embryo transfer. The participants were informed of the investigational nature of the study. They were randomized to the one or two embryo transfer groups using a computer generated random number table balanced in sets of 10.

Randomisation was done just before embryo transfer by the laboratory personnel. Confirmation of clinical pregnancies was confirmed by transvaginal ultrasonography. Frozen embryo transfers were carried out in natural or stimulated cycles.

The outcomes set for our literature is reported in Table 1.2. The two study groups were similar in relation to age, etiology of infertility and response to ovulation therapy. In the one embryo transfer group, ICSI was carried out in 20 cases (28.6%) and in the two embryo transfer group in 18 cycles (26.5%). The study cycle was the first treatment cycle in 107 cases (75%) (55 in the one embryo transfer group and 52 in the two embryo transfer group) and the second one in 37 cases (19 in the one embryo transfer group and 18 in the two embryo transfer group). The study found that the implantation rate of the fresh embryos transferred was quite similar (33.8 versus 30.7%) in the one and the two embryo transfer groups. The pregnancy rate was slightly but not significantly higher (47 versus 32%) when two embryos were transferred. In the two embryo transfer group 11 (39%) of the deliveries were twins and this result was statistically significant ($p< 0.01$).This study also looked into preterm birth and low birth weight and found that the number of preterm deliveries (gestation age <37 weeks) was six (21%) in the two embryo transfer and one (5%) in the one embryo transfer group and the number of low birth weight infants (<2500 g) was 10 (26%) in the two embryo and two (9%) in the one embryo transfer group. The outcome of the frozen embryo transfers found that 54 patients had single frozen embryo transfer and there were 84 transfer cycles and 38 patients had double frozen embryo transfer and 56. Clinical pregnancy was 15 % in one frozen embryo transfer and 16% in two frozen embryo transfer with 7 verss 8 live births respectively and 1 twin in one frozen embryo transfer and none in double frozen embryo transfer. The cumulative pregnancy rates after frozen embryo transfers was 47.3% in one embryo transfer group and 58.6% in two embryo transfer group; this was not statistically significant. The cumulative live birth rate per patient

was 39% in the one embryo transfer group and 51% in the two embryo transfer group and this was also not significant.

This multicentre randomisation (Martikainen et al 2001) was well described and so also the morphology of the good quality embryos. However, blinding was not mentioned and there was no method of concealment of group allocation described. Other limitations were that, there was no power calculation, intent-to-treat analysis was not used and dropout figures were not mentioned in the study. They (Martikainen et al 2001) had data collection at 4 centres and reported an average of 30.8 yrs for SET and 30.5 yrs for DET participant patients. However, one of the centres of this study did not consider the age of the participants and anyone coming for either the first or the second cycle of IVF was included in the study. This was in contrast to other two centres where patients < 36 years who were undergoing their first IVF cycle were included. This shows that in this study there was no uniformity in patient selection.

Thurin et al (2004): This study was designed to test the hypothesis that the rate of pregnancies resulting in at least one live birth in patients who had undergone the transfer of a single fresh embryo and, if no live birth resulted, the subsequent transfer of a frozen-and-thawed embryo, would be equivalent to the rate in patients submitted to the simultaneous transfer of two fresh embryos. Women who were <36 years of age at the time of fresh ET and who were undergoing their first or second *in vitro* fertilisation cycle, and had at least two embryos of good quality available for transfer or freezing were eligible for randomisation. The criteria for good-quality embryos included embryos with less than 20% fragmentation and 4 to 6 cells at day 2, 6 to 10 cells at day 3, or expanded blastocysts at day 5 or 6. In total 661 patients underwent randomisation. Of those, 331 patients were randomly assigned to undergo DET and 330 to undergo SET. In fresh embryo transfer, the SET group had an ongoing pregnancy rate (28.4%) statistically significantly lower (P < 0.001) than the DET group

(44.1%). Also, the SET group had a live birth rate (27.6%) statistically significantly lower ($P < 0.001$) than the DET group (42.9%). The multiple birth rate between the two groups was also statistically significant ($p<0.001$) 0.8% vs. 33.1 % in the SET and DET group respectively. This study has included day 2, day 3 and blastocyst transfers. However, there is no separate data on the difference in success rates with cleavage stage embryo and blastocyst transfer. This multi-centre RCT is the most robust trial till date and therefore we selected this study on recommendation from an expert in the field of IVF from NURTURE for our decision aid leaflet which is described later on in the thesis. An embryologist with the use of a computerised program performed randomisation at a ratio of 1:1 locally before the transfer, when the embryos could be evaluated. The study was double-blinded and neither the physician nor the patient were aware of whether one or two embryos were transferred and this blinding was carried on until a urine pregnancy test or serum pregnancy test was carried out for proper concealment. This study was designed as an equivalence study and the power calculation was done focusing on the primary outcome set by this study, which was cumulative pregnancy rate from one fresh SET cycle plus one frozen cycle and one fresh DET and a figure of 330 in each group was reached. Their primary analysis was carried out according to intention-to-treat principle and 661 participants were included, whereas the secondary analysis was carried out per protocol and had 634 patients and these were the actual number of patients who got the treatment, according to the power calculation done. The morphology of good quality embryos was clearly mentioned. Women lost to follow-up were also mentioned.

Van Montfoort et al (2006) This study performed a randomised controlled trial (RCT) to compare SET and DET in an unselected group of patients (i.e. irrespective of the woman's age or embryo quality). Patients who started their first IVF cycle were assessed for eligibility to participate in the

study. All had to have normal fertilisation of at least two oocytes (i.e. 2 PN embryos) in order to be randomly assigned to the SET or DET group. A total of 308 patients were included: 154 patients for SET and for 154 DET. Randomisation was performed immediately prior to embryo transfer using a non-transparent box containing sealed opaque envelopes. The clinical outcomes differed significantly between the SET and DET groups, with the respective percentages of positive pregnancy tests after transfer of fresh embryos being 33.1% versus 47.4%. The ongoing pregnancy rate after SET was significantly lower than in DET (21.4 vs. 40.3%, respectively) and the twin PR was reduced from 21.0% after DET to 0% after SET ($p<0.05$; 95% CI. 10.8-31.1).

It was a double-blinded study. However, they did not mention the method of randomisation but allocation concealment was taken care of. The laboratory personnel performing the randomisation did not know about the size of the groups. Patients were told of the number of embryos transferred after they had had their embryo transfer. They did power calculation based on their stored data on DET where they got a sample size of 150 for each group. The study mentions numbers lost to follow-up.

Except Van Montfoort et al (2006) all the other RCTs included in the review have focused on 'patients at risk' of having a twin pregnancy and were therefore randomised for either SET or DET depending on the number of good quality embryos they had. The selection criteria for 'patients at risk' varied between the studies, but were mainly based on female age from [<34 years by Gerris et al. (1999); <35 years, in Lukassen et al. (2005) and some of the patients in the study of Thurin et al. (2004); <36 years, in Martikainen et al. (2001) and some of the patients in the study of Thurin et al. (2004)], to no age limit in Van Montfoort et al (2006) and the number of good quality embryos available [≥2 in the studies of Gerris et al. (1999), Thurin et al. (2004) and Lukassen et al. (2005); ≥3 in some of the patients in the study of Thurin *et al.*; ≥4 in one of

the participating centres in the study by Martikainen et al. (2001) and irrespective of whether or not a good quality embryo was available in Van Montfoort et al (2006)]. Furthermore, no previous failed cycles were allowed in some of the studies (Gerris et al., 1999; Lukassen et al., 2005).

Results

Outcomes reported

Outcomes (Table- 1.2) were set because these parameters should be the main measure of any IVF treatment results (HFEA 2009). However, two of the studies, Gerris et al (1999) and Gardner et al (2004) did not report on the live birth rate and also did not mention about the miscarriage rate and at least one study Van Monfoort et al (2006) did not report either clinical pregnancy rate or live birth rate

At least four studies included in the review found statistically significant difference in the multiple birth rates between SET and DET group of patients and only one study which also had the largest number of participants (Thurin et al 2004) found significant difference between SET and DET for clinical pregnancy (33.6 % vs. 52.6%; $p<0.001$) and also for live birth rate (27.6 % vs. 42.9%; $p<0.001$). Another study (Van Montfoort et al, 2006) also reported significant difference between the groups in clinical pregnancy rates; however, this study has reported rates of positive HCG test (33.1% vs. 47.4%; $P<0.05$), and this cannot be taken as true clinical pregnancy rates. (Table 1.2).

Table- 1.2 Comparison between fresh single cycle SET with single fresh cycle DET

Study	Clinical pregnancy (% per ET)		Live birth rate		Twin/multiple birth rate	
	SET	DET	SET	DET	SET	DET
Gerris et al 1999 SET- n= 26 DET= n=27	14 (53.8)	21 (77.7)	NR	NR	1 (10)	6 (30)
Martikainen 2001 SET- n= 74 DET= n=70	24 (32.4)	33 (47.1)	22 (92)	28 (85)	*1(5)	*11(39)
Thurin et al 2004 SET- n= 327 DET= n=325	*111 (33.6)	*174 (52.6)	*91 (27.6)	*142 (42.9)	*1(0.08)	*47 (33.1)
Gardner et al 2004 SBT- n = 23 DBT- n = 25	?(12.5)	?(5.0)	NR	NR	0 (0%)	? (47.4)
Lukassen et al 2005 SET- n= 54 DET= n=53	20 (37)	25(47)	14(26)	22(41)	*0(0)	*7(37)
Van Montfoort 2006 SET- n = 154 DET- n =154	51 (33.1)*	73 (47.4)*	NR	NR	0 (0)*	13 (21.0)*

*P=<0.05; SBT/DBT= Blastocyst transfer; NR- Not reported;? - Actual numbers not mentioned

Four studies reported about miscarriage in the participants [(Martikainen et al (2001); Thurin et al (2004); Lukassen et al (2005); Van Montfoort et al (2006)] but none of these results were significant between the groups. The cut off point for miscarriages or abortion is different in different countries (ranging from ≤ 24 weeks to ≤28 weeks) and none of the studies, except Thurin et al (2004), where the cut off age for miscarriage is ≤28 weeks. Thurin et al (2004) have reported separate figures for spontaneous abortion ≤ 12 weeks (SET- 15.3%; DET- 15.5%) and > 12 weeks (SET-2 and DET-3) whereas Van Montfoort et al (2006) have only reported miscarriages at <13 weeks gestation.

Table-1.2 (cont) Comparison between single fresh cycle SET with single fresh cycle DET

Study	Preterm birth <37 weeks (%)		Low birth weight <2500gm (%)		Miscarriage		Cumulative live birth rate	
	SET	DET	SET	DET	SET	DET	SET	DET
Gerris et al 1999 SET- n= 26 DET= n=27	NR	NR	NR	NR	NR	NR	NR	NR
Martikainen et a 2001 SET- n= 74 DET= n=70	1 (5)	6 (21)	2 (9)	10(26)	1 (4.2)	3 (9.1)	NR	NR
Thurin et al 2004 SET- n= 327 DET= n=325	1 Ø	1 Ø	NR	NR	17(15.3)	27 (15.5)	128 (38.8)	142 (42.9)
Gardner et al 2004 SBT- n = 23 DBT- n = 25	NR	NR	NR	NR	NR	NR	NR	NR
Lukassen et al 2005 SET- n= 54 DET= n=53	2 (14)	5 (20)	*1(7)	*10(40)	6(11)	2(5)	22 (41)	19 (36)
Van Montfoort et a 2006 SET- n = 154 DET- n =154	NR	NR	NR	NR	18 (35.3) [a]	11 (15.1) [a]	NR	NR

Ø Still born ≥ 28weeks ; NR – Not reported; *P=0.002; [a]P<0.05

Two studies (Martikainen et al 2001 ; Lukassen et al 2005) reported lower percentage of preterm births in SET patients compared to DET (5% vs. 21%) and (14% vs. 20%) respectively which showed high DET rates, unlike Thurin et al (2004), who had equal numbers (1 in each group) in both groups and the percentage was negligible. All these results were not significant. Only Martikainen et al (2001) and Lukassen et al (2005) reported about low birth weight (< 2500gm). Again Martikainen et al (2001) found higher percentage of low birth weight in DET patients (26 versus 9) compared to SET patients. These results were however not significant. In

contrast, Lukassen et al (2005) found significantly higher rates of low birth weight infants in DET group compared to SET (40 vs.7; P=0.002). This study did not find any new low birth weight baby when carrying out the second cycle of SET, as they have also reported cumulative birth rates unlike many other studies in the review. Thurin et al (2004) did not report on low birth weight.

Two of the studies reported on cumulative live birth rates (Thurin et al 2004; Lukassen et al 2005). Thurin et al (2004) compared eSET and one Frozen ET with DET (38.8% vs. 42.9%) and Lukassen et al (2005) compared cumulative live birth rates of 2 cycles of fresh SET with one cycle of DET (41% VS.36%) respectively. Difference in cumulative birth rates in both the studies was statistically not significant.

The studies were sound enough to come to a conclusion about SET and DET even though it can be seen that all the studies had different parameters for measuring success of SET and therefore the parameters set up by us could not be reported by all the studies. However, all the studies except Gardener et al, (2004) reported higher clinical pregnancy rates, ranging from 47.1% to 77.7% with DET, compared to SET (32.7% TO 53.8%), and most reporting an average clinical pregnancy rate of 34% with SET and 48.5% with DET. Only Gerris et al, (1999) reported very high clinical pregnancy rates in both groups.

It can be seen that all except the Van Montfort et al (2006) et al study had younger age of patients as one of their inclusion criteria because of their previous experiences in treating IVF patients. Two studies (Thurin and Lukassen) reporting on cumulative live birth rate have demonstrated that with proper patient selection both SET and DET could be equally efficient and SET carries the additional benefit of decreasing the rates of twins. Gardner et al (2004) argued that if SET is used in the right group of

patients with high probability of success, there are no financial and medical implications in recommending SET.

Other studies

There were few other studies and few systematic reviews which we looked into. The most important conclusion of the earliest RCTs (Gerris et al., 1999) was that using the earlier described (in our literature review above) criteria of patient selection and embryo grading, it was possible to introduce SET into daily clinical practise without a significant decrease in ongoing pregnancy rate. This has moved a long distance and more and more studies looked either retrospectively or prospectively into the effectiveness of single embryo transfer, both in single fresh cycle and in cumulative transfers.Various other studies (Neubourg et al, 2002; Saldeen and Sundstrom (2005); Le Lannou et al, 2006; Veleva et al 2006) that were not RCTs, which looked into eSET had similar results with eSET. Although rates of implantation were lower in one fresh cycle with eSET, the rate of twins after DET was higher. However, the cumulative live birth rates following the transfer of fresh and frozen embryos was similar between SET (43%) and DET (45%) groups (Le Lannou et al, 2006) or even higher cumulative pregnancy (54.0% compared to 35.0%) and higher cumulative live birth rates (41.8% compared to 26.7%) in patients with DET, even in women between 36 and 39 years old.

One study which is worth mentioning is the retrospective analysis done by Saldeen and Sundstrom (2005). This study is unique as it was setup at 3 stages at 3 different periods. Part 1 of the study was carried out when there was a policy of DET. The second part of the study was the transitional period between SET and DET; during this period most private patients received DET while all new public patients received eSET. The third part of the study was carried out after the legislation to transfer only one embryo had come into force. It reported similar non significant

difference in clinical pregnancy rates (33.3, 32.8 and 37.4%, respectively) and the viable pregnancy rates (29.7, 30.6, 33.7 % respectively), over the 3 periods, but found a significant (P<0.005) decrease in twinning rates over the (22.6% to 16.3% to 6.2%) three phases. It was remarkable to see a significant rise in the rate of SET use in their IVF clinics over the three periods of the study by legislating SET (25.1%, 55.5% and 72.7%) (Kruskal-Wallis test P<0.0001).

Systematic reviews There were few systemic reviews and meta-analysis, looking into pregnancy, implantation, birth and twin rates comparison between SET and DET.

Dare et al 2004 - A systemic review was done in Australia with the aim of looking if single versus two or more embryos, or two versus three or more embryo transfer during IVF treatment, increases the chances of pregnancy and decreases the chance of multiple pregnancies and other adversities in an IVF patient. In all it included 20 studies out of which, 17 were cohort studies and 3 were randomised trials. Live birth at term of healthy baby (37 weeks gestation), normal birth weight, normal childhood development at 2 years and cost of care were the primary outcomes set by the review.

Of the 3 RCT in the review, 2 compared SET with DET (Gerris et al, 1999 and Martikainen et al 2001). Only one RCT reported live birth but this was not significant. The results from the RCT showed that clinical pregnancy in SET patients was lower than DET (RR 0.69; 95% CI 0.51-0.93) but the risk of twin pregnancy was also reduced (RR 0.12; CI 0.03-0.48) along with low birth weight (RR 0.17; CI 0.04-0.79).

Out of the 17 studies included, 4 studies were prospective, 8 retrospective and 5 used historical controls. Out of the 17 studies, 9 studies looked into SET and only 2 of these studies reported the live birth at term (at least 37 weeks). They showed that there was no significant impact on the incidence of live birth with SET (RR 0.45; 95% CI 0.16-1.28). Clinical

pregnancy was again lower, and similar to the RCT studies in patients having SET (RR 0.63; 95% CI 0.43-0.90). It needs to be mentioned here that there was statistical significant ($p < 0.0001$) heterogeneity between the studies and this dissimilarity did not go away even when only studies which were prospective were considered. Multiple birth rate was only reported by two studies and this was lower in the SET group (RR 0.02; 95% CI 0.00-0.13). Two studies also reported a lower incidence of twin birth with SET (RR 0.02; 95% CI 0.00-015), however, there was no change in the incidence (RR 0.75; 95% CI 0.19-2.93) of birth of singletons with SET. Multiple pregnancy was reported by eight studies and here too, less number of women (RR 0.03; 95% CI 0.01-0.09), who went for SET had multiple pregnancies. Twin pregnancy rates, reported by 7 studies (RR 0.03; 95% CI 0.01-0.09) showed decreased rates with SET. Only one study looked into the incidence of preterm (<37 weeks) and there was no difference reported, they did find lower incidence of low birth weight in SET group compared to DET (RR 0.22; 95% CI 0.08- 0.57).

This review also found that five studies from the cohort group looking into 5838 women in their data analysis found fewer (RR 0.82; 95% CI 0.37-1.85) singleton pregnancies from SET. Although there was statistical heterogeneity the review did not look further into these studies which differed in their methodology. Surprisingly, the review did not find risk of triplet or higher order pregnancy or birth decreasing with SET.

The cohort studies were not consistent in reporting about eSET and the outcomes that these studies reported also differed. It can be said that there was wide variation in the cohort studies included, and like the RCTs , none of the studies had any report of pre-study sample size calculation. There was no information whether the SET was elective or compulsory from any group.

Only one RCT was robust but it too had the problem of blinding, and therefore selection bias, and this was true for the cohort studies and other RCT included in the review also. The problem of heterogeneity in the studies meant that the comparison was not robust. None of the studies reported the follow up at 2 years which was one of the primary outcomes for the review and at 2 years follow up and the studies did not report of any losses. Only 3 studies included in the review (Martikainen et al, 2001; De Sutter et al, 2003 and Liao et al, 1997) reported about preterm birth and birth weight. The review had to abandon subgroup analysis because of the poor quality of the cohort studies, which reported those outcomes which reflect the limitation of this early review (Dare et al 2004).

Baruffi et al 2009 - A metanalysis was designed to compare data on single-embryo versus double-embryo transfer in fresh IVF/ICSI cycles with respect to implantation, ongoing pregnancy and live birth rates and included in the online surveys of data between 1995 to 2005. All published and ongoing randomized controlled trials (RCT) were included [Gerris et al (1999);Martikainen et al (2001);Gardner et al (2004);Thurin et al (2004); Lukassen et al (2005); Van Montfoort et al (2006); Moustafa et al (2008)] in the metanalysis. It found that though the implantation rate was not significantly different between DET (34.5%) and SET groups (34.7%) (P = 0.96; OR = 0.99, 95% CI 0.78, 1.25), DET produced a statistically significantly higher ongoing clinical pregnancy rate (44.5%) than single-embryo transfer (28.3%) (P < 0.0001; OR: 2.06, 95% CI = 1.64, 2.60) and a significantly higher live birth rate when DET (42.5%) (P < 0.001; OR: 1.87, 95% CI = 1.44, 2.42) was compared with SET (28.4%) (Baruffi et al 2009).

McLernon et al 2010 - Meta-analysis of individual patient data was conducted by Mclernon et al (20101), using data from systematic review of English and non-English articles from Medline, Embase, and the Cochrane Central Register of Controlled Trials (up to 2008) and other

studies were also identified by contact with clinical experts and searches of bibliographies of all relevant primary articles. They directly contacted the researchers for the data in case of any clarification or unpublished studies. The review included comparisons of the clinical effectiveness of cleavage stage eSET versus DET after fresh or frozen IVF or ICSI treatments. This review did not include studies reporting on blastocyst transfer. Women undergoing IVF, ICSI or both, with their own oocytes, were considered eligible for inclusion. After a lot of research 5 studies were selected for inclusion for the metanalysis [(Gerris et al (1999); Martikainen et al (2001)); Thurin et al (2004); Lukassen et al (2005); Van Montfoort et al (2006)].

Their primary outcomes included live births and multiple live births after the initial fresh embryo transfer, cumulative live births, and cumulative multiple live births (after fresh and frozen embryo transfers accruing from a single oocyte retrieval) whereas the secondary outcomes included miscarriage rates, rates of preterm delivery, term singleton delivery and delivery of at least one low birth weight baby (<2500 g).

Meta-analysis of clinical outcomes with individual patient data

Live birth

After one fresh cycle, the live birth rate in the elective single embryo transfer group (181/683, 27%) was lower than in the double embryo transfer group (285/683, 42%). The odds of a live birth in women randomised to single embryo transfer were half that for women who received a double embryo transfer (0.50, 95% confidence interval 0.40 to 0.63) P≤0.001), the adjusted odds ratio remained similar (adjusted odds ratio 0.50, 95% confidence interval 0.39 to 0.63 P≤0.001). The odds of live birth associated with transfer of grade A embryos were significantly higher than for grade B embryos (1.99, 1.26 to 3.13; P=0.003). The chance of a live birth was 66% greater after IVF than after ICSI (1.66, 1.15 to 2.38;

P=0.006). Compared with male infertility, female infertility was associated with a reduction in the odds of a live birth (0.58, 0.38 to 0.88; P=0.02).

Multiple live births

Fewer multiple births occurred after one elective single embryo transfer cycle (3/181, 2%) than after a double embryo transfer cycle (84/285, 29%) with an odds ratio of 0.04 (0.01 to 0.12; P<0.001).

Cumulative live births

The metanalysis found that only two trials had an additional frozen single embryo transfer after the initial fresh elective single embryo transfer (both Thurin trials). They found a cumulative live birth rate similar to that after one fresh double embryo transfer (132/350 (38%) vs. 149/353 (42%); 0.85, 0.62 to 1.15), with a minimal cumulative risk of multiple live birth (1/132 (1%) vs. 47/149 (32%); 0.02, 0.002 to 0.12).

Miscarriage

The rate of miscarriage in the elective single embryo transfer group (60/245, 24%) was higher than in the double embryo transfer group (63/355, 18%), with an odds ratio of 1.52 (1.01 to 2.28). There was, however, evidence of significant heterogeneity between the trials. When we excluded the two trials that caused the heterogeneity (Davies et al, 2003; Thurin et al, 2005) the odds ratio remained similar (1.51, 0.99 to 2.33; P=0.06).

Subgroup analyses

Age group

Younger women (<33) had a higher odds of a live birth than older women (≥33) (336/915 (37%) *v* 130/446 (29%); 1.37, 1.05 to 1.77; P=0.02). As before, the odds of a live birth in women randomised to elective single embryo transfer were half those for women who received a double embryo transfer (0.50, 0.40 to 0.63; P<0.001).The odds of a multiple live birth in women randomised to elective single embryo transfer were significantly smaller than for women who received double embryo transfer (0.04, 0.01

to 0.12; P<0.001). The rate of multiple live births for elective single versus double embryo transfer, however, were similar for younger women (3/131 (2%) *v* 61/205 (30%)) and older women (0/50 *v* 23/80 (29%)).

Embryo grade

Women who received grade A embryos had higher odds of a live birth than women with grade B embryos (423/1168 (36%) *v* 27/130 (21%); 1.93, 1.23 to 3.04; P=0.004). There was no difference between the odds of multiple live birth for grade A embryos versus grade B embryos (4/27 (15%) *v* 81/423 (19%); 1.59, 0.49 to 5.17; P=0.44). The rate of multiple live births for elective single versus double embryo transfer in the randomised women were similar for grade A (3/164 (2%) *v* 78/259 (30%)) and grade B (0/10 *v* 4/17 (24%)) embryos.

Duration of infertility

Couples with three or more years of infertility had similar odds of a live birth to couples with less than three years infertility (153/460 (33%) *v* 298/873 (34%); 1.02, 0.79 to 1.32; P=0.87). The effect of elective single versus double embryo transfer on live birth did not differ between shorter (60/234 (26%) *v* 93/226 (41%)) and longer (115/432 (27%) *v* 183/441 (42%), P=0.14) duration of infertility.

Couples with three or more years of infertility had the same chance of multiple births as couples who experienced less than three years infertility (28/153 (18%) *v* 56/298 (19%); 0.97 (0.55 to 1.72), P=0.91). The effect of elective single versus double embryo transfer on multiple live birth did not differ between shorter term (1/60 (2%) *v* 27/93 (29%)) and longer term (2/115 (2%) *v* 54/183 (30%)) duration of infertility (p=0.95). For couples with under three years infertility, the odds ratio for multiple live birth rates for eSET versus DET was 0.04 (0.005 to 0.29). In couples who were infertile for three years or more, the odds ratio was similar (0.04, 0.01 to 0.17).

Perinatal outcomes

Birth weight

The odds of delivering at least one low birth weight (<2500 g) baby after elective single embryo transfer were a quarter of those associated with double embryo transfer [0.26 (0.14 to 0.48)]. After adjustment for gestational age, this odds ratio rose, only slightly, to a third [0.36 (0.15 to 0.87)]. This review did not find significant difference in the mean birth weights for singletons born after elective single 3373 g (SD 591 g) or double embryo transfer 3275 g (SD 773 g), respectively.

Term singleton birth

The odds of a term singleton birth (>37 weeks) after eSET was nearly five times higher than those after DET (4.93, 2.98 to 8.18).

Preterm birth

They also found that eSET was associated with a significantly reduced risk of preterm birth at ≤37 completed weeks, with an odds ratio of 0.33 (0.20 to 0.55) and also of preterm birth at ≤34 completed weeks. The odds ratio for a preterm birth at ≤34 completed weeks (adjusted odds ratio 0.86, 0.77 to 0.97) decreased significantly with increasing maternal age.

Double embryo transfer, higher female BMI and longer duration of infertility were the covariates affecting the odds affecting outcome of very preterm (≤32 weeks) births. Analysis found that for each unit increase in BMI, the odds of a preterm birth at ≤32 weeks increased by 16% (1.16, 1.04 to 1.30; P=0.01), and for each yearly increase in duration of infertility the odds of a preterm birth increased by 52% (1.52, 1.15 to 2.03; P=0.004).

Strengths and limitations of the review

This meta-analysis is very unique and robust because they carried extensive literature search and had no language restrictions therefore less chance of missing information. Contacting researchers for data about

individual patients gave them the opportunity to get details which may not have been in the articles published and therefore better checks on the quality of the studies. The review has reported similar limitations about the studies included in our literature review, but because they contacted the individual researchers they were able to point out that the source of error was in the reporting rather than the design of the study.

They found that variations in the inclusion criteria and clinical protocols (for ovarian stimulation and embryo culture) among the trials restricted exclusion of clinical heterogeneity as a factor similar to Dare et al, (2004). Although this is a very robust analysis the results cannot be generalised for all patients except “good prognoses” patients.

It can be seen from our own literature review and the other systematic reviews and their analysis that implantation rate and live birth rate from a fresh IVF cycle was lower in SET patients, compared to DET, however all the studies found a lower rate of twin birth rates with SET compared to DET (Gerris et al 1999; Martikainen et al, 2001;Neubourg et al, 2002;Dare et al 2004; Gardner et al 2004; Thurin et al 2004; Lukassen et al 2005;Saldeen and Sundstrom 2005;Le Lannou et al, 2006; Veleva et al 2006;Van Montfoort et al 2006; Baruffi et al 2009; McLernon et al, 2010). However, with an added frozen single embryo cycle the cumulative birth rate was similar to that of DET with a very low risk of cumulative multiple births with SET (Thurin et al 2004; Lukassen et al 2005;McLernon et al, 2010). SET had higher chances (>37 weeks) compared to DET of term live birth which have more chances of preterm birth infants (Martikainen et al 2001; Dare et al, 2004;Lukassen et al 2005; McLernon et al, 2010).

Table 1.3 Details of studies included in the review (Blake et al 2007)

Studies	Implantation rate %	Live birth	Multiple pregnancy %	E. T policy	Embryo freezing %	Risk of bias
Bungum 2003	D_3 -43.9 D_{5-} 36.7	NS	D_3 -41.6 D_{5-} 40.6	2	D_3 -95 D_{5-} 59	No blinding
Coskun 2000	D_3 – 21 D_{5-} 24	D_3 -32.6 D_{5-} 35.0	D_3 -33.0 D_{5-} 38.0	2	D_3 -NR D_{5-} 0	No blinding
Devreker 2000	D3-3 D5-42	D3-8.3 D5-27.3	NR	max 3	NR	NR
Emiliani 2003	D2 29 D5 30	D2 44.1 D5 37.1	D2 22 D5 36	D2 2-3 depend on age and embryo quality D5 – 2	D2 73 D5 54	NR
Frattarelli 2003	D3 26.1 D5 43.4	D3 34.8 D5 57.7	D3 70 D5 27.7	D2 2-3 depend on age and embryo quality D5 – 2	NR	No blinding
Gardner 1998a	D3-37 D5 55.4	NR	D3 - NS D5 46	NR	D3 30 D5 64	NR
Hreinsson 2004	D3 20.8 D5 21.1	D_3 -31.3 D_{5-} 34.4	D_3 -16.0 D_{5-} 9.0	1-2- at start then 1 only	D3 42.5 D5 23.4	No blinding
Karaki 2002	D3 13 D5 26	NS	D_3 -47.6 D_{5-} 39.1	<35 yrs- 1-2 >35 yrs or > 2 previous failed cycles- 3	D3 42 D5 28	No blinding
Kolibianakis 2004	D3 24.5 D5 26.6	NR	D_3 -26.7 D_{5-} 20.0	1or2	D3 61.5 D5 50.4	NR
Levitas 2004	D2/3- 6.0 D5 21.2	D2/3 9.7 D5 13.0	D2/3 75 D5 40	D3 22.6 D5 13.0	D2/3 3-4 D5 2-3	Blinded
Levron 2002	D3 38.7 D5 20.2	D3 34 D5 17.4	D3 40 D5 50	max 3	D3 56.8 D5 26.1	Blinded
Livingstone 2002	D3 37.9 D5 56.2	D3 37.9 D5 46.7	D3 13.8 D5 0	D2/3- 2 D5-1	NR	NR
Motta 1998 A & B	D319.4 D5 30.1	NR	D3 57 D5 14	D3 3-5 D5 1-3	D3 5.1/cycle 74 D5 1.4/cycle 26	NR
Papanikolaon 2005	D3 20.6 D5 37.3	D_3 -27.4 D_{5-} 47.5	D_3 -29.6 D_{5-} 42.9	2	D3 36.3 D5 23.5	No blinding
Papanikolaon 2006	D3 24.2 D5 38.9	D_3 -21.6 D_{5-} 32.0	D_3 -5.0 D_{5-} 0	1	Not clear	No blinding
Rienzi 2002	D3 35 D5 38	D3 50 D5 48	D3 25.9 D5 31.0	Max 2	D3 87.5 D5 36	No blinding
Schillaci 2002	D3 13.7 D5 23.6	NR	NR	2-3	NR	NR
Van der Auwera 2002	D2 27.4 D5 51.1	D_2 -30 D_{5-} 50	D_2 -45.0 D_{5-} 31.0	2	D2 56 D5 39	Blinded

1.9 Cleavage stage versus blastocyst stage embryo transfer

More and more clinics promoting eSET are also changing their routine day 2 transfer to day 5 transfers. By day 5 the embryo has developed beyond the 4 cell stage and is called a blastocyst. A study retrospectively looking into the pregnancy outcomes of cycles undergoing fresh elective single-blastocyst transfer (eSBT, n = 52) and double-blastocyst transfer (DBT, n = 187) after IVF was conducted at the Massachusetts General Hospital Fertility Centre between January 2002 to March 2006 (n=1499). The study found comparable rates of biochemical pregnancy (76.9% vs. 77.6%), clinical pregnancy (61% vs. 63.4%), live birth (53.8% vs. 54.4%), and pregnancy loss (20% vs. 18.6%) per embryo transfer for fresh eSBT and DBT cycles respectively and these results were statistically insignificant. Rates of twins were significantly lower (3.1%) for eSBT, compared to DBT (51%). After 24 months of start of eSBT, the twin rate per transfer for all cycles undergoing blastocyst transfer (1, 2, or 3 blastocysts) was statistically significantly reduced from 47.2% to 22.9%.

For women younger than 35 years of age, the twin rate per transfer for all embryo transfers was reduced from 28.8% to 15.6%, and this difference was statistically significant (Styer et al, 2008). This study reiterates the fact that single blastocyst transfer showed equal rates of pregnancy to double blastocyst transfer but it had the benefit of decreased twin rate.

A review (Blake et al 2007) was conducted in Australia to establish if blastocyst transfer affected live birth rate compared to cleavage stage embryo transfer and the factors influencing this. The review only included randomised control trials (n=18) that compared cleavage stage embryo transfer to that of blastocyst transfer. The review set live birth rate as the primary outcome whereas secondary outcomes included rates per couple of clinical pregnancy, multiple pregnancy, high order miscarriage, failure to transfer embryos and cryopreservation.

The review found that blastocyst transfer had better live-birth rate results (36.0% vs. 29.4%; OR 1.3, 95% CI 1.05 to 1.74) in participant RCTs (n=9). These trials were randomised on day 3, patients had good prognosis (high number of 8-cell embryos on day 3) and equal number of embryos were transferred including SET. Cleavage stage embryo freezing rate was significantly higher (OR 0.45, 95% CI 0.36 to 0.56) than blastocyst freezing. Sixteen studies found that the incidence of cancelation of cycles was more in blastocyst group patients (n=16) (8.9% vs. 2.8%; OR 2.85, 95% CI 1.97 to 4.11), however, there was a significant difference between the two in better prognosis patients (n=9) (OR 1.50, 95% CI 0.79 to 2.84).The review concluded that in good prognosis patients, SET can be done using blastocysts (Table 1.3).

Scientists understanding about difference in the in-vitro environment for cleavage stage embryo to blastocysts resulted in specific media (Blake et al 2010). Development of embryos in the more stage specific media has shown to have high implantation rates (60-65%) for blastocysts stage embryos (Schoolcraft & Gardner 2001). Blastocyst culture has higher implantation rate than cleavage stage as it has been found that only the best quality embryos have the potential to develop to blastocysts. Day 3 embryos which seem to be morphologically normal can be chromosomally abnormal and can therefore have an implantation rate failure of more than 80% (Magli et al 1998). Staessen (2004) have found that in women above 36 years of age, chromosomal abnormality decreases (35% vs. 59%) if blastocyst is transferred instead of cleavage stage. Valbuena et al (2001) reported that exposing the cleavage stage embryos to uterine environment is physiologically challenging, especially in conditions of high oestrogen level after superovulation. The uterine pulsality also decreases during blastocyst transfer, decreasing the chance of embryo expulsion (Fanchin et al 2001). However, blastocyst culture can have some implications because more cycles may get cancelled because of failure of

development of some cleavage stage embryos to blastocysts and therefore fewer embryos for freezing and storage (Blake et al 2010). This review also found that studies looking into blastocysts transfer have found higher rates of monozygotic twins and higher rates of males. In a spontaneous pregnancy the ratio of monozygotic twinning is 1 in 330, compared to more than 1% with blastocyst transfer. Some researchers have argued that the extended culture of embryos was responsible for high rates of monozygotic twins.

1.10 Role of Cryopreservation

Very few studies have looked into multiple pregnancy reduction by using frozen single embryo transfer (Min et al, 2010; Edgar et al, 2007). However, a study carried out in Australia retrospectively looked into the success rate of single embryo transfer using cryopreserved embryos and found that certain important characteristics of the embryo can be looked as pointers of success when using single cryopreserved embryos. Using these embryos can result in success rates equivalent to those achieved when transferring two cryopreserved embryos. The study analysed a total of 6916 women under 36 years of age who had frozen embryo transfer, and found that frozen DET resulted in higher pregnancy rates when compared to frozen SET but with the risk of higher multiple pregnancy (26.7%). However, those women <36 years who had frozen 4-cell stage transfer, loss of fewer than two blastomeres, followed by cleavage of at least two surviving blastomeres resulted in an implantation rate of 30.9% in comparison to transfer of two cryopreserved embryos in women under 36 resulted in pregnancy and implantation rates of only 25.5 and 16.1% respectively (Edgar et al, 2007).

This is a also another step forward towards further decreasing the rate of multiple birth without compromising the implantation rate by using single cryopreserved embryo transfer SCET in patients <36 years of age who are

the most common group undergoing IVF treatment. The success of day two SET definitely seems to be dependant on the quality of the embryo available for transfer and cryopreservation. Recent practice of transferring blastocysts and frozen embryos are also on the rise, which, as discussed, has a better implantation rate.

A report by Nygren (2007) argues on the possibility of SET becoming the standard of IVF treatment around the world. It presents the report from Nordic countries and Belgium, which shows 70% IVF patients in Sweden have SET. These patients have a twin rate of 5% but their pregnancy rate per transfer remaining continually at 30%. The above success has another positive effect. Using eSET for most patients has shown a steady decrease in the chances of prematurity, indirectly decreasing the perinatal mortality and infant and child morbidity. This article has further looked into the other prospects of IVF treatment regime. The study proposes the option of natural cycle/ soft stimulation IVF cycles where the “selection of the most beneficial rather than the most aggressive ovarian stimulation” (p601-2) should be considered for patients undergoing eSET. This would not only be safer because of a reduced chance of implantation of twin foetuses but also less costly for the patient. It seems, therefore, that eSET seems to work in decreasing the twin rate without compromising the success rate (Nygren 2007).

With recommendations for more frequent use of frozen embryo transfer, the rates of frozen embryo cycles have increased over the past decade. A large register-based, Finnish cohort study found that compared to fresh embryos transfers (n = 4151), using frozen embryos (FET) (n = 2293), does not appear to have a negative effect on perinatal outcomes such as prematurity, low birth weight and being small for gestational age and in fact foetal growth is better with frozen embryos (Pelkonen, 2010). Although they did show poorer outcomes compared to spontaneous singletons (n = 31 946). The study found a statistically significant (P<

0.0001) higher mean birth weight by 134 g in the FET singletons versus the fresh embryo transfer singletons. Compared to spontaneous singletons, FET singletons had increased risks of preterm birth (AOR 1.45; 1.25-1.68) and low birth weight (AOR 1.22; 1.03-1.45) and a decreased risk of being small for gestational age (AOR 0.71; 0.54-0.92). However, when compared to fresh embryo transfer singletons, FET group showed decreased risks of preterm birth [adjusted odd ratio (AOR) 0.83, 95% confidence interval (CI) 0.71-0.97], low birth weight (AOR 0.74; 0.62-0.88) and being small for gestational age (AOR 0.63; 0.49-0.83) compared with the fresh embryo transfer group. Perinatal and infant mortality was similar in all the 3 groups (Pelkonen et al, 2010).

1.11 Is eSET associated with better infant outcomes?

As reported in above studies, single-embryo transfer (SET) has been established as an efficient method of reducing multiple pregnancy rates in IVF treatment. Our literature review of the available RCT's have shown worse outcome for DET infants in terms of both low birth weight [(Martikainen et al (2001) ; Lukassen et al (2005)] and preterm birth [(Martikainen et al (2001);Thurin et al (2004); Lukassen et al (2005)] (Table-1.2).

A study using database of the Ghent University Hospital Infertility Centre compared 404 SET and 431 DET patients. All patients undergoing a first, second or third IVF or ICSI cycle between 2000 and 2004 and having obtained a singleton pregnancy after fresh SET or DET, resulting in the live birth of a child of >500 g, were included in the study. The analysis of the results found that singletons born after SET (3324.6 ± 509.7 g) have a significantly ($P < 0.01$) higher birth weight than that after DET (3204.3 ± 617.5 g). Apart from lower birth weight, singletons after DET were at a higher risk of being born preterm birth (<37 weeks) (OR1.77, 95% CI 1.06–2.94) and more number of DET singletons had low birth weight

(<2500 g) (OR 3.38, 95% CI 1.86–6.12) (De Sutter et al, 2006). Similar results were reported in their earlier study where the birth weight of the SET singletons was 3303 ± 481 g and of the DET singletons 3175 ± 641 g (statistically significant difference of 128 g) (Sutter et al, 2003). As this was not a randomised study there were clinical differences between both the groups. However, another study that was randomised which compared 129 neonates born after SET with 189 neonates born after DET, also did find that the mean gestational age and birth weight was higher in the SET group compared to DET (Thurin et al 2006).

1.12 Factors influencing success of eSET

Quality of embryo and day of transfer

Embryo quality is one of the most important factors for a successful SET. Early cleavage (Brezinova et al, 2009) of embryo; amount of fragmentation and pronuclear morphology of the embryo are necessary factors for successful implantation.

Gerris et al, (1999) found that the quality of the embryo for transfer was an important parameter in determination of the success of the IVF treatment in terms of implantation. According to their observation, top quality embryos were defined as exhibiting all of the following characteristics: 4 or 5 blastomeres on day 2 and at least 7 blastomeres on day 3 after fertilisation, absence of multinucleated blastomeres and <20% of fragments on day 2 and day 3 after fertilisation.

Cleavage stage (day 2 or 3) vs. Blastocyst (day 5) transfer (Table 1.3) Compared to single cleavage-stage (day 3) embryo, single blastocyst-stage embryo showed better delivery rate (21.6 %vs. 32.0 %; relative risk, 1.48; 95 percent confidence interval, 1.04 to 2.11) and lower risk of monozygotic twins (2 vs. 0) (Papanikolaou et al,2006). It has been found that even slower developing blastocysts cryopreserved on Day 6, but at the same stage of development as those developing to the blastocyst

stage on Day 5, have similar clinical pregnancy and ongoing pregnancy/live birth rates following frozen-thawed blastocyst transfers (Sunkara et al, 2010).

Freezing technique

A review of four prospective studies found that survival rate of both, cleavage stage embryos (odds ratio 15.57, 95% confidence interval 3.68-65.82; random effects model) and blastocysts (odds ratio 2.20, 95% confidence interval 1.53-3.16; fixed effects model) was significantly higher after vitrification compared with slow freezing (Loutradi et al 2008). Similar results were found by other studies (Smith et al 2010; Cao et al, 2009). Smith et al (2010) found oocytes survival was significantly higher the vitrification/warming (81%) group compared to freezing/thawing (67%) and fertilisation was more successful in oocytes vitrified/warmed compared with frozen/thawed. Cleavage rates of fertilized oocytes was significantly better from vitrification/warming (84%) compared with freezing/thawing (71%) and resultant embryos were significantly of better morphology. Following similar numbers of embryos transfer, embryos resulting from vitrified oocytes had significantly enhanced clinical (38%) pregnancy rates compared with embryos resulting from frozen oocytes (13%). Both rates of miscarriage and spontaneous abortion was similar in both groups.

Age of female partner

One of the most prominent factor in almost all studies mentioned above, looking into single embryo transfer is age of the female partner undergoing the IVF treatment. Women less than 36 years of age had higher chance of success with single embryo transfer and it has been found that cumulative pregnancy in these groups of patients is similar to those having DET. Women over 36 years of age have poor quality of embryos and so the success rate with SET is not as encouraging as in women who are younger than 36 years, when using their own embryos. These groups

often need oocyte donation for a better chance of implantation even with DET. Studies have found that these women have higher rates of twins because of better quality of donated oocytes. There have been reports that these groups of women can also have equal chance as those younger, when using donated oocytes with SET (Veleva et al, 2006). Similar factors such as age of women <36 years, four-cell stage transfer, loss of less than two blastomeres and cleavage of at least two surviving blastomeres influence frozen single embryo transfer (Edgar et al 2007).

1.13 Cost comparison

Cost of IVF treatment has been another issue both for the patient and the government. The cost-effectiveness is the calculation of the costs of the IVF treatments per live birth. The medical costs of an IVF treatment in The Netherlands were €2532, including the medication (CTG 2003). A retrospective cost analysis done from a database containing all couples with a live born singleton or at least one live born twin (24 % twins) after IVF treatment from induction to 6 weeks after deliveryused mode of antenatal care, mode of delivery, and maternal and neonatal hospital admission days for the cost calculation. The study found that the medical costs per singleton and twin pregnancy after IVF treatment, was significantly ($p<0.001$) higher (five times) per twin pregnancy (€ 13,469) than per singleton pregnancy (€ 2,550) (Lukassen et al., 2004). Another study by the same author (Lukassen et al., 2005) found that the mean number of IVF cycles performed per live birth was 4.3 in the SET group randomised to two consecutive cycles of SET compared to 2.8 in the DET group who had only one treatment cycle. This showed that comparatively, 1.5 more SET cycles were needed per live birth. The medical costs of the IVF treatment per live birth in the SET group was €10 888 (4.3×€2532) compared to €7090 in the DET group (2.8×€2532) which showed extra treatment costs per live birth after SET of €3798 (€10 888–€7090). Combining the medical costs of the IVF treatments (where 1.5 more SET

cycles were required to achieve each live birth) and of pregnancies up to 6 weeks after delivery, the total medical costs of DET per live birth were 13,680 and 13,438 for SET. Higher overall cost of the DET group was because the study had found that the percentage of live born twins was 0% in the SET group compared to 37% in the DET group. (Lukassen et al, 2005).

A study by Fiddelers et al (2006) analysed and compared the 'societal' cost of eSET versus DET and found that whereas eSET cost only €7334 per patient, the cost for DET was higher at €10,924. This would only be true if the government is responsible for the IVF treatment only. Apart from this, DET patients had an extra burden of €19,096 as incremental cost-effectiveness ratio (ICER) for each successful pregnancy. ICER is the expense incurred for looking after the baby in neonatal unit, meaning that each additional successful pregnancy in the DET group would cost additional €19,096. However, if the government was also to provide the after care of the new born during the neonatal period then actually the societal cost would be much higher i.e. €10,924 plus €19,096.

The study Fiddelers et al (2009) also looked into different combinations of IVF treatment and calculated the ICER. They found that comparing one-cycle eSET + two-cycle STP (STP= standard treatment policy, i.e. eSET in patients <38 years of age with at least one good quality embryo and DET in the remainder of patients) strategy with a three-cycle eSET strategy resulted in an ICER of €7405, comparing a three-cycle STP strategy with a one-cycle eSET + two-cycle STP strategy resulted in an ICER of €8190 and finally, comparing a three-cycle DET strategy with a three-cycle STP strategy resulted in an ICER of €17,746. A further analysis using the Markov model found that ICER for 3 cycles of eSET was €16,593 cheaper compared to 1 cycle of eSET+ 1 cycle of STP. Three cycles of STP have an ICER of 17,636 euros compared with one cycle of eSET + one cycle of STP + one cycle of DET, and 3 DET cycles have an ICER of 26,729 euro

compared with 3 STP cycles. In other words, elective single embryo transfer at all cycles and not combination treatment, as carried out in some centres around the world, is the most cost effective way to reduce ICER cost for IVF infants (Fiddelers et al 2009).

The medical cost was five times greater in twins than in singleton IVF pregnancy (Lukassen et al 2004). A detail into the revenue spent by the NHS on twins and the singletons is shown in (Table 1.4).The cost ratio for twins is nearly double (1:1.94) compared to singletons. A similar picture came out at the cost estimate of 2002 by NHS for twin and single IVF. The cost for rearing a singleton in the neonatal unit was 1.6 times less than a twin pregnancy. IVF singletons which were 73% of total live births cost the NHS only 46%, whereas the IVF twins that represented 25% cost 43% of the NHS revenue (Ledger et al, 2006). This shows that the cost involved for NHS is potentially comparatively less for SET compared to DET.

Table-1.4 Summary of costs to the NHS of singleton, twin and triplet births resulting from IVF infertility treatment in the UK (RCOG 2006)

	Singleton	Twin	Triplet
Estimated maternal cost	£3122	£6058	£11,534
Estimated neonatal cost (per family)	£191	£3064	£20,820
Total cost per family	£3313	£9122	£32,354
Number of IVF births in UK (1)*	4621	1579	109
Cost of IVF births to the NHS	£15,309,373	£14,403,636	£3,526,586

*(1) Twin and triplet figures are number of sets, rather than individual babies.

Definitely the impact of having a twin pregnancy is immense, not only on the mother's mental and physical health but also on the child both intrauterine and after birth. Both mental and physical health of a child from a twin pregnancy can be affected either because of improper care or maternal medical complications or due to their own developmental deficiencies because of preterm birth and prematurity. The financial implications of caring for a twin have been proved to be greater both for the family and the NHS. Until now we have looked into how eSET could be fit for purpose if chosen intelligently for patients with high probability of success. However, there has still been a lot of debate on its universal application in the UK, because of the many barriers which needs an honest evaluation for the benefit of the patients.

1.14 Barriers to eSET

As more than one embryo is available and for the fact that IVF treatment has limited success rate in terms of live birth, the usual tendency of clinicians is to transfer more than one embryo in the desire to have at least one successful implantation leading to successful live birth. However, the transfer of more than one embryo unavoidably increases the chance of a multiple pregnancy.

In most European IVF clinics number of embryo transfer is decided jointly by the health professional and the couple in a process of shared decision-making (van Peperstraten 2008). Presumably, this is the reason that with the exception of Belgium and Sweden, there are no national SET legislation systems or compulsory SET protocols (De Neubourg et al., 2006; Karlström & Bergh, 2007). Elective single embryo transfer use is rising but still has barriers which need to be addressed to before it can be universally used as a rule.

1.15 Conclusion

With increasing rate of infertility, there is also rise in the rates of patients undergoing IVF treatment (HFEA, 2009). IVF treatment has come a long way since 1978 after its first successful use. With greater advances in the methodology of this treatment process the chances of success of IVF treatment has increased over the years.

Most clinics around the world have standardised their IVF treatment to double embryo transfer, after it was realised that triplets and other higher order pregnancies were complicated and risky for both the mother and the child, both during intrauterine life and after birth. It was soon realised that DET was producing an acceptable live birth rate and also helping to reduce the rates of triplets and higher order pregnancies in a drastic and efficient way. However, the rate of twins was not falling but instead rising. Soon it became evident that the rates of twins around the world was higher (1 in 80 births) than the natural incidence of twins (1 in 100 births).

Countries all around started noticing the effect of the higher rates of twin pregnancy and twin births on the health of the mother and the child. A recent meta-analysis looking into the studies focussing on the effects of IVF twins showed higher rates of preterm birth and lower birth weight compared to natural twins (McDonald et al, 2010). Similar results were reported by (Kanat-Pektas et al 2008), who also found behavioural problems, along with mental and psychomotor retardation in ART children apart from problems of parent-child interaction. This chapter has in detail laid out the various medical and psychological problems both in the children and the mother due to IVF twins. Studies have shown that the rise in IVF twins not only have health implications but financial implications as well. The cost is not only that of IVF treatment but also the cost of caring for the infant which is many times the responsibility of the national health system (Lukassen et al 2004, 2005; Fiddelers et al 2009). Therefore for

countries like the UK, where the National Health Service (NHS) or the government is responsible for providing the healthcare, it can be a he burden on the economy. Therefore Scandinavian countries where healthcare is the responsibility of the government were the first to research (Gerris et al, 1999) about the impact of DET on twin birth rates and that of twins due to IVF treatment on the health of the mother and the child. They also looked into the options of decreasing the rates of twins due to DET and methods of doing so without affecting much on the live birth rates for patients undergoing IVF treatment.

The proportion of single embryo transfers is slowly rising and approaching 19%, a slow but steady rise (Andersen et al., 2005). Focusing on targeted treatment in selected younger group of patients using embryos with the best probability of implantation such as good quality embryos, using blastocyst instead of cleavage stage embryos and better method of cryopreservation such as vitrification could all work towards decreasing the rates of twins without compromising the cumulative pregnancy rates which have been found to be comparable in SET with DET and huge reduction in twin rates even though eSET do have lower pregnancy rates with single fresh cycle when compared with DET.

Elective single embryo transfer seems to be an effective way of decreasing the rates of twins from IVF treatment by delivering an acceptable cumulative pregnancy rate similar to DET with fresh and frozen embryo transfer. It also seems to be the method to decrease the cost of the treatment. Countries (Table 1.5), which have used it since 2002, such as Sweden and Belgium, have definitely provided us with the results. However, the approaches of the two countries are different as is the situation in these countries. This is also true for other countries considering eSET as a rule for IVF treatment, because the conditions without doubt differ from place to place, and so the decision about making

SET compulsory should be viewed in the context of the country concerned.

Most evidence shows that increasing the number of embryos per transfer would increase the chances of implantation or the birth rate and the risk of multiple births did increase independently with the number of embryos transferred. The probable reason could be the uncertainty of the implantation rate. This may be the reason why clinicians perceive a better chance of implantation with transfer of more number of embryos. There is uncertainty due to lack of a reliable measure to predict the implantation potential for each individual embryo (Van Royen et al 1999, 2001). It is the difficulty in maintaining a balance between an acceptable pregnancy rate and the prevention of multiple pregnancies which is probably the reason why the implementation of eSET in clinical practice has not been universally accepted (van Peperstraten et al, 2008). Howard Jones in 2003, referred to “inductor isolation” which he felt should be addressed. He argued that the fertility specialists are the inductors of the multiple pregnancy problem but they are isolated from the consequences because they are not involved directly with caring for the new born. If this ‘self serving isolation’ continues, the problem will certainly not improve and some kind of legislation may be necessary.

Although this seems to be a bit too harsh, it does point us in the direction that the attitudes of everyone concerned with IVF treatment should be looked into and evaluated before making any firm judgement. There should also be a detailed look into the decision-making process and the factors that influence the number of embryos transferred as in van Peperstraten et al (2008a; 2008b). The development of a measure of attitudes to eSET and twin IVF pregnancies could be a useful tool to judge which factors most influence eSET and to evaluate the impact of interventions.

In many countries including the UK, decisions about eSET is made based on clinical judgement and not by legislation. The latest move by the HFEA (to curb the rise in twin birth rate) was introduced in 2009 and clinics all around the UK had the target set to bring down their multiple birth rate to 10 % over three years from the then rate of 25%. A leaflet provided by the HFEA is given to all IVF patients before their treatment to make them aware of the complications of twin birth. This is done to convince them to choose single embryo transfer for their IVF treatment. However, this clearly did not have much impact on patient choices which was evident with rising rates of twins as a result of IVF treatment until the latest data of 2007 was published by HFEA in 2009 after which the target reduction was set by HFEA.

Understandably, the way forward could be building a consensus among clinicians and patients and giving patients more power for making informed choice. Giving patients the liberty to make a choice will make them more aware of the complications of a twin birth and weigh it intelligently with the benefits and success rate of single embryo transfer and take responsibility of their decisions. This will not only increase the confidence in patients but also the clinicians who are often not very optimistic about single embryo transfer because of the lower success. Clearly the level of understanding of the risks associated with multiple pregnancies and attitudes to the implications of a twin birth, in both patients undergoing IVF treatment and doctors providing that treatment, will be the key to patient decisions about whether to risk a multiple birth by accepting multiple embryo transfer or have similar chances of success with lower twin rates. It is our understanding that the cost of IVF treatment is also a very powerful influencing factor in this decision making process.

When the idea of this research was compiled, single embryo transfer (SET) was already being practised routinely in many Scandinavian countries. Some of these countries offered elective SET and others had

legislation to routinely promote SET to all IVF patients. At the time HFEA had started looking into the rising rates of twin births from IVF treatment but nothing had been done to control the rising rates of twins, although there was substantial progress in both laboratory and clinical parts of IVF treatment. It is important in the UK that patients undergoing infertility treatment are able to make informed choices about the number of embryos to transfer.

The thesis is arranged in a manner that focuses on the issues raised above. Having established in the introduction that a twin birth is a risk factor for prematurity and that prematurity is associated with an increased risk of developmental delay, chapter 2 explores rates of developmental delay in premature twins and explores whether a twin birth is an additional risk factor for poor outcomes. Chapter 3 reviews the literature on attitudes towards IVF twins and describes the development of the long and short ATIP scale. Chapter 4 uses the ATIP scale in patient and IVF clinician population from a large private IVF provider around UK and a revised ATIPS-R is created. Chapter 5 focuses on the development of a decision aid tool and Chapter 6 evaluates the of decision aid in randomised control trial. Finally, chapter 7 presents the final discussion of the findings of this research.

Table 1.5 – IVF regulations around the world (HFEA, 2010)

Countries	Policy	Result
Canada	No state regulation On SOGC & CFAS advice, transferring no more than 2 embryos in fresh cycles for women < 35 yrs	Twin rate 30%
United States	No state regulation Women <35yrs encouraged for SET; 35-37 no more than 2 embryos; 38–40 no more than 3 cleavage stage embryos or no more than 2 blastocysts.	Twins continue to rise
Australia	Fertility Society of Australia guidance requires all centres to transfer no more than two embryos to women under 40 years. It also recommends that women under 35 years on their first fresh treatment have no more than one embryo transferred	Twin rate 23.5% (2005) SET- 57% (2006)
Germany	No more than 3 immature eggs can be cultured beyond an early stage, embryo selection practices are not permitted, and no cleavage stage (2–3 day) embryos can be frozen, all embryos have to be transferred	Very high triplet and twin rate
Austria	Same as above with slight difference, restrictions are voluntary, with a general trend towards transferring no more than 2 embryos for most patients	Very high triplet and twin rate
Switzerland	Same as above	Same as above
Greece	3 embryos for women ≤ 40 yrs.; 4 embryos for women >40yrs	No data available
Netherlands	No state regulation, but eSET widely used, and a maximum of two embryos are transferred. As of January 2007, the first 3 IVF cycles are fully funded (SET or double embryo transfer (DET))	No data available
Norway	No state regulation, but eSET widely used	Twin rate 25.2%
Denmark	No state regulation, but eSET widely used	Twin rate 22.7%
Sweden	State regulation, only one embryo should be replaced, apart from in exceptional circumstances	Twin rate 5.0%
United Kingdom	Reduce multiple birth rates to 10 % in 3 yrs since 2009. 2 embryos in women under 40, and to 3 for older women	Twin rate 24%

1.16 Aims of this thesis

1- To explore whether a twin birth is an additional risk factor for poor developmental outcomes in infants born very premature.

2- To develop a valid and reliable questionnaire to assess attitudes to multiple IVF births and elective single embryo transfer.

3- To assess attitudes to elective single embryo transfer in patients and health professionals and explore factors influencing those attitudes

4- To develop and evaluate a decision aid tool to help patients make informed decisions about elective single embryo transfer.

THE IMPACT OF BEING BORN VERY PREMATURE ON NEUROBEHAVIOURAL DEVELOPMENT IN TWINS

2.1 Introduction

Preterm birth which carries increased risk of morbidity all through childhood is the most important risk factor for neonatal morbidity and mortality (Msall & Park, 2008; Saigal & Doyle, 2008). This incidence of prematurity is higher in twins compared to singletons (Rydhsttroem & Heraib, 2001). Prematurity as mentioned earlier in chapter 1, increases the risk of developmental delay. The increased rate of prematurity in twins is considered to explain poorer developmental outcomes in twins generally. However, development is affected not only by biological risk but also by environmental factors such as quality of environment and so twins may be additionally disadvantaged because they may have a less stimulating environment as there are two young infants to care for at the same time. There is evidence for poorer cognitive outcome in twins regardless of prematurity therefore twin status may represent an additional risk factor (Rydhsttroem & Heraib, 2001).

Most studies evaluated and reviewed in chapter one have looked into the outcomes of preterm-premature deliveries at birth and some at 1 year or at a much later stage at 4 and 8 years. However, most studies on outcome of premature birth either exclude twins or do not consider multiple births as a separate risk factor and most studies on outcomes in twins do not control adequately for prematurity, and therefore there is a need to develop a study to look and compare the effects and factors affecting development of preterm singletons with preterm twins after controlling for their prematurity. This study re-analyses data from a randomised controlled trial of a parenting intervention with infants born before 32 weeks gestational age to explore the impact of twin status on outcomes at birth and on cognitive and motor development at 2 years follow-up.

2.2 Aims

1) To compare health status and other risk factors at birth in twins and singletons born very premature.

2) To explore the impact of twin status on cognitive and motor development at 2 years adjusted age in infants born very premature

2.3 Method

Participants

Participants were recruited from six neonatal centres, three from the south-west and three from Trent, and recruitment began in July 2002. The inclusion criteria stipulated that the infants should be born at 32 weeks of gestation or less and admitted to one of the six participating neonatal centres. Infants were excluded if they resided outside the study's catchment areas and / or if they had an illness incompatible with life.

The sample was originally recruited to participate in a large cluster randomised trial which examined the effects of a parenting intervention (Glazebrook et al., 2007). Depending on the phase of the trial and the neonatal unit, infants either received standard care or the Parent Baby Interaction Program (PBIP). The PBIP is a supportive, educational program which is aimed at parents of premature infants. Its goal is to enhance parents' sensitivity to their infants' cues and promote attachment, in turn improving the infant's developmental and behavioural outcomes. Analysis of two year follow-up data revealed no impact of the intervention of motor or cognitive outcomes at two years adjusted age (Johnson et al 2009).

Measures and Procedures

Participants were recruited by research nurses between 7 and 14 days postpartum. Demographic and clinical information was obtained through

maternal interviews and from examining the mother's and the infant's medical notes. Mother's occupation was obtained using a free response question and status was coded using the National Statistics Socio-economic Classification (NS-SEC). An index of multiple deprivation (IMD) (Noble et al., 2004) was calculated for each infant using postcode analysis. The IMD score is derived from data on deprivation at the small area level in seven domains, including income, employment and crime. Scores for England range from 0.59 (least deprived) to 86.36 (most deprived) with a median of 17.02. At 2 years adjusted age one of two researchers carried out a home visit and administered a developmental assessment.

Developmental outcome at 24 months' corrected age was assessed using the Bayley Scales of Infant Development 2nd Edition (BSID-II) (Bayley 1993). This is a norm-referenced test that yields standardised scores (mean, 100; SD, 15; range, 50 to 150) for cognitive (Mental Development Index; MDI) and motor development (Psychomotor Development Index; PDI). Scores within 1 SD of the standardized mean (85 to 114) are considered in the normal range for development. Comparison of both MDI and PDI scores between singletons and twins were the primary outcome measures for this study.

Those children who could not be assessed as a result of severe disability and those whose index scores fell below test limits were assigned a nominal index score of 49 (1 point below the basal test score) for quantifying severely delayed outcome (Johnson et al 2008) Psychologists were formally trained in test administration before the research started, which helped to achieve excellent inter-rater reliability (MDI, 97% item-by-item agreement; PDI, 94% agreement) in 11 randomly selected assessments scored simultaneously by both examiners throughout the period of data collection. Developmental delays were classified by using conventional SD-banded cut-offs. Mild impairment was more than 1 SD

below the standardized mean but less than 2 SDs below (70 to 84), moderate delay was more than 2 SDs below the mean but less than 3 SDs (55 to 69) and severe impairment was more than 3 SDs below the mean (score less than 55).

2.4 Ethics approval

The study was approved by the South-West Multicentre Research Ethics Committee and subsequently approved by the Local Research Ethics Committee in each participating hospital.

2.5 Analysis

Data were analysed using SPSS version 16 for windows. Appropriate parametric and non-parametric univariate analyses were conducted, followed by step-wise regression analyses. The probability level was set at 0.05.

2.6 Results

Response rate

Of the 496 infants indentified in the study neonatal units, 156 were excluded because they were born outside the study and transferred into the study units or because they were resident outside the study. A further 33 infants died before consent could be obtained. Of the remaining 307 babies who were eligible for inclusion in the study, 233 (76%) were recruited to the study. Parents of 62 infants (20%) refused to participate and 12 (4%) could not be contacted. Infants who were recruited to the study did not differ significantly from those who were not recruited in terms of gender, birth weight, gestational age and proportion of multiple births. Of the 233 infants in the study, 46 (19.7%) were twins. The characteristics of twin and singleton infants are shown in Table 2.1.

Infants' characteristics

Two of the twins, both from the same family, showed serious malformation at birth, compared to none in the singleton group, and this difference was significant (Fisher exact probability= .038). There were no other statistically significant differences between the twin infants and singleton infants.

Table 2.1.Infants' Characteristics

	Singletons	Twins
	n=187	n=46
Gender		
Male (%)	93 (49.7)	18 (39.1)
Female (%)	94 (50)	28 (60.9)
Allocated to intervention (%)	86 (46)	26 (56.5)
Mean birth weight (SD)	1.68 (0.47)	1.65 (0.48)
Mean Multiple Deprivation Index(SD)	19.11 (15.24)	16.37(15.05)
Mean Apgar score at 1 minute (SD)	6.41 [a] (2.22)	6.98 (1.95)
Mean cord arterial pH (SD)	2.33 (3.40)	2.86 (3.61)
Mean days ventilated to discharge (SD)	7.92 (15.51)	4.38 (8.89)
Mean days on oxygen to discharge (SD)	36.64 [b] (50.07)	35.44 (51.92)
Mean days on NICU to discharge (SD)	12.72 [b] (18.17)	11.20 (13.37)
Birth weight <1000g (%)	60 (32.10)	16 (34.80)
Malformation present (%)	6 (3.20)	4 (8.70)
Gestation age <29 weeks (%)	89 (47.60)	16 (34.80)
Serious malformation	0 (0%) [c]	2(4.4%) [d] *

a = 9 missing b= 15 missing c= 3 missing d= 1 missing * p<0.05

Mothers' characteristics

23 mothers in the group had 2 twins recruited into the study and the remaining 187 mothers had 1 infant. A detailed description of the maternal characteristics of both twins and singletons are in Table 3.2. Mothers in the twin group were older than mothers in the singleton group (t= -2.26, df= 208, p= 0.025). They were also more likely to have professional or managerial jobs (X2= 5.139, df=1, p=0.023).

Table 2.2 Mothers' Characteristics

Characteristics	Singletons (n=187)	Twins (n=23)
Mean maternal age (SD)	28.87 (6.51)	32.09 (5.75)*
Married/cohabiting (%)	155 (82.8)	19 (82.6)
First time mothers (%)	103 (55.10)	14 (60.90)
Hypertensive disease (%)	35 (18.70)	3 (13.00)
Highest qualification		
NVQ/GCSE/Standards (%)	81 (6.40)	6 (26.10)
Degree or above (%)	29 (15.5)	7(30.4)
Socioeconomic status (%)		
Professional or managerial	64 (34.20)	14 (60.0)*
Lower order jobs	80 (42.90)	6 (26.00)
Mother smoking (%)	120 (64.20)	15 (65.20)
Exclusively formula fed at discharge (%)	95 (55.2)	10 (50)
Intention to feed (%)		
Breast feeding	139 (74.30)	14 (60.90)
Bottle feeding	33 (17.60)	6 (26.10)
Delivery type (%)		
Vaginal vertex	83 (44.40)	10 (43.5)
Urgent CS no labour	40 (21.40)	5 (21.70)
Urgent CS in labour	18 (9.60)	5 (21.70)
Elective CS no labour	26 (13.90)	2 (8.70)

*P<0.05, CS=Caesarean section

Follow up at 24 months corrected age

Of the 233 infants recruited to the study, 195 (83.8%) were assessed using the BSID-II at 2 years corrected age. Sixteen infants (6.9%) had been withdrawn from the study, 7 (3%) could not be contacted and 11 (4.7%) infants had died and for one infant the parent refused the BSID assessment.

9 twins (19.6%) and 29 (15.5%) singletons were missing at follow-up which was a non significant difference. In the twins 5 (10.9%) had died before discharge and a further 4 (8.7%) had been withdrawn. In the singletons, 8 (4.3%) had died before discharge, 1 (0.5%) had died after discharge, 11 (5.8%) had been withdrawn and 4 (2.1%) had been lost to contact.

Mental Development Index (MDI) Scores

A small MDI score was assigned for 7 infants with scores below test limits. All 7 infants were singletons. An MDI score was excluded for 1 child for whom a valid assessment could not be obtained because of child's inability to respond in English. The mean MDI score was 4 points higher in the twins (S= 91.03 ± 19.8; T= 94.84 ± 16.75), but this difference was not significant (t=-1.080; df: 192) (Table- 2.3).

Table- 2.3 MDI scores by twin status

	Mean MDI	SD (±)
Singletons n=157	91.03	19.82
Twins n=37	94.84	16.75

Of the total 157 participants from singleton group available for analysis of mental development, 57 of them showed a delay in their mental development, compared to 10 out 37 twins. Although the frequency of delay in mental development was slightly higher in singletons (36.3%) compared to twins (27.0%), this was not significant (Table 2.4).

Table 2.4 MDI delay- Singletons and Twins

	Significantly delayed	Mildly delayed	Within normal limits	Accelerated performance	Total
Singletons	14	43	84	16	157
(%)	(8.9)	(27.4)	(53.5)	(10.2)	(100)
Twins	3	7	24	3	37
(%)	(8.1)	(18.9)	(64.9)	(8.1)	(100)
Total	17	50	108	19	194
(%)	(8.8)	(25.8)	(55.7)	(9.8)	(100)

In order to control for potentially confounding factors a stepwise regression analysis was carried out with MDI scores as the dependant variable. The independant variables included were number of days ventilated before discharge, gender, birth weight, gestational age, index of material deprivation score, maternal age, maternal education (degree level and above/no higher education), social class (managerial and above/other), twin (yes/no), group (intervention/control). Higher cognitive function was associated with fewer days ventilated, female gender, higher maternal education and residence in an area of lower material deprivation

(Table 2.5). These variables accounted for 27% of the variance in MDI scores (adjusted r^2 = 0.271). Birth weight, gestational age, social class, maternal age, twin status and intervention group made no contribution once these variables were accounted for (Table 2.5).

Table 2.5 MDI index score Coefficients for all infants

	Standardized coefficients Beta	T	Significance
Days ventilated to discharge	-0.40	-6.370	0.000
sex	.232	3.744	0.000
Degree level education	.127	2.002	0.045
Index of multiple deprivation	-0.13	-1.983	0.049

Psychomotor Development (PDI Scores)

A small PDI score were assigned for 9 infants. PDI scores were not included for 2 children in whom the assessment could not be completed due to language or behavioral difficulties (both in the intervention group).

Mean PDI score was 2.1 points higher in twins group than singletons (S=92.46 ± 18.59; T=94.59 ± 13.78). Table 2.6, but this difference was not significant (t=-.656; df=191). A nearly equal percentage of singletons (27.6%) and twins (24.3%) showed delay in their psychomotor development and this result was not significant (Table 2.7).

Table- 2.6 PDI scores by twin status

	Mean	SD (±)
Singletons		
n=157	92.46	18.59
Twins		
n=37	94.59	13.779

Table 2.7 PDI delay- Singletons and Twins

	Significantly delayed	Mildly delayed	Within normal limits	Accelerated performance	Total
Singletons	14	29	108	5	156
(%)	(9.0)	(18.6)	(69.2)	(3.2)	(100)
Twins	2	7	27	1	37
(%)	(5.4)	(18.9)	(73.0)	(2.7)	(100)
Total	16	36	135	6	193
(%)	(8.3)	(18.7)	(69.9)	(3.1)	(100)

Regression analysis with PDI scores found that higher psychomotor scores for all infants and twins only were only associated with 2 factors. Days ventilated to discharge and the genders of the child were the two dominant, dependant factors for PDI index. Higher PDI scores were noticed for females and those ventilated for fewer days. These variable accounted for 27% of the variance in PDI scores (adjusted r2 = 0.272) (Table 2.8).

Table 2.8 PDI index score Coefficients for all infants

	Standardized coefficients Beta	T	Significance
Days ventilated to discharge	-.485	-7.880	≤0.001
sex	.196	3.180	0.002

2.7 Discussion

This study compared neurobehavioural outcomes at 2 years in twins and singleton infants born very premature. Baseline characteristics, such as mean birth weight, mean cord arterial pH, mean days on NICU to discharge, a gestational age of <29 weeks at birth were not significantly different between singleton and twin infants. However, there was a significant excess in rates of malformation in twins with 2 infants, both from the same family, (4.4% of twins) having a serious malformation compared to none in the singleton group. This is not a particularly high rate since it has been found that a major congenital anomaly (including structural, chromosomal, genetic, and biochemical anomalies, presumed to be of prenatal origin) affects 2–3% of newborn babies (Stevenson 2006). A study looking at the BINOCAR registers found that the most frequent anomalies were serious cardiac anomaly (14.1 per 10,000 births, 1 in 710 births [95% CI 13.0–15.2]) and cleft lip with or without palate (9.7 per 10,000 births, 1 in 1,032 [95% CI 8.9–10.5]) (Boyd et al 2011). Rates in a sample of premature infants might have been expected to be higher. However, parents with severely disabled infants might have been less likely to have agreed to participate and children with life threatening illnesses were excluded.

Studies have found that VLBW twins who survived till 1 year had 25% rate of major developmental handicaps (Gardner et al, 1995). However, specific details about these serious malformations in twins were not recorded in our database. Other studies have also faced similar problems. Specific morbidities in multiple foetal pregnancies are controversial. Neonatal outcomes at specific gestational ages and birth weights are similar to singleton pregnancies. Neonatal mortality rate of preterm-premature infants in multiple pregnancies is similar to that in singletons and it increases with decreasing gestational age. Infants born from multiple foetal pregnancies can be at higher risk of conditions like acute respiratory distress syndrome (Shinwell, 2005) but they do not have higher incidence of chronic lung disease. Other major medical complications such as intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity, necrotizing enterocolitis, patent ductus arteriosus, nosocomial infection, and length of hospital stay have demonstrated no statistical difference between singletons and multiples (Garite et al,2004; Lee et al 2006).

Prematurity may have different origins for twins and singletons. For example, pregnancy induced hypertension has been found to be higher in mothers with singletons compared to twins and could be a cause of preterm delivery in singletons. Similarly, significant decrease in birth weight of singletons was associated with pregnancy induced hypertension and not in twins (Ochsenkhun et al, 2003).

Our study found that mean MDI and PDI Index scores were below the expected mean of 100 and although the mean was higher for twins, there was no significant difference between the groups. Compared to an expected percentage of 16% of a normative population having delayed development, 27% of twin infants fell below the cut-off for delay. This was despite the fact that twin infants had older mothers and were significantly more likely to have mothers with professional occupations, both factors

which would be expected to be associated with better neurodevelopmental outcomes (Hogan & Park 2000). In effect this was a population that might be expected to have fewer children with delayed development. Singleton infants had non-statistically higher rates of delay (36%) that were twice the expected rate, confirming the expected effect of prematurity on developmental outcomes. Twin infants also had a smaller proportion of males (39% vs. 50%) in the singleton group and had been ventilated for fewer days (mean of 4.38 vs. 7.92 for singletons). Both differences were non-significant using appropriate statistical tests but the findings suggest a pattern of advantage for the singletons. Male gender was an independant risk factor for poorer cognitive outcomes in the sample. Other studies have confirmed this disadvantage. For example, one study found that male-male twin pairs tend to be delivered earlier than a female-female or a female-male twin pair and male VLBW infants independently have higher mortality rate (Donovan et al, 1998). Many studies have shown that a high proportion of preterm infants either as singletons or twins experience chronic diseases extending sometimes to their adult life (Hack et al 2005), but looking into this aspect was beyond this database study.

This study found that more mothers of twins were better qualified which would make them more aware of their condition and obviously should have made them better prepared, and with higher order jobs they would have less financial stress and would be in a position to get outside help, and they also had higher average age which at the time of birth compared to mothers of singletons. All these factors can give an infant a better environment for cognitive development and as mentioned earlier, environmental factors do hold importance in the development of an infant. This is in accordance with studies which have found maternal age as a factor for twinning (Ochsenkühn et al, 2003).

Various studies done on infertility patients have found that patients conceiving after fertility treatment in general have increased risk of

preterm birth and low birth weight babies (McDonald et al, 2007; Filicori et al,2005; Buitendijk et al 1999; Schieve et al 2002;. McDonald et al 2005; Weghofer et al, 2009) and have higher chances of being admitted to NICU compared to those born through natural conception (Wisborg et al, 2010). As we do not have details about any fertility treatment in our study groups, our study cannot compare this. Use of gonadotrophins during IVF treatment results in higher levels of relaxin throughout the whole gestation period, and this could be another reason for higher PTB in IVF pregnancies (Mushayandabvu et al 1998). This can have implications for IVF in developing countries and those without state health care. The outcome for multiple IVF birth could be worse either due to lack of affordability or lack of high grade neonatal care or a combination of both especially for the not so affluent who have already spent substantial amount for their IVF treatment. It is quite evident that caring for a premature baby carries risk to the health and development of a child. This is an issue for parents making choices about embryo transfer because between 40% and 70% of twins are born preterm and a high proportion of these preterm twins are premature (Steer, 2007). Studies have shown that twins have worse outcomes than singletons with long term neurological problems, higher rates of perinatal mortality and neonatal morbidity (Blondel and Kaminski, 2002).

The increased risks in IVF twins is attributed to factors such as the IVF process with older mothers and causes of infertility could in itself be an additional risk for prematurity in pregnancies conceived after sub fertility treatment (Malcolm, 1991). A possibility that mothers of IVF twins are keener in getting intensive prenatal care (Kanat-Pektas et al, 2008), in the desire to reduce any possible maternal and foetal risks. Also, often, clinicians tend to have a more watchful eye on IVF patients as these pregnancies are considered precious, and therefore, it can be argued that IVF patients have more frequent preterm birth and more so when the patient has an IVF twin to offset any complications which would be difficult

to tackle; however, with the neonatology advances, tackling twin preterm in clinicians' perception is less complicated.

As found in previous researches, both clinical and environmental factors are important (Hayiou-Thomas, 2008 Caughey, 2007) in the developmental outcome of a premature infant, not only during neonatal period or infancy, but even in early childhood and sometimes in adult life too. In two large placebo-controlled studies, regular use of progesterone in high-risk singleton pregnancies reduced the risk of preterm labour but there is no such evidence for twins (Krampl and Klein, 2007) and this can certainly have implications for preterm and small for gestational age, premature twins' survival. This study, unlike those mentioned earlier, found that very premature twins were at the same risk for cognitive delay as singletons. The mothers of twins in the study were better educated and in better jobs than singleton mothers, which might be the factor for better care of twins in the study. It can be argued that IVF mothers in general are older than naturally conceiving women, partly because of the delay in diagnosis and also trying different treatment regimes before going for IVF treatment. IVF mothers in general are also more aware of all the facts and the complications of twins which may help them prepare better for the future and therefore even IVF twins may not be at a greater risk of poor cognitive than IVF singletons. At the same time this study reported that more twins died before discharge (10% vs. 4%), although this was not significant, and also had serious malformations which are another risks of prematurity and more so for a premature twins as found in our study.

As twins are more prone to be born premature and preterm, because of the underdevelopment of the brain and the neurons as mentioned earlier, these twins are at a greater risk of cognitive delay and also caring for two underdeveloped infants can be more stressful both financially and emotionally than a singleton and this can have an impact on their development. In this relatively homogenous sample there may not have

been the variability in socio demographic background in the small sample of twin infants to demonstrate an effect of environmental factors. However, it may be that the demands of caring for two infants offset any advantage of social class, maternal education and maternal age. Although the better educated mothers may potentially provide a more stimulating environment, twin infants would have less exposure to high quality and focused interaction.

This study found that in the sample as a whole, after controlling for infant health at birth days ventilated, gender, socio demographic factors (index of material deprivation and maternal level of education) were associated with better cognitive outcomes at 2 years of age, thus social class acted as resilience factor.

Certainly awareness has increased about the difficulties faced by preterm children such as depression, anxiety, unsocial behaviour, social withdrawal, and attention deficit hyperactivity disorder (ADHD), Autism and Schizophrenia (Mathur and Inder, 2009) and it would be in the best interest of parents undergoing ART treatments like IVF and ICSI who are at risk of having higher rates of twins and related preterm delivery to be fully aware of the risk of prematurity associated with preterm birth. This risk also increases twofold with twins and the whole development process of the child could not be in an ideal way with the increase in parental stress, both for financial reasons and for the fact that caring for two babies at the same time would not provide the best parental attention and care possible.

Strength and weakness of this study

The strengths of this study include the good initial response rate, the excellent follow-up rate and the prospective study design. As a prospective study it avoids selective bias at the 2 year assessment. The study used a valid and reliable assessment of neurobehavioural

development conducted by trained researchers. As mentioned earlier, the limitations were the relatively small sample of twins which may have led to type two errors and the lack of information about whether the twins were the result of IVF. Also we did not have any data on the chronic illness or specific disease status of the babies.

Conclusion

The best way forward could be to engage fertility specialists involved in the treatment of the infertile couple for discussion, more so in those centres that provide services outside the National Health Service as all the premature multiple births require intensive care in the national health service (Malcolm 1991). A big responsibility lies on the shoulder of the clinicians to encourage their patients to be fully aware of their treatment choices, risks and implications of having a premature child and the increased chances of having twins from ART treatment and indirectly double responsibility of two preterm babies. Encouraging their patients making informed choice about the number of embryos to be transferred would be an ideal way forward in decreasing the rise in number of preterm premature twins due to IVF treatment. Evaluating and measuring the attitude of both patients and clinicians towards twin IVF birth would be important at this stage. Measuring this with a universal scale would be helpful. There is no such scale and therefore the next chapters describe the development and validation of a scale which could be easily used both in patients and clinicians.

DEVELOPMENT AND PRELIMINARY VALIDATION OF A QUESTIONNAIRE TO MEASURE ATTITUDE TO RISK ASSOCIATED WITH TWIN IVF PREGNANCIES AND BARRIERS TO ELECTIVE SINGLE EMBRYO TRANSFER

3.1 Attitude and behaviour

Evidence from the previous chapter demonstrates that eSET is an effective method of reducing rates of twin birth and that in selected patients and where cryopreservation is used to allow for repeat cycles eSET can achieve comparable pregnancy rates. In countries such as the UK and the US however there has been a reluctance to impose eSET on patients and implementation has therefore been slow. In the absence of strict protocols of treatment it is likely that decisions about embryo transfer are driven by patient and clinician choice. This chapter aims to explore patient and clinician attitudes to the risks associated with a twin birth and beliefs about eSET.

Gordon Alport in 1935 was the first to express that “the concept of attitude is probably the most distinctive and indispensable concept in contemporary American social psychology.” He defined attitude as “a mental and neural state of readiness, organised through experience, exerting a directive and dynamic influence upon the individual’s response to all objects and situations with which it is related” (Allport, 1935). Since then various attempts have been made by many different psychologists. Many definitions of attitude have been proposed. Rosenberg & Hovland (1960) stated that “attitudes are predispositions to respond to some class of stimuli with certain classes of response”. The various classes of responses are 1) Affective 2) Cognitive and 3) Behavioural. Hogg & Vaughan (1995) tried to explain attitude as “basic and pervasive in human life. According to them attitudes form the basis of our “reaction to events” and also our decision making power.

In simple terms attitude can be described as the opinion a person has about something which could be influenced by his knowledge or his feeling or sometimes his experience. Usually actions and decision making by an individual is influenced by this attitude. It can be positive or negative. For proper evaluation, attitudes should be measured. Fenberg & Frey (1988) proposed that a reliable method of attitude measurement should be found and indicators of attitude measurements are based on the fact that people's beliefs and opinions about the object. Various methods are available for the measurement of attitude of which Likert scale is the most in use. In this answers range from strongly agree to strongly disagree. Under this scale, agree represents a positive attitude and disagree a negative attitude.

This chapter evaluates the literature on attitudes to multiple IVF births and eSET in clinicians and patients. The evidence will be used to select items for a questionnaire to assess attitudes to risk associated with twin and barriers to eSET. Many studies have explored attitudes to multiple IVF but none has used a reliable and valid questionnaire which makes it difficult to evaluate factors influencing attitudes. A standardised questionnaire will allow evaluation of the impact of informational interventions aimed at promoting informed patient choice and increasing uptake of eSET.

3.2 Clinicians' attitudes to eSET and twin births

As established previously in chapter 1, twin births are associated with greater health risks to both the mother and the infants in comparison to singleton births. They also are an increased social and psychological responsibility for parents. Despite this it has been recognised by some studies that patients with problems of infertility and in particular those undergoing IVF treatment consider twin births as an additional benefit and not a complication of their treatment (Murray et al, 2004; Pinborg et al 2003). Not many literatures are available that look into the attitudes of

clinicians about eSET. Some studies have shown that the clinicians perceive twins as high risk and a complication of ART treatment (Hazekamp et al 2000) even though there is strong evidence in literatures of medicine regarding the increase in risk to mother and the child or the foetus (Ventura et al, 1999). However, more recent studies have shown that clinicians have a rather positive attitude to twins and do not seem to be much concerned about the risks associated with a twin. Twin pregnancy has been considered a high risk compared to singletons in "relative terms" but the "risk differential" at the modern state of care does not seem to be so high in "absolute terms"(Kogan et al.,2000). Researches, however, show that risk due to triplets and beyond is not acceptable (Gleicher et al., 2000) but twins are considered safe when compared with triplets (Lipiz et al., 1989).

However, there have not been many studies looking into the attitudes of doctors involved in IVF treatment about eSET and factors influencing them. Some evidence even suggests that doctors involved in IVF treatment do not have an encouraging opinion regarding eSET (Gleicher & Barad, 2006). A survey was conducted in Scotland on fertility professionals involved in IVF treatment and support. These participants mostly had direct experience of couples having problems with twin pregnancies. Although healthcare professionals did show concern about complications associated with twin birth. They felt it was 'quite horrendous' for patients to experience the trauma of loosing their twins at any stage, but even then they were not willing to randomise SET for all patients coming for IVF treatment (Porter & Bhattacharya 2005).

In one of the RCT's mentioned in chapter 1, an extra five to ten percent of cumulative pregnancy was predicted if DET was used instead of eSET with an extra cycle with cryopreserved embryos, however there was higher rates of twins with DET and clinicians' considered this risk of nearly

twenty five percent twins for just a five percent increase in chance of conceiving was worth taking (Martikainen et al 2001).

Another study has looked into the attitudes of Nordic IVF doctors towards single embryo transfer and its management. The study found that nearly all doctors thought that singletons were better than twins but there was significant difference (p=0.024) among the doctors in acceptance of twin rate of >10%. Where as, only 5% Swedish doctors supported a twin rate greater than 10% of IVF births in comparison to 35% of Danish and Norwegian doctors who supported a twin rate greater than 10% twin rate. It can be seen that even in Finland 21% doctors were content with a twin rate more than 10%. (Fig 3.1)

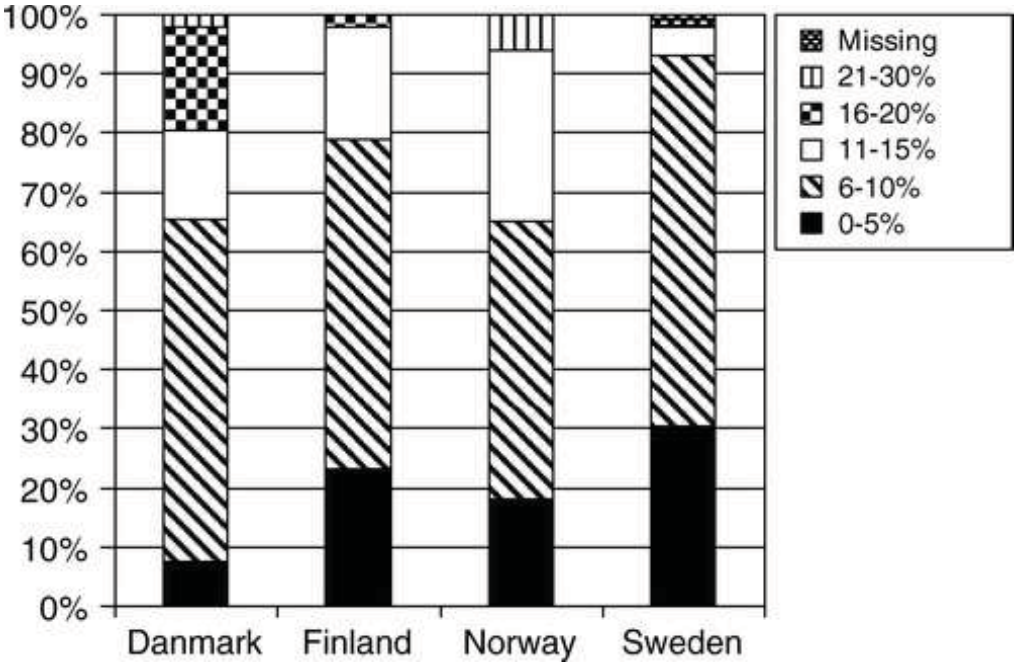


Figure 3.1. The attitude of Nordic IVF doctors towards what is an acceptable twin pregnancy rate after ART. Iceland is excluded, since only one doctor answered the questionnaire. The specific pattern represents acceptable twin rate according to the questionnaire and the size of the piles in the bars represents the percentages of doctors giving the different answers. (Bergh et al, 2007)

The study found that almost all patients under the age of 36 years undergoing the first IVF cycle with two good quality embryos would be recommended for eSET with all the participating doctors. In spite of this, only doctors from Sweden and Finland would recommend eSET for women ≥ 36 years old (Bergh et al, 2007). Analysis of the participant

group shows that the study (Bergh et al, 2007) did not reflect the true perception of the clinicians' because the sample was dominated by mostly by public IVF clinics (51%) and only 30% participants came from private IVF centres. Majority of doctors (53%) were in the age group of 50 and above and only 3% of the participants were in the age group 30 to 39 years. The study found highly significant difference in response between doctors when questioned about recommending elective SET to their patients. Whereas, 100% patients were recommended for eSET in Sweden only 55% patients in Denmark were selected for eSET ($p<0.001$), reflecting the influence of legislation. Although there was a difference in recommendation rates for eSET in all the four countries but there was unanimous consent for SET in women ≤ 36 years in their first cycle with at two good quality embryos. The general positive attitude to recommending eSET for younger women (≤ 36 years) shows the positive attitude of clinicians to eSET which could be a reflection of their daily experience of treating these younger women with eSET which is also shown in their desire to recommend SET for a second time for patients whose cycle failed the first time. However, although a significant proportion of the Swedish doctors were optimistic about recommending SET after two failed cycles in patients' ≤ 36years but almost all doctors from other countries felt the need to transfer two embryos. There was significant ($p <0.001$) positive attitude to SET among female doctors for patients <36 years of age with two IVF failures. There was also highly significant difference between Swedish doctors and others in recommending SET for a second cycle ($p <0.001$) in patients ≥ 36 years old. This study has argued that it's not only clinicians' attitude but patients' outlook; number of cycles reimbursed, the law of the country, the health regulations and also the rate of success at different centres are the factors that influence the number of embryo to be transferred (Bergh et al, 2007).

A survey of Dutch gynaecologists and fertility specialists to explore barriers to eSET found the most frequent barrier to eSET identified by 96 % of the IVF doctors participating was the low level of success from cryopreservation (van Peperstraten et al 2008).. Their perception about twins as not a complication of IVF was the next most common barrier in the endorsement of eSET. Doubts about consequences of full implementation of eSET, uncertainty about eSET technique (lower pregnancy rate per cycle/more cycles necessary with eSET) and low cost-effectiveness of eSET were some of the other dominant factors in influencing the IVF clinicians' attitudes to eSET practise. These clinicians also thought that there were other factors also which play a role in influencing and these were "absence of eSET protocol", "no legislation or leadership stimulating eSET in their country" and also the patients' "unwillingness to consider eSET after they have undergone DET before" apart from clinicians own perception about twin pregnancies as not a complication of IVF and doubts about consequences of full implementation of eSET.

In all 107 IVF doctors participated in the study (van Peperstraten et al 2008) which is a good number which was average response rate of 66 %. The desire for legislation shows how a good number of clinicians wanted a set protocol which they could follow and therefore would not be in a dilemma of choosing the right number of embryos for a patient. This attitude is also reflected in the survey by Bergh et al (2007), where all the Swedish doctors show unanimity for eSET because they have a set protocol and a legislation which help them make their firm decision.These questions of the survey were based on themes identified in a previous qualitative study (van Peperstraten et al.2008). To find the barriers to universal use of eSET van Peperstraten and colleagues (2008) conducted a qualitative study of views of health professionals and patients towards elective single embryo transfer. Nineteen health professionals were

recruited from seven IVF clinics in the Netherlands, a response rate of 95%. Individual interviews were conducted with each health professional to determine factors influencing the choice for SET or DET. Responses were classified into different domains. One domain was "Characteristics of eSET" which included factors such as uncertainty about the eSET technique "…and because of this decrease (in pregnancy rate) per cycle, you give people an extra burden. Because every treatment is an additional burden" (p2037). One factor within the Characteristics of health professional domain was the health professionals' negative attitude towards eSET "I think a twin is not always a drama, for some people it is blessing" (p2038). Within the Characteristics of the patient domain an important factor was lack of patient knowledge "They don't always have the knowledge to make the right decision" (P2039). The final domain identified within the health professionals' responses was Characteristics of the context "I talk to a lot of colleagues around the country and I know that some clinicians care a lot more about the prevention of twins than others" (p2039). Through this study the researchers were able to identify factors influencing decisions about eSET.

One of the strongest points of the study (van Peperstraten., 2008) is that the survey has very explicitly included all the possible factors which can influence attitudes to eSET and which have posed a barrier to the universal use of SET. After factor analysis for two of the domains to remove items which did not load on the domain, an acceptable Cronbach's α value (0.61, 0.62, 0.79 and 0.61) was obtained for each of the 4 domains previously identified as themes in the qualitative research. These domains were the eSET technique (e.g. Lack of prognostic factors and models to determine eSET candidates), the professionals' views (e.g. not perceiving twin pregnancies as a complication of IVF the patients (e.g. patients' desire for twins) and the context of treatment (e.g. Absence of eSET protocol) respectively. The study found that doctors scoring high on

the professional domain rated themselves as less willing to perform eSET. The study surveyed all consultant gynaecologists in the Netherland and doctors involved in fertility treatment which is a strength of the study but the results may not be applicable to settings outside the Netherlands. The second limitation is that the survey asked a hypothetical question about willingness to perform eSET and it was not possible to support this with information about actual clinical behaviour for each individual professional. They have argued that these factors may look different but the dilemma faced by many doctors in the field is not only present in Netherlands but many other countries around the world where there is no set legislation and the doctors are the decision makers for their patients. The second point raised shows that problem when carrying out a sensitive research this, however it is a good and robust research and one of its kind to look into detail the attitudes of the clinicians and the factors influencing these attitudes which can be very useful in understanding the problem from all perspective and providing a better treatment for the patients (van Peperstraten et al 2008).

These studies provides an insight into the problems in universally acceptance of eSET and are a step forward towards recognition of the fact that elective single embryo can only be accepted all over if there is an universal consensus involving both clinicians and patients. Attitude of both patients and clinicians are equally important and of great significance.

3.3 Patients' attitude to eSET and twin pregnancies

Many literatures are available that look into the attitudes of the couples undergoing IVF treatment. Gleicher et al (1995), Goldfarb et al (1996) and Murray et al (2004) all found that although patients were aware of the risks but they were still ready to accept twins. A review looking into infertile couples' attitudes to a multiple birth from their own survey of 68 participants in which none of them had received single embryo transfer,

reported that only 19% of the participants said that their desire for not having single embryo transfer was prejudiced by the desire to have twins. However, the majority (92.7%) and 95% on their male partners said that their decision was influenced by the desire to increase their chance of pregnancy. 'Medical advice' was identified by 91.2% of women and 85% of male partners as influencing their decision to have 2 embryos transferred. The researchers have identified that this survey had its limitation because of being based at only one centre of a fertility clinic and also did not look into couples' perception about the risk of multiple birth. The questions were sent anonymously and at the point of embryo transfer and therefore minimising chances of recall bias (Table 3.1) (Glazebrook et al 2007). The review found that percentage range of patient preference varied from 100% Porter & Bhattacharya. 2005) to 20.3% (Ryan et al 2004), however one study (Goldfarb et al 1996) did not give any percentages but their preference was high on the Likert scale with a mean score of 4.5 on a 1 to 5 scale with 5 being the highest and very favourable.

The review reflects the variations in the measurement of the desire for a twin apart from the diversity in the response. The strongest result from one of the survey done is UK found that 100% of participants were 'accepting the possibility of twins as an outcome of DET'; although the sample size was very small (Porter & Bhattacharya (2005).

Table 3.1 Preferences for a Multiple Pregnancy in Infertile Women (Glazebrook et al, 2007)

Author	Year	No	Country	Question/scenario	Timing of question	Preference for multiple pregnancy
Leiblum et al.	1990	51	USA	% of women responding "would like to have more than one child in a single pregnancy?"	During participation in University hospital IVF program	89.8%
Gleicher et al.	1995	582	USA	% of couples responding "we would have loved to conceive twins"	During treatment or <1 year after treatment	67%
Goldfarb et al.	1996	27	USA	Women's favourability rating for twin outcome	On entry to I IVF treatment program	4.5[+]
Murdoch	1997	150	UK	% of couples responding "one baby" the ideal outcome of IVF treatment	Survey of CHILD support group, 30% of respondents had conceived.	31%
Grobman et al.	2001	200	USA	% of women rating twins desirable or very desirable	Attending infertility clinic, at different stages of treatment	66.5%
Hartshorne & Lilford	2002	20	UK	% of women preferring outcome of blastocyst transfer as higher chance of pregnancy even if same/increased risk of multiple pregnancy	Attending patient support group meeting, majority at least one failed IVF/ICSI attempt	78%
Pinborg et al.	2003	870	Denmark	% of mothers wishing for twins as the first child	IVF/ICSI mothers of twins and singletons gave birth in 1997	62.3% (singletons) 84.7% (twins)
Kalra et al.	2003	90	USA	% of women rating twin pregnancy most desirable outcome	Attending university based infertility clinic	38%

Table 3.1 Preferences for a Multiple Pregnancy in Infertile Women (Glazebrook et al, 2007) (Cont)

Author	Year	No	Country	Question/scenario	Timing of question	Preference for multiple pregnancy
Ryan et al.	2004	449	USA	% of women rating twin/ multiple pregnancy as preferred outcome	New patients at 3 clinical sites presenting with infertility	20.3%
Child et al.	2004	460	Canada	% of women saying twins ideal number with next fertility treatment	Attending university hospital fertility clinic	38.9%
Murray et al.	2004	200	UK	% of couples responding no to "would you prefer a single baby?"	Attending at Assisted Reproduction Unit for first IVF cycle	38.5%
Steures et al.	2005	40	The Netherlands	% of couples wishing to continue even if 100% chance of multiple pregnancy	First visit to gynaecologist for sub-fertility	77%
Blennborn et al.	2005	137	Sweden	%of women having 2 embryos transferred	After embryo transfer	58.8%
Porter & Bhattacharya	2005	12	UK	Number accepting the possibility of twins as outcome of DET	On waiting list for IVF treatment	12
Coetzee et al.	2007	298	New Zealand	% of SET IVF/ICSI cycles	Year following policy change to SET and emphasis on healthy singleton birth	49%
Newton et al.	2007	79	Canada	% of women rating a twin pregnancy as very or extremely desirable	Immediately after fresh embryo transfer	45%

[+] Mean rating (1 very unfavourable - 5 very favourable

The review can clearly divide the studies included in the study into two groups according to their preference for twins. However, majority of the studies have found that their sample had preference for twins. Some studies like Leiblum et al (1990) used sentences “would like to have more than one child in a single pregnancy?” where 89.8% of patients responded positively to this. Similarly, Gleicher et al (1995) found that 67% of their participants from a sample size of 582 responded positively to “we would have loved to conceive twins” and Grobman et al, (2001) where 66.5% rated as desirable or ‘very desirable’. Only 3 studies Kalra et al (2003); Ryan et al 2004 and Child et al (2004), all of which had good sample size varying from 90 to 460, found that their participant patients had negative attitude to twins.

We have looked into some of the studies from the review some of which have been used in developing our research material. In a randomised survey of infertile couples, it was found that although the participants expressed concerns about multiple births independent of the number of multiples, however majority (64%) did not have fear about multiple conceptions. Participants did not consider twins as a risk however higher order pregnancy like triplets (50-62%) and quadruplets (71-72%) were considered a risk by majority of the participants. The majority of the participants expressed a desire for the conception of twins. It was surprising that even after education about the risks of selective embryo reduction, equal number of participants were ready to use it. The desire for twins and triples, however, was correlated significantly with maternal age (twins, P = 0.032; triplets, P = 0.03). The length of infertility was correlated with a positive attitude towards multiples beyond triplets (P = 0.029) but was not correlated with a desire for twins or triplets. Having previous children did not affect the attitude towards multiples at all. This study showed that patients did not perceive twin and multiple births as a complication unlike those associated with providing the medical treatment

(Gleicher et al 1995). This paper is one of the earliest surveys on attitudes of infertility patients and has a large sample.

Another survey which we referred to and pooled items for our research development (Appendix 2- long ATIPS) looked into the attitudes of those women who had given birth to twins after having IVF/ICSI treatment. The study was a register based cohort study which looked into the long term morbidity of all twins born in Denmark after IVF or ICSI treatment. At the time of the study these children were between 3 to 4 years of age. The analysis showed that more (84.7%) IVF/ICSI-twin mothers preferred twins as their first child compared to (62.3%) IVF/ICSI-singleton mothers and non-IVF twin mothers (60.0%). IVF/ICSI-twin mothers had a significantly higher wish for twins (OR = 4.4, 95% CI 2.8-6.9) compared with the non-IVF/ICSI-twin mothers. The positive attitude of the IVF twin mothers is surprising because the study was conducted when the children were 3 or 4 years and these mothers had experience of caring for twins (Pinborg et al 2003). This response was influenced by the fact that it could be the only chance to have a baby, and that “twins are a joy to each other”. Even those IVF/ICSI twin mothers with dead children at the time of study, the ratio between those favouring twins to singletons was much higher at 7:1. As this study was done in the year 1996-1997, when double embryo transfer had just replaced triple embryo transfer in Denmark it could be that this influenced perceptions about twins. Having a set guideline with legislation can sometimes help patients make a decision in the belief that the legislation is there to serve their interest (Pinborg et al 2003).

A study conducted by Blennborn.et al, (2005) on patient and their partners, choosing single embryo transfer and those choosing double embryo transfer found that majority of the participants in both the study groups (SET and DET) were completely satisfied with the information and only a small proportion were ‘less satisfied’ (20%) or ‘not satisfied’ (4%), however, more than a quarter of the whole study population said that they

had not received information about the embryo transfer procedure. Females felt more satisfied with the information about embryo transfer compared to men [106 (83.5%) versus 77 (67.5%); *P*=0.004] and more women said that they had received information about the embryo transfer [113 (83.1%) versus 97 (70.8%); P=0.02]. Females were also more aware of increased medical risks with twin pregnancies than the males [106 (77.4%) versus 90 (65.7%); *P*=0.03]. The midwife was most important for 39.8% of the patients, the IVF physician for 29.7%, the outpatient doctor for 29.3%, and for 35.4% of the patients the individual search for information was the most important source. A strong opinion regarding the possible increased pregnancy chance per transfer with two embryos transferred was almost always present in the groups of patients that chose two embryos, while the group that chose one embryo was more worried about having twins. There was a good knowledge about complications associated with multiple pregnancies. Patients who chose one embryo took more time to decide compared to those who chose two embryos. They said that choosing one embryo was a difficult decision. Of those who had one embryo, more females (36.5%) than males (14.6%; P=0.008) thought it was a hard decision. The most important person in making the decision regarding one or two embryos was the partner. This was particularly true for the one embryo group. The importance of the partner in decision-making was equal among the males and the females in the one embryo group. The study found that for the women participants, woman's age and the physician's advice were more important than the male participants. The males were more concerned about the medical risks of twin pregnancies than the females. When all males and females were compared the difference was significant (P=0.05) (Table 3.2).

A recent review found that the majority of IVF patients and their partners, showed a desire for twins rather than singletons (Leese & Denton, 2010). It also noted that patients have accepted the transfer of two rather than

three embryos as standard practise as success rates of IVF have improved and the risks and consequences of multiple pregnancies are well-documented. This shows a change in attitude of patients and their perception about success. It therefore argued that if patients were offered only SET, it is likely that this would be acceptable as the normal expectation of pregnancy is one baby (Leese & Denton 2010). We could not the full version of the review and therefore cannot comment any further.

Table 3.2 Variables important for decision-making in female and male IVF patients who chose either one or two embryos to be transferred (Blennborn et al 2005)

	Females (n=137)		Male (n=137)	
	One embryo	Two embryos	One embryo	Two embryos
Important or very important				
	n (%)	n (%)	n (%)	n (%)
Previous children	15 (55.6)	11 (42.3)	11 (50.0)	8 (36.4)
Duration of infertility	41 (71.9)	69 (86.3)	33 (58.9)	63 (78.8)
Age, woman (years)	38 (67.9)	68 (85.0)	31 (55.4)	52 (64.2)
Spare embryos to freeze	39 (68.4)	19 (23.8)	38 (67.9)	21 (25.9)
Medical risk, twin pregnancy	21 (36.8)	8 (10.0)	31 (55.4)	12 (14.8)
Pregnancy possibility	49 (86.0)	78 (97.5)	46 (83.6)	77 (95.1)
Physician's advice	50 (89.3)	61 (76.3)	48 (85.7)	65 (82.3)

The study found that women who had one embryo transferred were younger (34.0 years) than those who had two embryos transferred (mean age 36.0 years, *P*=0.0001) and therefore patients with longer duration of infertility chose DET. Previous IVF treatment was significantly associated with choosing two embryos. For majority (80%) patients choosing SET the most important factor was that there was at least one good-quality embryo to freeze unlike the DET group where for only 19% patients possibility of

embryo transfer was the most important factor. Among the male partner, previous IVF treatment significantly [27 (48.2%) vs. 63 (77.8%); P=0.0003] differed between the single and the double embryo groups respectively, similarly, spare embryos to freeze [37 (82.2%) vs. 14 (20.6%); P=0.0001] also differed significantly between the one embryo and two embryo groups respectively.

3.4 Attitudes influenced by the timing of questioning

The earlier mentioned review (Glazebrook et al 2007) reporting on attitudes of couples to a multiple birth have reported on the different points at which the questions about multiple births were asked. Analysis of this data found that there was no influence of the stage of the treatment cycle. In all the three studies which showed that patients had more positive attitude towards singletons, the survey was done when the patients were either attending for treatment [(Kalra et al (2003); Child et al, (2004)] or were starting as new patients (Ryan et al (2004). Similarly out of the 10 studies which were positive about twins some were also like the other group either attending treatment [(Leiblum et al (1990); Grobman et al (2001); Murray et al (2004)] or starting treatment [(Goldfarb et al (1996); Steures et al, (2005)]. However, this review had its own survey at the point of embryo transfer and found that only 19.1% patients wanted twins or their purpose of choosing DET was not influenced by the desire to have twins but as mentioned earlier to raise the chances of getting pregnant (Glazebrook et al 2007).

Clinicians and patients often have to balance the thin line between a good pregnancy rate and a low rate of multiple pregnancies and the associated complications (Van Peperstraten, 2010). Contrary findings of Gleicher, Grobman et al (2001) like, Leiblum et al (1990), found that participants' attitudes to twin pregnancies changed dramatically from more positive to negative when accurate information about complications of twin birth to

the foetus and the baby was given. However some studies have shown that even taking that extra mile in explaining the patients about multiple pregnancies and eSET has not changed the attitudes of the patients. Contrary to Grobman et al (2001), Murray et al (2004) found that using extra and alternative methods of information about the complications of multiple pregnancies did not change the attitudes of patients towards eSET. Patients seemed to be more concerned about decrease in fertility rate with eSET, rather than complications to mother and foetus as a result of IVF treatment. He also found that eSET was not acceptable to most of his participants even after the assurance of a competitive success rate. Murray et al (2004) found that, nearly all the couples in the study were aware of the risks of twin pregnancy and that two third of them preferred a single child, but the prospect of twins did not dissuade them. This finding was after having done counselling for sub fertile patients about the risks of twin pregnancy and the number of embryos to be transferred.

An anonymous study to evaluate patients' attitude towards twins and SET was conducted in a Danish public fertility clinic, where the DET was the common practice, and the number of reimbursed treatments was limited to three. Patients and partners coming to the clinic were given detail both oral and written information about the IVF/ICSI treatment including twin probability following DET and the risk of preterm delivery and neonatal complications associated with twins. In all 414 women and 404 men answered the questionnaire adequately for analysis. The study found that majority about 58.7% preferred having twins to having one child at a time (37.9%). The most important reasons for preferring twins were desire for siblings (23.3%), a positive attitude towards twins (22.5%), and a wish to minimize physical and psychological stress through having as few IVF treatments as possible (19.3%). Interestingly, economic considerations were not important in this group of patients (Højgaard, 2007). These study echoes similar reports by Murray et al (2004) where it was reported that

providing additional information did not change patients' desire for twins. It also shows that these participants as reported earlier considered having siblings as important and similar to '"twins are a joy to each other" (Pinborg et al, 2003).

In a prospective analysis done in Canada, providing risk information increased the desirability of elective single-embryo transfer and decreased the desirability of twin pregnancy among both men and women in women who initially had shown preference for two-embryo transfer (2ET) which was indirectly related to the belief that the chance of pregnancy was higher with DET compared to eSET. This choice however was not related to a specific desire for twins. Information about risks did have an effect on this group of patients. Patient motivations may require tailored information to ensure informed consent (Newton et al, 2007).

A randomised prospective educational study of 110 infertile couples coming for a mandatory single blastocyst transfer (mSBT) found that a 1-page educational summary of comparative risks of twins vs. singletons to maternal and child health improved knowledge and a significant number of subjects changed their desired outcome to a lower gestational number. Simple educational materials can improve knowledge of twin pregnancy risks and affect decision making (Ryan et al 2007). This study has some drawbacks, first of all it was a mSBT, so many will argue that the patient had a pressure on their decision making process.

Although the studies have highlighted a very big concern resulting from the IVF treatment but none of these studies could be measured on a single universal scale that could be used to measure their perception about twins. There are considerable variations in the questions asked and in many studies the choices were hypothetical and the beliefs expressed retrospectively. The lack of a valid scale could be big factor when reporting about the attitude and therefore discrepancies cannot be ruled

out. This research comes to fill that gap by developing a universally acceptable scale which could be easily used in a patient population anywhere in the world. The varied nature of the studies reflect the impact of changes in policy and probably changes in the perception of health professionals delivering infertility treatment and illustrates the importance of assessing the attitudes of health professionals and patients to elective single embryo transfer.

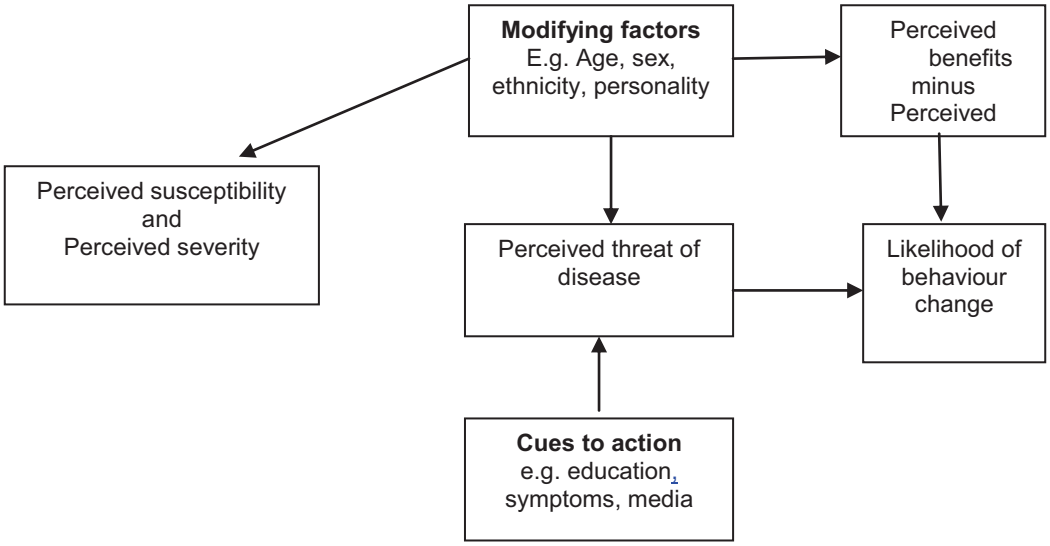
3.5 The Health Belief Model (HBM)

Educational interventions to address patients' beliefs and barriers to eSET can arguably help to increase health protective behaviours such as eSET (Bellamy et al 2004). It is important that the design of interventions to change behaviour should be driven by a theoretical framework. Our research selected the Health Belief Model (HBM) (Becker 1974) which was developed by a team of social psychologists as the best theoretical model for my thesis because it clearly fits in our study model. According to the HBM, the likely hood of someone changing their behaviour is basically determined by the perceived threat of their current situation, coupled with an evaluation of the outcome if they change. Perceived threat is thought to be influenced mainly by the perceived susceptibility to negative consequences and the perceived severity of these consequences for the person. Perceived susceptibility and severity then combine to produce a level of perceived threat that motivates people to take action or change their behaviour. Apart from this a person's own evaluation of the outcome if they change is also important and is affected by perceived benefits and perceived barriers.

This is the only model that clearly recognises the significance of 'cues to action' that will prompt people to change and these cues can be internal such as perceived symptoms or external such as health promotion, advice of a doctor or nurse or illness or death of a known person. It has been

found that cues to action can take many forms. For example, even a short simple physicians' advice can make it more likely for a smoker to quit smoking and remain a non-smoker 12 months later (Ayers & Visser 2011). Health motivation as a factor has been included in HBM lately and relates to how much a person about their health and prepared to consider behaviour change. It has been found that health motivation and cues to action has not been used much at research and therefore not much evidence of their importance. Ayers & Visser (2011) have reported that a study found that health motivation might have a small but significant effect on behaviour. The HBM has been used widely to explain patients' health behaviour and is a useful tool to identify targets for educational intervention and it has also been used to explain health professionals' clinical behaviour, for example adherence to guidelines from preventing antimicrobial resistance (Brinsley et al, 2005). Where health professionals perceive that the risks associated with a twin pregnancy are high and that the patient is susceptible to those risks (perhaps because the patient is young or has previous children) and where the benefits of single embryo transfer outweigh the costs, then arguably the health profession is more likely to suggest eSET (Fig.3.1). For patients an appreciation of the benefits of eSET (e.g. reducing risk of prematurity) and reducing barriers (e.g. an appreciation of the cumulative effectiveness of eSET), together with an understanding the threat from a twin birth based on their susceptibility (e.g. are they under 26 years) and the severity of outcome (e.g. the stress associated with caring for 2 infants) could also increase the likelihood of uptake of eSET. This a useful model in that it provides an excellent framework for the development of information which address the barriers to barrier and increase motivation for behaviour change by promoting the benefits of change and the stimulus to change behaviour (in this case deciding to opt for SET rather than DET).

Figure--3.2 The Health Belief Model (Becker 1974) applied to eSET.



To design interventions and to evaluate the effectiveness of these interventions it is necessary to develop a valid and reliable outcome measure. This study represents the first step in the development of such a tool.

3.6 Aim

To produce a short, valid and reliable measure of attitudes to multiple births associated with IVF treatment, for use with health professionals and couples undergoing IVF treatment.

Objectives

- To develop an *Attitude to Twin IVF Pregnancy Scale* (ATIPS) based on evidence from a literature review of studies of attitudes to
- Reduce the *Attitude to Twin IVF Pregnancy Scale* (ATIPS) from 44 items (Appendix 2)
- To use item analysis to produce reliable and coherent sub-scales
- To establish internal consistency of ATIPS and sub-scales
- To assess readability of ATIPS

- To examine demographic and occupational factors associated with more positive scores on the sub scales

3.7 Method

Participants

Three groups of participants were selected to reflect a range of views about single embryo transfer and the risks and benefits of twin pregnancies. Our sample consisted of medical students, health professionals and UNESCO delegates. This shows the diversity of our group selection. Including medical and non medical professional gave us the ability to identify if the medical knowledge played any role.

Sample 1 Healthcare professionals recruited through a relevant conference or through the Nottingham University Research and Treatment Unit (NURTURE). These consisted of consultants, Senior House Officers, nurses, midwives and researchers interested in multiple pregnancies and involved in obstetrics and gynaecology practise. Some were more specifically associated with infertility and IVF treatment.
Sample2: Medical students in years 1, 3 and 5 of a medical course at one University were recruited to the study.

Sample3: Delegates with an interest in population studies were recruited during a UNESCO conference.

Measure

Attitude to Twin IVF Pregnancy Scale (ATIPS) A 44 item questionnaire (Appendix 2) assessing attitudes to single embryo transfer and perceptions of risk associated with twin pregnancies was framed. Items such as “The best outcome of IVF treatment is a twin pregnancy”, “A twin pregnancy increases the risk of medical complications for the mother during the birth”, “Patients having IVF should be told about the risks of a

twin pregnancy", "If IVF treatment was government funded patients would choose single embryo transfer" were derived from previous research (e.g. Pinborg et al 2003, Gleicher et al 1996) or based on established risks associated with a multiple birth (eg Glazebrook et al 2004) or through expert consultation. Items were rated on a 7 point Likert scale from 1 (strongly agree) to 7 (strongly disagree). The questionnaire was prefaced by a short explanation about current regulations about embryo transfer. The measure also included demographic questions (e.g. age, gender and occupation of the participants).

The scale's items were designed using the guidelines from Kline (2000). The IVF related items associated with risk of twins, use of SET used in the item pool were selected as useful examples and important issues concerning twins born from IVF treatment and the use of single embryo transfer. The items were framed on the basis that, a) There are higher risks associated with twins both for the mother and the child, b) single embryo can help to reduce the high rate of twins c) SET carries low risk because it has more singleton births d) twins carry increased financial and psychological burden for the family. Piloting of the items in terms of readability was done with colleagues based in the department. They were a mix of those who were aware of IVF and those who were not, like the mixed nature of our participants. The readability was measured on the online readability tool and a Flesch Reading Ease Score of a 6th grade with a reading age 12 was obtained for the items.

Procedure

The ATIPS, together with an information letter (Appendix 1) and self-addressed envelope for return was distributed to sample 1 (health care professionals) and sample 3 (conference delegates). The participants in sample 2 (medical students) received the study pack at the end of a lecture. The questionnaires were anonymous. Health professionals were

approached during the RCOG conference on multiple pregnancies at London. The UNESCO conference (UK branch) was held at the Midlands conference centre at the University of Nottingham.

3.8 Ethics approval

Ethics approval for the study was obtained from the Medical School Ethics committee.

3.9 Analysis

The results were analysed using SPSS (Statistical Package for Social Sciences) version 13.0. A probability value of $p<0.05$ was taken as statistically significant. Responses from the three populations were pooled and analysed using item analysis in order to obtain a discriminatory and reliable attitude questionnaire, *Attitude to a Twin IVF Pregnancy Scale (ATIPS).* Associations between demographic and occupational factors and ATIPS scores were examined using stepwise regression analysis. Two ways ANOVA was used to compare ATIP scores between the groups with post-hoc tests.

Sample size calculation

Kline has suggested that 3 participants per item would be an acceptable number (Kline 2000) which would indicate a minimum sample size of 142. Tacbachnick & Fidell (2001) have recommended a minimum sample size of 300 participants for questionnaire development.

3.10 Results

Response rates

A total of 411 questionnaires were returned which comfortably exceeded the minimum requirement as described above. Eight respondents had more than 5 (10%) missing values and were excluded from the analysis (6

medical students and 2 delegates) giving a usable sample of 403. In the health professionals group a total of 141 completed questionnaires were returned of the total 225 distributed giving a response rate of 63%. In the medical student group the usable response rate was 243 of the 400 questionnaires distributed (60.8%). In the conference delegates group 19 completed questionnaires were returned out of 125 packs distributed, giving a response rate of 15.2%.

Sample characteristics

The samples characteristics of the 403 participants are shown in are shown in Table 3.3. Although the response rate of the delegates was low, we still included it because it gave the perspective of the responders who were some experts in studies about population and therefore in a good position to respond to the items of the ATIP scale.

Table-3.3 Demographics of participants

	Medical students (n=243)	Health Professionals (n=141)	Delegates (n=19)	Total (n=403)
Age in yrs (± SD)	23.68 4.30	42.0 9.53	47.5 9.22	31.23 11.6
Male	89 (36.6%)	66 (46.8%)	8(42.1%)	163 (40.4%)
Female	154 (63.4%)	75 (53.2%)	11 (57.9%)	240 (59.6%)
Usable response rate in %	60.8%.	62.7%	15.2.%	53.7%

Item Analysis

Responses for the 44 items were subjected to item analysis and items with high uncertainty (items where more than 30% of respondents had

been uncertain about whether they agreed or disagreed) or poor discrimination (< 10% or >90% agreement) were also excluded. Cronbach's alpha was calculated for the remaining items. Items were excluded if their removal would increase the scale's alpha value. The remaining 12 items, which had good face validity, formed the first subscale (Attitude to risks and benefits of a Twin Birth) (A-Twin). Scrutiny of the items suggested that it was a measure of participants' feelings about the risks and benefits of a twin pregnancy. A similar procedure was performed with remaining items to form a second subscale, Attitude to single embryo transfer subscale (A-SET) which assessed participants feelings about the benefits and costs of limiting the number of embryos transferred.

Risk and Benefits of a Twin Birth Subscale

Twelve items reflecting views on the advantages and costs of a twin birth formed the first subscale. The scale had good face validity and good item-total correlations (>0.3) for 7 items, with a balance of positive and negative correlation coefficients.

The items had Cronbach's alpha of 0.7, which is considered good. Removal of any single item would not have increased the Cronbach's alpha. Possible scores for Risks and Benefits of a Twin Birth Scale ranged from 12 to 84. Higher scores indicate more positive attitudes to twin IVF births. The mean score for the whole sample was 40.12 / 84 (SD = 8.7, range 17 to 69) showing a good range of scores and an absence of floor or ceiling effects. The good Cronbach's alpha indicates that the items had good internal consistency and therefore is reliable. The Flesch reading ease score was 76% indicating that the text would be easily understood by a 12 year old. We could not include the target group for readability score but assessed by The Readability Test Tool the online version which can test the readability.Table-3.4 shows the items included in the Risk and Benefits subscale.

Table-3.4 Risk and Benefits of Twin Birth Subscale with item total correlations

Item	Item-total correlation	Alpha if item removed
The best outcome of IVF treatment is a twin pregnancy.	0.282	0.69
A twin pregnancy increases the risk of medical complications for the mother during the birth	0.412	0.67
A twin pregnancy is bad for the health of the baby.	0.261	0.69
A single pregnancy is better for the woman's body	0.428	0.67
Caring for twin babies is very stressful for mothers.	0.402	0.67
The rewards of a twin birth are worth any risks to the babies.	0.252	0.69
Twin infants are hard to care for.	0.307	0.69
Mothers of twin infants find it harder to return to work.	0.272	0.69
There are plenty of hospital facilities to cope with a twin birth.	0.179	0.70
The best outcome of IVF treatment is a single pregnancy.	0.379	0.68
A twin birth carries very little additional risk to mother and babies.	0.467	0.66
The risks associated with a twin pregnancy are not so great.	0.420	0.67

Single Embryo Transfer (SET) Subscale

Eight items were selected assessing the attitudes to SET. This subscale scale had Cronbach's alpha of 0.53 which has been considered adequate (Bowling, 2005). Like the above subscale, this subscale also showed reliability due to adequate Cronbach's alpha so internally consistent. Although only 2 items had item-total scores above 0.3, none of the items would have increased the scale alpha in that item had been removed. The possible scores ranged from 8 to 56 with higher scores indicating less

positive attitudes to single embryo transfer. The mean score was 34.10 (SD 5.3, range 19 to 56).

Table--3.5 Single Embryo Transfer Subscale with item-total correlations

Item	Item-total correlation	Alpha if item removed
Younger patients should have single embryo transfer.	0.39	0.43
If IVF treatment was government funded patients would choose single embryo transfer	0.213	0.50
A twin pregnancy avoids the need for further IVF treatment.	0.157	0.52
Doctors involved in IVF treatment favour single embryo transfer.	0.204	0.50
Patients undergoing IVF treatment favour single embryo transfer.	0.397	0.43
All patients undergoing IVF treatment should have single embryo transfer.	0.245	0.49
Better to have more treatment cycles than risk a twin birth.	0.245	0.49
The more embryos replaced the better the chance of pregnancy.	0.253	0.49

This indicates a good spread of scores and an absence of floor and ceiling effects (only 1 participant scored 56). As a whole the group is slightly negative towards single embryo transfer as a mean score of 32 would indicate a neutral position on average. The Flesch reading ease score was 60.7% indicating that the text would be easily understood by 13-15 year old students. The Table-3.5 below shows the items of SET subscale.

Comparison between scores on the risks and benefits subscale between groups

A two way ANOVA was carried out with gender and group as the independent factors and the risk subscale as the dependent variable. Results showed a significant effect of group ($F=56.1$, $df =2,400$, $p<0.001$)

but not of gender. Post-hoc tests (LSD) showed medical students had less positive attitudes to twin IVF births than the health professional group ($p<0.001$) and also the UNESCO delegates ($p=0.004$). There was no difference between delegates and health professionals (Table 3.6).

Table-3.6 Mean sub scale scores by group

	Twin Subscale Mean (SD)	SET subscale Mean (SD)
Health professionals	45.74 (7.8)	31.23 (4.7)
Medical students	37.00 (7.5)	35.83 (5.1)
Delegates	42.47 (9.9)	33.26 (3.7)
Total	40.31 (8.7)	34.10 (5.3)

Comparison within the health professional group revealed no significant difference between scores on the risks and benefits subscale for the health professionals involved in IVF treatment (mean=45.8) and other health professionals (mean =45.6). Although health professionals involved in IVF treatment were more likely to agree that a twin pregnancy increased the chance of a premature birth ($X^2=4.38$, df=1, $p=0.036$), nearly 50% of the group disagreed with this statement. Only 27% of non-IVF health professionals agreed that the best outcome of IVF treatment is a twin pregnancy compared to 39% of IVF professionals (Table 3.7). More than 40% of both groups agreed that the rewards of a twin birth are worth any risks to the baby (Table 3).

Table-3.7 Number and percentage of health professionals agreeing with statement

	Health professionals involved in IVF treatment (n=79)	Health professionals not involved in IVF treatment (n=62)
The best outcome of IVF treatment is a twin pregnancy.	31 (39.2%)	17 (27%)
Caring for twin babies is very stressful for mothers.	43 (54.4%)	37 (59%)
A twin birth carries very little additional risk to mother and babies.	30 (48.4%)	32 (51.6%)
The rewards of a twin birth are worth any risks to the babies.	26 (41.9%)	35 (44.3%)
A twin pregnancy increases the chance of a premature birth	42 (53.2%)	22 (35.5%) *

*p<0.5

Comparison between scores on Single Embryo Transfer subscale

Two way ANOVA found significant effect of group (F= 39.79, df=2,400, p<0.001), but not with gender. Medical students had less positive attitudes to eSET than health professionals (P<0.001) and UNESCO delegates (p<0.03). Scores for the single embryo transfer scale did not differ between the health professionals involved in IVF treatment and the health professionals who did not work in IVF treatment.

3.11 Discussion

Developing the long 44 item scale from previously used items in similar studies (Gleicher et al 1996, Pinborg et al 2003) and through expert consultation meant that the most suitable items were put in the scale. The questionnaire had good response rate and comfortably exceeded the minimum requirement recommended (Kline 2000 and Tacbachnick &Fidell

2001). In the health professionals group a total of 141 completed questionnaires were returned of the total 225 distributed giving a response rate of 63%. Although the response rate of the delegates was low, we still included it because it gave the perspective of the responders who were some experts in studies about population and therefore in a good position to respond to the items of the ATIP scale. Important psychometric properties for assuring that the instruments consistently measure the constructs that they were intended to measure are validity and reliability and the analysis of the results have shown that the long scale was validated and measured for reliability.

For the face validity framing of the items was done on the basis that, a) There are higher risks associated with twins both for the mother and the child, b) single embryo can help to reduce the high rate of twins c) SET carries low risk because it has more singleton births d) twins carry increased financial and psychological burden for the family. The readability was measured on the online readability tool and a Flesch Reading Ease Score of a 6^{th} grade with a reading age 12 was obtained for the item which shows that the items were easy to read.

Responses for the 44 items were subjected to item analysis and items with high uncertainty (items where more than 30% of respondents had been uncertain about whether they agreed or disagreed) or poor discrimination (< 10% or >90% agreement) were also excluded to increase the reliability of the scale. This shows that the scale was valid enough to discriminate and therefore the study was in a position to pool out two different scales measuring attitudes to two completely different things (twins and SET). For better reliability, items were excluded, if their removal would increase the scale's alpha value. The remaining 12 items, which had good face validity, formed the first subscale (Attitude to risks and benefits of a Twin Birth) (A-Twin).These 12 items reflected views on the advantages and costs of a twin birth and had good face validity and

good item-total correlations (>0.3) for 7 items, with a balance of positive and negative correlation coefficients. The items of the scale had good Cronbach's alpha of 0.7 indicating that the items had good internal consistency and was therefore reliable. The mean score for the whole sample was 40.12 / 84 (SD = 8.7, range 17 to 69) showing a good range of scores and an absence of floor or ceiling effects. The Flesch reading ease score was 76% indicating that the text would be easily understood by a 12 year old. The other remaining items which had good face validity and inter-item correlations, together (eight) formed the second subscale. The Attitude to single embryo transfer subscale (A-SET) which assessed participants feelings about the benefits and costs of limiting the number of embryos transferred showed adequate correlation between the items (Cronbach's alpha of 0.53) and therefore was independently reliable also. The mean score of 34.10 (SD 5.3, range 19 to 56) indicates a good spread of scores and an absence of floor and ceiling effects (only 1 participant scored 56). The Flesch reading ease score was 60.7% indicating that the text would be easily understood by 13-15 year old students.

This, first part which involved development of the scale from previous literatures and piloting experts has proved to be reliable by being internally consistent and the measure also showed validity by discriminating between the groups. Health professionals were more positive about twin birth than medical students which accords with opinion pieces in the published in the medical literature for example, [(Gleicher & Barad, (2006) ; van Wely et al (2006)] have argued that because most twin births are uncomplicated and because infertile couples prefer twins, a twin pregnancy should not be seen as an adverse outcome. The medical students who were comparatively less positive perhaps because they were relying on their knowledge of risks associated with multiple pregnancies rather than clinical experience with infertile couples. These

medical students had significantly higher scores on the risks and benefits subscale than the qualified health professionals suggesting that they were more aware of the risks associated with twin pregnancies despite their relative lack of experience. The conference delegates were on average two points less positive about twins than this failed to reach statistical significance, probably reflecting a lack of statistical power resulting from the small sample size in the delegate group.

Analysis of the scale (Table-3.6) brought a few predictable but some more surprising outcomes. Although health professionals involved in fertility treatment were more likely to perceive that a twin birth increased the chance of prematurity, more than 40% still disagreed with the statement. Further examination of individual items revealed that health professionals involved in IVF treatment varied in their views about the risks and benefits of a twin birth. Nearly 60 % of the health professionals actively involved in caring for twins did not consider twin birth as the best outcome of IVF treatment. The majority (54.4%) of IVF professionals considered caring for twin was stressful similar to some of the recent studies that have shown that twin mothers are more stressed not only due to caring for two infants at the same time but also their chances of returning to work is bleak compared to singleton mothers (Glazebrook et al, 2004). This causes a financial burden to the family and also increases the stress level in an already stressful environment. All these certainly have an impact on the psychology of these families. Nearly half of the participants agreed that twins carried only little additional risk to mothers which correspond with similar findings by Campbell & Templeton (2004). Although the majority of health professionals did not agree with the item that a twin birth is worth any risk (Table 3.6), an equally high proportion did think that the risks were worth taking which reflects the fact that these health professionals are also aware of the trauma caused by prolonged infertility and similar findings was reported by a study by Gleicher et al, (2009) which argues

that although the main aim of an IVF treatment is having a successful conception but when an opportunity of completing the family at one go is available both clinicians and patients feel positive about twins (Gleicher et al, 2009). This is also reflected in the analysis of the study output where, even health professionals not involved in IVF treatment (27% see Table 3.6) think that a twin pregnancy is the best outcome of an IVF treatment. ATIPS identifies perceptions of risk associated with a twin birth and barriers to eSET and so could be used to identify need for education and training. Interventions based on the Health Belief Model (Bellamy, 2004) could be effective in addressing some of the barriers to implementation of eSET.

The fact that 39% of the doctors involved in IVF treatment in this study considered that the best outcome of IVF treatment was a twin pregnancy shows the scale of the attitude change needed. Earlier studies have contradicted themselves. It has been suggested to perceive only those IVF twin births which do not have a good prognosis as a complication, and not all IVF twins in general (Wely et al., 2006). As mentioned earlier, that although some clinicians perceive twin birth as a complication they were certainly not comfortable with randomising eSET for all IVF patients (Porter & Bhattacharya, 2005). Van Peperstraten and colleagues, (2008; 2008) also highlighted contextual and professional barriers to implementation of eSET.

This study is based on the HBM model which is very widely used in many health based researches. Not many researchers have reported on health motivation and cues to action and therefore the evidence is limited. Ayers & Visser (2011) have reported that a study found that health motivation might have a small but significant effect on behaviour. ATIPS scale also provides a step forwards understanding this gap in the Health belief model.

Strengths and weaknesses of study

The study response rate was over 50% which is moderate but the sample size could be considered to be large which is important in item analysis (Kline, 2000). The analysis of the cross sectional study helped us to develop a scale that would measure the perceived benefits and barriers to eSET and perceptions of risk associated with a twin pregnancy. As it was an anonymous survey the chances of biased reports are less unlike focus group interviews and one to one interview where the chances of leading and prompting the participants are quite high.

The aim of this study was to develop a measure that had reliability and was valid. This measure seems to be a reliable method of measuring the attitudes in the Risk and benefits subscale which had a good Cronbach's alpha 0.7 and also the Single embryo transfer subscale with a satisfactory Cronbach's alpha of 0.53 (Bowling, 2005). Both these subscales were developed after grouping together items which had good item total correlation and good inter item correlation. The scales have a good spread of scores and an absence of floor and ceiling effects suggesting that the scale would be useful outcome measure to detect changes in attitudes and to compare groups. The scales have good face validity in that they seem to measure perceptions about the risks and benefits of a twin pregnancy and attitudes to single embryo transfer respectively. The readability of the subscales items at 6th grade of Flesch Reading Ease Score which increases the ability of the participants to understand. The scales are comprehensible to people who are not experts in IVF treatment, with a reading age around 12 years but more research is needed to see if they would be suitable for use will lay people and patients undergoing IVF treatment.

Conclusion

This present study acts as a bridge to cover this vacant area of the current debate by developing a valid and reliable scale which can be used as a universal platform for measuring the attitudes of healthcare professionals and patients of IVF. This study is the first part of the development of the ATIP scale which we have seen to be reliable and valid enough to discriminate between different groups. However, for using it universally, testing the scale in a patient population is important and our next study (Chapter 4) focuses on this.

COMPATIBILITY OF THE ATIP SCALE IN A PATIENT POPULATION

4.1 Introduction

Despite the growing evidence of the risks of a twin birth and the increased success of elective single embryo transfer (eSET) programs (Saldeen & Sundstrom 2005), the transfer of two embryos is still routine practice in most UK and USA clinics (Braude & Muhammed 2003; Reynolds & Schieve 2006). One frequently quoted argument in the long running debate about embryo transfer has been that prospective parents want a twin birth and in support of this a recent review of the literature found that in eight of the 13 studies reviewed couples favouring a multiple birth were in the majority (Glazebrook, et al. 2007). There is growing evidence, however, that rather than actively desiring a twin birth couples perceive their chance of pregnancy as increased after double embryo transfer (Murray, et al. 2004; Porter & Bhattacharya 2005; Newton et al. 2007). Studies have explored attitudes towards multiple birth and single embryo transfer at different time points and this may have had an impact on their findings. For example, one might expect women who had conceived twins after IVF treatment to prefer twins and disagree with single embryo transfer (SET) compared to IVF mothers of singletons or mothers of naturally conceived twins (Pinborg, et al. 2003).

Although there is widespread condemnation among clinicians of a multiple birth beyond twins, attitudes towards twins appear less clear cut. Van Wiley and colleagues argue that typically twin pregnancies result in the successful birth of two babies and should not be seen as an adverse outcome (van Wely et al. 2006). However a recent survey of Nordic IVF doctors found almost all thought twins was a less favourable outcome than a singleton pregnancy (Bergh et al. 2007). Given that advice from their physician is reported by couples as strongly influencing their decision about the number of embryos to transfer (Blennborn et al. 2005;

Glazebrook et al. 2007), measures which reliably explore clinicians' attitudes are needed.

Studies have found a number of factors including mother's age, parity, length of infertility and knowledge of the risks of a multiple birth affect expressed attitudes towards a multiple birth (Grobman, et al. 2001; Ryan et al. 2004). Such findings have prompted researchers to try to influence attitudes towards multiple births and eSET using informational and educational materials about the associated risks (Hartshorne & Lilford 2002; Newton et al. 2007; Ryan et al. 2007). To date research in this area has used quite lengthy questionnaires developed for each individual project. Couples have been asked to rate risk, to rank their preference for different treatment outcomes or even to indicate their preference for hypothetical choices (Borkenhagen, et al. 2007; Hojgaard et al. 2007; Ryan et al. 2007). The previous study (study 2, chapter 3) developed a 20 item attitude questionnaire with 2 subscales assessing attitudes to a twin birth and to single embryo transfer. The scales had adequate internal consistency, a good spread of scores and discriminated between medical student and clinicians. In the present study we will seek to explore the reliability of the measure further, to explore whether the measure is acceptable and a valid tool for use with patients and to compare attitudes of patients and staff in the same group of clinics using a standardised measure. The aims of the study are to evaluate the use of a standardised attitude questionnaire originally developed for use with health professionals in a sample of patients undergoing IVF treatment and clinicians. Secondly the study aims to compare attitudes of patients to those clinicians involved in IVF treatment.

4.2 Aims

- To see if ATIPS is valid and reliable for use with IVF patients
- To assess attitudes to twin births and eSET
- To compare attitudes of health professionals and patients

- To explore factors influencing attitudes of patients undergoing IVF treatment

4.3 Method

Study design and Participants

The study was a cross sectional survey of IVF clinicians and patients attending one of the UK's largest independent fertility clinics. Ethics approval was given by the clinic's internal review committee. In total 17 IVF clinicians involved in IVF treatment at the fertility clinic who attended an internal medical meeting on 13th January 2007 were asked to complete the questionnaire. There were no exclusion criteria. IVF clinicians were only considered because we had included combination of healthcare professionals involved in providing service and caring for twins and multiple births. It was therefore a good idea to have separate evaluation of the group who are the major decision makers for the patient groups.

All female IVF patients and their partners visiting the clinic for treatment between June 2007 and May 2008 were eligible for inclusion in the study. There were no exclusion criteria. The target sample size was 100 completed questionnaires from female patients and their partners based on less than 10% error with 95% confidence (http://relevantinsights.com/research-tools).

Measures

*Attitudes to Twin Pregnancy Scale (ATIPS) (*Appendix *2b)*

This questionnaire was initially developed to assess the attitudes of health professionals towards twins and SET (Rai & Glazebrook 2007) (see chapter 3 for a for full description of the scale development)**.** Informed by research literature, expert opinion and HFEA publications, 44 statements were generated. Participants were asked to indicate the extent to which

they agreed with each using a Likert scale from 1 to 7 with 1 indicating "I strongly agree" and 7 indicating "I strongly disagree". The scale was piloted with health care professionals interested or actively involved in obstetrics, gynaecology or multiple pregnancies, as well as medical students from one UK medical school and delegates interested in population studies attending an UNESCO conference. The 411 completed questionnaires received from health professionals (n=141), medical students (n=249), and delegates (n=21) were subjected to item analysis which was used to reduce the scale to 20 items consisting of two sub-scales: the 12 item Risks and Benefits of a Twin Birth subscale (A-Twin) and the eight item Attitudes Towards Elective Single Embryo Transfer (A-SET), both assessed using the Flesch-Kincaid grade level as having item readability appropriate for readers of 12 years and younger.

Risks and Benefits of a Twin Birth subscale (A-Twin)

The 12 statements comprising this scale are phrased to reflect both the positive benefits and negative risks of a twin birth, with scores reversed where appropriate so that higher scores reflect a more positive attitude towards a twin birth. Scores for each statement are summed to give a possible range from 12-84 from least positive to most positive to twins. See chapter 3 (Table 3.3) for study items and scoring. The scale had been found to have good internal consistency (Cronbach's alpha=0.7).

Attitudes towards Embryo Transfer subscale (A-SET)

This scale comprises eight statements all except one which is reversed for scoring, reflecting a positive attitude towards single embryo transfer. Scores are summed to give a possible range from 8 to 56 with higher scores indicating a less positive attitude towards SET. See chapter 3 (Table 3.4) for study items and scoring. The scale was shown to have satisfactory internal consistency (Cronbach's alpha=0.53).

Demographic Questionnaire

Both IVF clinicians and patients were asked to complete a short demographic questionnaire. In addition patients were asked about their infertility treatment and history.

Procedure

Questionnaires were distributed to IVF clinicians attending a medical meeting at the IVF clinic. These were completed and given back at the end of the meeting. Clinic receptionists were asked to distribute questionnaires to all male and female patients in the clinic waiting room at one East Midland's clinic. These were returned in the freepost envelope provided either the same day or after completion at home. Patients were given a pack containing information sheets for themselves and their partners and questionnaires which they were asked to complete and return in the freepost envelope provided.

4.4 Ethics

The study was approved by the internal ethics committee at CARE. The questionnaires were anonymous and consent was assumed by questionnaire completion. Each questionnaire had a covering information letter which explained the purpose of the study, the fact that participation was voluntary, and reassurance that their care would not be affected if they decided not to participate.

4.5 Analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 15.0, with a P value of <0.05 considered significant. The subscales were explored for internal consistency and item-total correlations were calculated.

4.6 Results

We explored the internal consistency of both the subscales. Internal consistency for the A-twin subscale was good with Cronbach's alpha of 0.88 for the total sample of patients, partners and clinicians (n=138). All 12 items in this subscale had an item-total correlation which was greater than >0.35 (Table 4.1). Scores for the total sample showed a good range of scores (15-71) with no obvious floor or ceiling effects.

Fig 4.1 Item total correlations. A-Twin scale

	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
q1 recoded	.595	.870
q2 twin pregnancy increases the risk of medical complications for the mother during the birth	.512	.875
q4 A twin pregnancy is bad for the health of the baby	.673	.865
q8 A single pregnancy is better for the woman's body	.708	.863
q9 caring for twin babies is very stressful for mothers	.651	.866
q11 recoded	.376	.882
q12 Twin infants are hard to care for	.680	.864
q13 Mothers of twin infants find it harder to return to work	.588	.870
15 recoded	.462	.877
q16 The best outcome of IVF treatment is a single pregnancy	.546	.874
17 recoded	.634	.868
19 recoded	.525	.874

However internal consistency for the 8 items of the A-SET was unsatisfactory. Scrutiny of the results suggested item-total correlations were poor for two items and removal would improve internal consistency. They were "The more embryos replaced the better the chance of pregnancy" and "A twin pregnancy removes the need for further IVF

treatment". These items were removed and Cronbach's alpha for the new 6 item A-SET subscale recalculated. For the total sample (n=138) Cronbach's alpha was 0.81 and the item-total correlation was >0.4 for all 6 items. Internal consistency was excellent for both the patient group (0.81) and the IVF clinicians (0.82). Item-total correlations exceeded >0.42 for each of the 6 item (Table 4.2). The six item subscale was therefore used for all the remaining analyses. The lowest score was 17 indicating that no participant was extremely positive about eSET. Four female patients had maximum scores (42) indicating that they were extremely negative about eSET.

Fig 4.2 Item total correlations-A-SET scale

	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
q3 young patients should have single embryo transfer	.652	.772
q5 If IVF treatment was government funded, patients would choose single embryo transfer	.587	.791
q7 Doctors involved in IVF treatment favour single embryo transfer	.420	.819
q10 Patients undergoing IVF treatment favour single embryo transfer	.584	.789
q14 All patients undergoing IVF treatment should have single embryo transfer	.653	.789
q14 All patients undergoing IVF treatment should have single embryo transfer	.639	.775

Examination of the distribution of the two subscales showed that while the A-Twin was normally distributed for both the patients and IVF clinicians, the A-SET was not normally distributed for the patients and so non-parametric analyses, which do not assume normal distribution, were used for analysing their scores on the A-SET subscale.

Response rates

Clinicians' response rate was 100% with all clinicians returning their questionnaires. The target sample size of 100 female patients was met within the study period. The estimated response rate was 50% of patients who received a questionnaire during the period of the study.

Twenty-one male partners also returned questionnaires during the study period. There were no significant differences between the male and female patients' subscale scores for the A-Twin or the A-SET and so to avoid over representation of the views of couples when both partners had responded only female patients' data were analysed to explore factors influencing attitudes to single embryo transfer and twin pregnancies.

Table 4.3 Demographic characteristics of female patients

	n=100
Mean age (range)	35.9 (27-47)
White European	95
Black/ Black British	1
Other	4
Married / cohabiting	99
Divorced/ separated	1
Highest level of education* Degree level or higher	53 (54%)
Occupation** Managerial or professional	40
Children	33
First cycle of IVF	26
Mean number of previous IVF cycles if applicable (range)	3.5 (1-13)

*information missing for 2 participants**information missing for 1 participant

Female Patients

The women were in their mid thirties, predominantly white European and all except one were married or living with a partner. Forty percent were in managerial or professional occupations and the majority were educated to degree level or beyond. Only a minority of women 26% were having their first cycle of IVF and a third had children already (Table 4.3).

Scores for the A-Twin showed a slight bias towards negative attitudes towards twins (mean = 43.25 / 84, SD=11.45) since a sample mean of 48 would indicate that on average women had scored at the mid point indicating neither agreement nor disagreement. Exploration of responses to some of the individual statements making up the scale revealed that while 59% of the women agreed that the best outcome of IVF is a twin pregnancy, review of other questions suggested many did appear to recognise some of the risks for the mother. Eighty four percent of women agreed twin pregnancy increases the risk of medical complications for the mother during the birth and 70% agreed that caring for twin babies is stressful. However, only 30% agreed that a twin pregnancy is bad for the health of the baby and only 38% felt that it would be harder for a mother of twins to return to work.

A number of factors previously found to influence attitudes towards twins were explored. Age was not significantly correlated with the A-Twin subscale. Women who were educated to degree level or higher, or had managerial or professional occupations were not significantly less positive towards twins (Table 4.4). However, women with no previous children were significantly more positive about twins than women with previous children ($t=2.21$, $n=100$, $p=0.031$). Women having their first cycle of IVF were significantly less positive about twins than women on their second or subsequent cycle of IVF ($t=2.52$, $n=100$, $p=0.013$), (Table 4.4).

Table 4.4 Factors influencing A-Twin scores

		Mean	SD	P value
Group	IVF clinicians (n=17)	27.94	7.96	**<0.001**
	Female patients (n=100)	43.25	11.45	
Education to degree level or higher*	Yes (n=53)	42.40	12.07	0.305
	No (n=45)	44.78	10.53	
Managerial or professional occupation*	Yes (n=40)	42.65	12.45	0.655
	No (n=59)	43.71	10.91	
First IVF cycle*	Yes (n=27)	38.63	12.45	**0.013**
	No (n=73)	44.96	11.75	
Previous children*	Yes (n=33)	39.48	12.61	**0.031**
	No (n=67)	45.10	10.44	

* Female patients only

These findings are further supported by responses to the statement the best outcome of IVF treatment is a twin pregnancy with 65.7% of women without children agreeing compared to 45.5% of those with children but this difference was not significant. More women with children were also more likely to agree that a twin pregnancy is bad for the health of the baby (39.4% compared to 25.4%), although again this failed to reach significance. Parents with children were significantly more likely to recognise that a twin birth would make it harder for them to return to work (57.5% vs. 28.4%; X^2= 8.1, df=2, p=0.017).

Table 4.5 Factors influencing A-SET scores

		Mean	SD	P value
Participants	IVF clinicians (n=17)	25.88	6.36	**0.001**
	Female patients (n=100)	32.04	6.04	
Education to degree level or higher*	Yes (n=53)	32.21	6.09	0.963
	No (n=45)	32.09	5.98	
Managerial or professional occupation*	Yes (n=40)	31.83	5.90	0.650
	No (n=59)	32.17	6.22	
First IVF cycle*	Yes (n=27)	28.15	5.52	**<0.001**
	No (n=73)	33.48	5.59	
Previous children*	Yes (n=33)	31.03	6.48	0.295
	No (n=67)	32.54	5.79	

* Female patients only

The A-SET subscale was positively correlated with the A-Twin (r=0.544, n=100, p=<0.001) indicating that more favourable attitudes towards twins were associated with more negative attitudes towards eSET. Scores on this A-SET scale reveal very unfavourable attitudes towards single embryo transfer (mean = 32.04/42, SD=6.04). This attitude is clearly revealed in the responses to individual statements with only 5% agreeing that patients favour single embryo transfer and only 2% agreed that all IVF patients should have single embryo transfer. Older women had less positive attitudes towards eSET although this did not quite reach significance (r=0.18), n=100, p=0.076). This is supported by the finding that 24% of women agreed with the statement “younger patients should have single embryo transfer”. Women with previous children were not significantly more positive about single embryo transfer. However, women who were having their first IVF cycle were significantly more positive about single embryo transfer (z=3.94, n=100, p=<0.001) (Table 4.5). Experience of

fewer previous cycles of IVF was also associated with significantly more positive attitudes towards eSET (r=0.31), n=100, p=0.002).

IVF Clinicians

Only three (17.6%) of the IVF clinicians who completed the questionnaire were female. The majority of the clinicians had extensive experience of IVF with 58.8% having more than twenty years experience (range 5 to 30). IVF clinicians' scores on the A-Twin are low (mean A-Twin = 27.94, SD=7.96) indicating that, as a group, they recognise the risks associated with a twin birth. This is further illustrated by their response to some of the individual statements with 100% agreeing the best outcome of IVF treatment is a single pregnancy and over 80% agreeing that caring for twins is stressful and that it will be harder for the mother to return to work. Interestingly they seem a little more ambivalent about the risks for the babies themselves with 17.6% agreeing the rewards of a twin birth are worth any risks to the baby and 23.5% that the risks associated with a twin pregnancy are not so great.

Comparison with the female patients' scores on the A-Twin reveal that the IVF clinicians have significantly less favourable attitudes towards twins than the patients (t=5.29, n=117, p=<0.001) (Table 4.4).How IVF favourable clinicians are towards twins does not appear to be related to either their age or number of years of experience: both correlations were non-significant.

Scores on the A-Twin correlate significantly with IVF clinicians' scores on the A-eSET (r=0.611, n=17, p=0.009) indicating that the less they favour a twin birth the more they favour single embryo transfer. However, their scores are relatively higher than their scores on the A-Twin (mean A-eSET= 25.88, SD=6.36) indicating they are not as expressive of positive attitudes towards eSET as they are towards a single pregnancy. Responses to individual statements reveal some of the conflicting

attitudes towards eSET; for example although 64.7% agree young patients should have eSET only 17.6% agree that all patients should have eSET. Moreover, less than half (41.2%) agree it is better to have more treatment cycles than to risk a twin birth. IVF clinicians perceive their colleagues as not favouring SET with only 23.5% agreeing doctors involved with IVF favour SET. They also regard patients as very against single embryo transfer with only 11.8% agreeing patients favour eSET. Scores on this subscale do not correlate significantly with either the clinician's years of experience or their age. IVF clinicians have significantly more positive attitudes towards eSET than female patients ($z=3.54$, $n=117$, $p=0.001$) (Table 4.5). However, they do not have significantly more favourable attitudes towards eSET than female patients having their first cycle of IVF (mean score 25.88 Vs 28.15, $z=1.22$, $p=0.22$).

4.7 Discussion

The study showed that a questionnaire originally developed for use with health professionals was acceptable to both IVF patients and clinicians in terms of ease of use and understanding and was able to detect differences within and between the two groups. The subscale assessing perceptions of risks and benefits associated with a twin birth had excellent internal consistency and each item had good item-total correlations. Removing two items from the A-SET scale resulted in excellent internal consistency for that scale too. Item-total correlations were also strong. The scales were also able to discriminate between health professionals and parents, with parents being substantially more positive about twin births and more negative about eSET compared to clinicians. This supports the validity of the scales and suggests that the two sub-scales could become a useful resource for exploring attitudes towards twin births and single embryo transfer. Validity is further demonstrated by the fact that, as expected, women with previous children were less positive about twin

pregnancies compared to childless patients and women on their first cycle of IVF treatment were more positive about single embryo transfer.

IVF clinicians who took part in this study were not in favour of a twin birth despite some clinicians arguing that a twin birth should not be seen as an adverse outcome, similar to many other studies (van Wely et al. 2006, Gleicher & Barad, 2009.). Female IVF patients did hold quite favourable attitudes towards a twin birth and were significantly more in favour of a twin birth than the clinicians. Examination of responses to the individual statements indicates both the IVF clinicians and the female patients seemed to be underestimating the risks of a twin pregnancy to the baby in comparison to the mother. Providing couples with more information about the potential risks to the babies may be an effective strategy to change their attitudes towards a twin birth as they appear knowledgeable about the risks for the mother and prepared to accept these. Given that, as already mentioned, advice from their physician is reported by couples as strongly influencing their decision about the number of embryos to transfer (Blennborn et al. 2005; Glazebrook, et al. 2007) this advice may be best received from clinicians. However, clinicians themselves may need to be provided with additional evidence about the possible risks of a twin birth for the babies, such as, for example, the problems associated with a vanishing twin; a Danish study found one in ten singleton deliveries had originated from a twin pregnancy (Pinborg et al. 2005). Other studies have reported a lower foetal loss rate in the first trimester in ICSI patients due to vanishing twins. They further reported a higher live birth in pregnancies associated with vanishing foetuses (Mansour et al, 2010). Although the ratio of vanishing twins in IVF/ICSI pregnancy is similar to any natural pregnancy where the ratio reported is 1 in 8 (Hall 2003), it is evident from (Chapter 1) that the implantation rate and the successful pregnancy rates from IVF/ICSI treatment has increased over the years and so also the rates of twins. The rate of implantation is further on the rise with blastocyst transfers and better understanding of the uterine implantation. This

produces a vicious cycle of better implantation, a higher live birth rate but also more vanishing twins. Shebl et al, (2008) found that survivors of the vanishing twin syndrome were at a higher risk of lower birth weight and of being small for gestational age. Pregnancies from vanishing twins needed careful and constant monitoring which can often be stressful for parents and can increase the anxiety level of the IVF patient along with increased use of health services resources. These parents should therefore be informed about the associated risks when transferring more than one embryo (Shebl et al, 2008).

Although some earlier studies have reported finding a more favourable attitude towards a multiple birth was associated with increased age in female IVF patients (Gleicher, et al. 1995; Grobman et al. 2001) this study did not find a significant correlation. However, in accord with previous studies (Gleicher et al. 1995; Grobman, et al. 2001; Child, et al. 2004; Ryan, et al. 2004) parity and previous cycles of IVF were associated with a more favourable attitude towards twins. This may reflect the desire for an instant family. For IVF clinicians neither age nor years of experience were associated with more favourable attitudes towards twins. Given the increasing research and publicity about the risks of a twin birth one might have expected younger and less experienced clinicians to have less favourable attitudes towards a twin birth but these clinicians seem to be more influenced by their day to day experience of treating infertility patients. However, the sample was small and most of the clinicians were very experienced.

Female IVF patients did not express very favourable attitudes towards single embryo transfer (SET). Although younger women were more in favour of SET this did not reach significance. This attitude was reflected in their response to individual statements with nearly a quarter of women agreeing with the statement “younger patients should have single embryo transfer”. Women having their first cycle of IVF were significantly more

positive about SET than women who had had previous cycles and this is in accord with the finding that experience of fewer previous cycles of IVF was associated with significantly more positive attitudes towards SET. These findings suggest that women having their first cycle of IVF may be most receptive to education about SET or interventions to promote SET.

IVF clinicians are, like the female IVF patients less positive about SET than they are towards a single pregnancy. However, they are significantly more positive about SET than the female IVF patients. Of interest is their response to individual statements which show they do perceive IVF patients as being negative about SET with only just over 10% agreeing patients favour SET. Clinicians also perceive their colleagues as against SET with less than a quarter agreeing doctors involved with IVF favour SET. These findings suggest a need for considerable intervention and education in order to change these attitudes, especially considering there was no correlation with years of experience or age.

The HBM argues that the likelihood of carrying out protective health behaviour, such as single embryo transfer, is increased if the benefits outweigh the barriers and the person feels a sense of threat associated with the outcome: in this case twins. The results of this study suggest that patients underestimate the threat associated with a twin birth, particularly for the baby. They also have low appreciation of the benefits of a single birth. Patients undergoing IVF receive information on the risks of a twin birth but this research suggests more emphasis could be placed on the risks to the infants. Another strategy, based on the health belief model would be to provide information on the advantages of a single birth, such as the economic and health advantages.

Strength and weakness of the study

This study is the only work to use a valid and reliable measure to assess attitudes to twin IVF pregnancies and single embryo transfer. A limitation

is that it sampled clinicians and patients in only one infertility service. However, this group is one of the leading providers of IVF treatment in UK with 11 clinics spread across England. Both, the clinical pregnancy rate (42.4 % vs. 35.7%) and live births (42.1% vs. 32%) at this centre are above the national average rate in women below 35 years of age. This trend is reflected in other groups of patients as well. It would be useful to compare responses from different centres in order to explore factors associated with more positive attitudes to single embryo transfer. The questionnaire was anonymous which is likely to have enhanced the validity of the responses; however it also meant that it was not possible to determine how representative the sample was. We were also not able to get the participant women to comment on the acceptability of this measure because the Clinic's ethics committee had not given us the permission to talk to any patients. The questionnaire was piloted in a small non-clinical group. Another limitation of the study was its cross-sectional design. In order to further evaluate the validity of the measure it would be useful to use the measure to predict patient choices or clinical decisions.

Conclusion

Patients have more positive attitudes to a twin birth and are more negative about single embryo transfer than clinicians in the same service. However, both clinicians and patients were less likely to endorse the risks for the infants associated with a twin birth. The women also failed to recognise the social impact of a twin birth. As patients are particularly negative about single embryo transfer this suggests that interventions could focus on promoting the effectiveness of single embryo transfer and its advantages for infant health. ATIPS (see detail development in chapter 6A) seems to be a reliable scale that can be used internally and externally to measure attitudes towards risks and benefits of twin IVF births and also attitudes to Single Embryo Transfer in IVF treatment. There is no other validated scale like ATIPS that can be used universally in assessing

attitudes towards twins and single embryo transfer and ATIPS could prove a useful tool for evaluating interventions to promote single embryo transfer and for evaluating service factors associated with high rates of twin IVF conceptions.

The need of a decision aid for use in IVF patients is another important thing which needs to be looked into because of the more frequent use of informed decision making in all fields of medicine and recent recommendation by Van Peperstraten et al, (2010). There is need for intervention and this can be done by a DA. Use of a decision aid will have more involvement of patients and their partners in deciding about the number of embryos to be transferred and will also have more say in their treatment, apart from the awareness of the latest developments and success rate. This ATIP scale can then be used before and after the decision aid, given during IVF treatment.

It will be interesting to see if at all any change in attitudes of these IVF patients towards risks and benefits of a twin birth and elective single embryo transfer with the use of a decision aid and the influence it would have from the current practise. Our next step in the study focuses on the development of a decision aid (Chapter 5) and its randomised use. The same study uses the ATIP scale before and after the use of the decision aid (Chapter 6) and looks into the influence it has on the attitudes of the participants, if any.

DECISION AIDS

5.1 Introduction

Decision aids (DAs) are means to help patients understand their treatment, the options available and the need to make an informed choice. DAs are targeted to improve and support decision making by supporting the capability to educate patients. A DA also has the potential to highlight the benefits and risks of the options available to patients in addition to helping patients consider the personal importance they place on each of the options available (Connor et al, 1999). This is important when there is a decision to be made, either because more than one option is available or because different treatment options could be suitable for different patients. In an ideal situation the most expected outcome in clinical decision making should be to select a service that increases the chances of quality health outcomes while simultaneously decreasing the undesired outcome. A DA can be used in a complex situation where patients are perplexed by the treatment choices open to them in order to enable patients to judge accurately the costs and benefits of alternative options (Claire et al, 2007).

DAs are tools built around evidence based medicine to help patients make a decision regarding the choice of treatment after being made aware of all the information and any consequences of the treatment. An impactful decision aid should have the benefits, harms, the scientific uncertainties and options of treatment available (Graham et al 2007). The aim of a decision aid should be to improve “decision making” and the quality of the decision and to supplement counselling or consultation with the clinician but not to replace it. A DA should, therefore, cover the most important unanswered worries associated with the treatment or test and demonstrate relevant evidence based facts to support decision making. This would not only reduce the uncertainty and apprehension but also

increase patients' knowledge about the unanswered queries (Lobb et al 2002).

A decision aid can be considered effective if it achieves at least one of the two key objectives (Connor et al 2009). The first objective is to enhance the concordance between the chosen treatment and the aspects of treatment that are most important to the patient and reduce the decisional conflict in choosing the best possible option while indirectly enhancing satisfaction with the decision making process, influencing the decision itself. The second objective is to highlight that a decision is to be made and thus involve the patient in the decision making process. This is important because this gives opportunity to the patient to understand not only about the condition and the treatment options available but also the benefit of making a decision. A Canadian, qualitative study (Potter et al 2008), which explored women's decision making with regard to prenatal screening by blood test for Down's syndrome and open neural tube defects, found that some women did not realise that that there was a decision involved, "I guess we kind of thought it was something that you had to get done. I didn't really know there was a choice to make" (P360). Others felt that they were following professional advice, "It's sort of a recommended thing…" (p360). This is of concern since a positive screen test result results in a further decision about amniocentesis which carries a risk of miscarriage. A false positive screen could result in unnecessary worry for the mother.

Involving the patient in the decision making process will increase patient confidence (Connor et al, 2007) in their healthcare professionals and the treatment options available and patients will be in a better position to understand the consequences of the decision made. This is seen in many European IVF centres where IVF patients/couples are engaged in discussions about the number of embryos to be transferred when a choice

is to be made between single embryo transfer and double embryo transfer.

5.2 Design of DA

The recommendation for readability of a DA by experts of health communication (Butow et al 1998) and the International Patient Decision Aid Standards (IPDAS) collaboration is at 8th grade (Elwyn et al 2009) which corresponds to 12 years. Complex information is often made easier by a DA which can be used easily by the recipients. Pilot testing a DA before a randomised controlled trial can give an insight into the pitfalls and the probability and space for any improvement. Pilot testing also brings to the forefront valuable feedback about the design of the DA, the layout and the amount of information (Claire et al 2007).

A study looking at patient satisfaction in breast cancer patients found that almost all (93%) patients read the DA thoroughly before completing the questionnaire (Claire et al 2007). In the same study 93% of the patients felt that introducing a DA during genetic testing for breast cancer would be 'very relevant.' A high proportion, (75%), thought a DA would have been very relevant in coming to a decision about genetic testing in their situation and all 100% of the participants were optimistic about recommending the booklet to other people in similar situation (Claire et al 2007). This highlights that if presented and explained properly about the use of a DA, patients tend to read it thoroughly and seem positive in recommending to others in a similar position.

Recently the International Patient Decision Aid Standards Instrument (IPDASi) has developed a tool to assess the quality of a decision aid. Twenty-five researchers in the field collaborated to identify the features of an effective DA (Elwyn et al 2009). It follows on from the previous IPDAS measures for a decision aid. The IPDASi has 47 items describing different dimensions including: Information (the DA describes the decision that

needs to be considered); Probabilities (the DA allows the user to compare outcome probabilities across options using the same denominator and time period); Values (e.g. the DA asks patients to think about which positive and negative features of the options matter most to them); Decision guidance (e.g. the DA provides a step by step way to make a decision); Development (e.g. the DA included expert review by health professionals not involved in producing the DA); Evidence (e.g. the DA includes citations to the studies selected); Disclosure (e.g. the DA provides information about the funding used for development); Plain language (e.g. the DA reports readability levels using one of the available scales).

Various studies have been carried out around the world which has investigated different aspects of a DA from layout, formatting, benefits and the attitudes of clinicians towards the use of a DA (Connor et al, 2009; Volk 1999; Gattellari in 2003). The recent Cochrane review looking into DAs for people facing health treatment or screening decisions focuses on the effectiveness criteria of the International Patient Decision Aid Standards (IPDAS) collaboration: attributes of the decision and attributes of the decision process. In total, 55 Randomised Controlled Trials (RCTs) are included in this review of which 25 studies are new (RCTs) since the previous Cochrane review (Connor et al 2009). The review includes 27 trials which explore the impact of DA on knowledge scores, 11 trials on impact on accurate risk perception, 4 trials looking into the extent to which the patients' values were congruent with the chosen option. Other things that have been looked into by the review are decision process attributes in which 15 trials looked into feeling informed and 13 trials looked into feeling clear about values (Connor et al 2009).

5.3 Types of DA

Layout and structure

Decision aids can be laid out in various formats and structured in various forms. They can incorporate pictures, texts, videos or just audio. Some can be in audio-video form, some as interactive videos, decision boards, personal computers, audio tapes, work books and booklets. Apart from having a structured format and text for informing the patients, they can also incorporate a step-by step decision making process (Connor et al, 2009). Sometimes DAs can contain experiences and decision outcomes in similar situations to those of other patients (Connor et al 2009).

DA can also differ in their presentation. It could be designed as a video with a brochure (Volk et al 1999) for PSA (prostate-specific antigen) screening or simply a video (Partin et al 2004). A study carried out by Woolf et al (1996) on PSA screening used scripted information whereas a 32 page booklet was used by Gattellari et al (2003). Decision aids can also be internet based as used by Frosch et al (2003) for PSA screening.

Content

Carefully written information is effective in promoting knowledge, adherence, and satisfaction among well-educated, interested women. Women can understand complex information, including tradeoffs regarding treatment options (Rothert et al, 1997). Decisional aids can either be detailed or simple. Various studies have compared detailed DAs with simple DAs. Seven studies out of the total nine looking into HRT included in Cochrane review (2009) compared detailed DA with simple DA (Rothert et al 1997, Connor et al 1998, Connor et al 1999, Dodin et al 2001, Rostom et al 2002, Legare et al 2003, Deschamps et al 2004). These detailed DAs included all the design elements options/outcomes, clinical problem, probabilities of outcomes, values clarification, other's

opinions and guidance in decision making and /or communicating. Some of these DAs were provided with audio guided workbooks (Connor et al 1998 and Dodin et al 2001).

Frosch et al (2001) used the simple comparison for providing information about the risks and benefits of screening for prostate specific antigen (PSA). Similarly, in patients for pre-natal screening, Hunter et al (2005) compared an audio guided decision aid to individual counselling and group counselling and Leung et al (2004) compared an interactive multimedia DA to a video and pamphlet one. When simpler decision aids were compared to more detailed decision aids, the relative improvement in knowledge was significant (mean difference 4.6 out of 100; 95% CI 3.0 to 6.2) and there was some evidence of greater agreement between values and choice (Connor et al 2009). Most DAs are simple in structure and based around the framework which includes keeping a balanced approach about the benefits, the risks, the outcome that was developed by O'Connor and Colleagues (Connor et al, 1998; 1999). A DA should be simple and eye catching. Only having text or only having pictures might not be the ideal DA. A balance between text, figures and graphs should be maintained. Too much text can distract the patient during consultation (Claire et al 2007).

The review explores the use of probabilities in DAs. Most simple decision aids provided information about the clinical problem, options and outcomes (Cochrane 2009). Patients who received a detailed DA, one that described outcomes and the probabilities, were more likely to have an accurate risk perception unlike those who did not receive all the information. This was clearly evident in participants on a study considering hormone replacement therapy (HRT). Those participants who were given an audio tape with a booklet which then took them step by step through the information had less decisional conflict compared to the control group

who was just given a standard leaflet produced by the Obstetrics and Gynaecology Society of Canada. Percentages of women whose general knowledge increased and of women with realistic expectations were significantly higher in the experimental group ($P < .003$ and $P < .0001$, respectively). Congruence between personal values and decisions about HRT increased significantly more in the experimental group ($P = .003$) (Dodin et al 2001). This shows that a detailed DA can be effective in decreasing conflict and at the same time provide the information needed for making a decision.

Other studies compared an audio guided aid with values clarification to one without value clarification (Connor et al 1999). An audio guided decision aid was compared with a 40 min pharmacist consultation (Deschamps et al 2004). Benefits and side-effects of HRT were compared on an audio guided decision aid to a general information pamphlet (Legare et al 2003). Some studies used a combination of a group lecture, handouts and personal decision exercise (Rothert et al 1997) while some others (Rostom et al 2002) compared the same information in an audio booklet with a computer version, which also provided feedback to correct any misunderstandings of the information. Cochrane (2009) also shows comparison of detailed aid as mentioned above explaining the probabilities and outcomes, in the form of an interactive video along with a booklet to a simple DA in the form of just a booklet for back surgery patients (Deyo et al 2000). Two other studies looking at breast cancer surgery compared detailed DA to a simple DA (Street et al 1995) used an interactive multimedia presentation and used an audio guided workbook for their detailed DA (Goel et al 2001). Audio guided DA was used by Hunter et al (2005) for prenatal screening and an interactive multimedia decision aid was used by Leung et al (2004). Information contained in a DA was conveyed to patients in different modes, such as a video cassette (Pignone et al 2000), read scripted information to participants (Wolf et al

(2000) and Dolan et al (2002) used an “analytic hierarchy process via computer" for Colon cancer screening. A study carried out to evaluate an evidence-based booklet for men designed to encourage informed decision-making in about the controversy surrounding prostate cancer screening, compared with those receiving conventional information. It was found that men receiving the evidence-based booklet showed significantly better knowledge (50% of items correct, 95% CI 46-53%; versus 45% correct, 95% CI 42-48%) ($p = 0.048$) and decreased decisional conflict (mean 21.6, 95% CI 20.7-22.5; versus mean 24.3, 95% CI 23.4-25.2) ($p < 0.001$). Curiosity in PSA screening was significantly reduced in both groups ($p < 0.001$). EB booklet was helpful for all patients whether active or passive about decision-making (Gattellari & Ward, 2003).

A study carried out on breast cancer patients found that younger women with breast cancer showed a preference for paper based DAs compared to internet and CD-ROM. Participants using paper based were more satisfied and more participants wanted to use the paper form of DA. They also felt it was easier to concentrate and understand with a paper based DA compared to the CD-ROM. This was a surprising finding because these participants were regular users of the internet and computer services (Green et al 2004, 2005).

5.4 Patient preference

Depending on the condition for which a DA is used, researchers in the area have categorised patients’ decision making into two classes (Weingarten et al, 2002). “Effective health services” are situations where there is certainty that joining the decision making process would be advantageous for the patient. This is usually true in more chronic conditions where taking a decision would definitely increase the quality of life. In this case the perceived benefit will be more than the harm which can be experienced by the patient. An example would be in the case of

statins where there are side effects but the benefits of taking the medication arguably outweigh the side effects when taken by a patient with strong risk factors for cardiovascular disease such as diabetes. However, in “preference sensitive health services” there seems to be more uncertainty and less demarcation between the advantages and disadvantages, and the patients’ values play a major role in decision making (Weingarten et al, 2002). The name “preference sensitive” was given by Wennberg and colleagues as the decision for the best choice depends on the patient’s judgement about the known risks and benefits of treatment options and the uncertainties of the benefits of the treatment (Wennberg et al, 2003). Participants in the “preference sensitive” group have shown to be better in decision making, resulting in less overuse of the services compared to others not participating in decision making (Connor et al,2009).

When “preference sensitive” choices are made, the benefits of the treatment are less clear, perhaps because there is not much evidence to support the treatment decision or because the goal of the treatment may have been influenced by the patient’s values or preferences. An example of a preference sensitive decision might be the decision whether or not to prescribe HRT. The value to the patient depends on the impact of the menopausal symptoms and the patient’s view of her risks associated with HRT. Antenatal screening is another potential example of preference sensitive choice. Here the decision is likely to be influenced by the personal value of the outcome, for example diagnosis of a genetic abnormality, the risk of abnormality and the risk of the test, for example increased risk of miscarriage (Potter et al 2008). Potter et al (2008) found some women in their study felt pressurised to have antenatal screening and advice around the issue clearly needed to take account of women’s values, for example their views on abortion.

5.5 Effectiveness of a DA

The decision taken by the participant and the decision aid used determines the outcome on the actual decision (Connor et al 2005). A Cochrane review of more than 200 DAs showed that they were helpful in increasing patient knowledge and creating a reasonable expectation. This indeed helped in decreasing the uncertainty in the majority of the participants after their participation in the intervention (Connor et al 2005). Different DAs are effective in different conditions and sometimes other methods of communicating risks may be more helpful. Research has shown that genetic counselling was more helpful than the interactive computer program at reducing women's anxiety and helping them to understand more accurately the risk perceptions about breast cancer and genetic testing. The counsellor group had lower mean scores on a decisional conflict scale (P=.04) and, in low-risk women, higher mean scores on a satisfaction-with-decision scale (P=.001). Mean state anxiety scores were reduced by counselling. It shows that just counselling was more effective and advantageous compared to the CD-ROM-based decision aid in women with a low-risk of breast cancer, hence reducing the anxiety the patients felt (Green et al 2004).

However, another review found that decision aids performed better than usual with care interventions, in terms of lowering decisional conflict related to feeling uninformed (MD -8.3 of 100; 95% CI -11.9 to -4.8), lowering decisional conflict related to feeling unclear about personal values (MD -6.4; 95% CI -10.0 to -2.7), reducing the proportion of people who were passive in decision making (RR 0.6; 95% CI 0.5 to 0.8) and reducing the proportion of people who remained undecided post-intervention (RR 0.5; 95% CI 0.3 to 0.8) (Connor et al 2009).

Knowledge

A meta-analysis of 27 studies included in the most recent Cochrane review (2009) found that knowledge scores were 15.2% higher in people exposed to decision aids in comparison to usual care. Direct and targeted information has shown to be effective and helpful for people, enabling them to form precise judgements about risk (Natter et al 2005). A study showed that women made more knowledgeable decisions when they were provided with an evidence-based decision-aid leaflet prior to a scheduled consultation about choices of pregnancy termination methods and lower risk-perception scores about methods of termination (Wong et al, 2006). Out of the three hundred and twenty-eight women who participated in the study, there was no significant difference in the method chosen between the groups. In the decision-aided group, 60 out of 162 selected a medical method compared to 54 out of the 164 women in the control group (OR 1.2; 95% CI 0.76–1.9). Most participants confirmed that they had read most of the leaflet (Wong. et al, 2006). However the DA had influenced the perception of risks associated with both treatment methods in the 162 participants in the decision aided group. They had lower risk-perception scores for heavy bleeding and infertility for both methods and for perforation of uterus in relation to the medical method and incomplete termination and anaesthetic complications for surgical method of termination. Women participants certainly showed awareness about the choice of termination method. This was more obvious after the process than during the decision making. A highly significant (P=0.0001) number of women in the intervention group felt that they were well informed and rated the information as very useful. There was significant change in the attitude towards surgical method of termination after the intervention and participants felt positive about the process (P= 0.05). Women in the

decision-aided group demonstrated more positive attitudes about the medical method and had more firm evaluations of the decision information over time. Decision aids performed better than usual care interventions in terms of greater knowledge (MD 15.2 out of 100; 95% CI 11.7 to 18.7) (Connor et al 2009).

Decisional conflict

Decisional conflict occurs when there is hesitation with regards to decision making. The conflict happens when there is risk or uncertainty concerning outcomes with high stakes in terms of potential gains and losses (Connor, 1995). Often decisional conflict in choosing a treatment method may arise from a lack of knowledge which could come from incorrect or insufficient information. Decisional conflict can also arise when there is evidence of lack of conviction regarding the effectiveness of a treatment method on the part of the doctor taking care of the patient and who is also the decision maker. Many other factors such as 'individual motivational predispositions' to change, economic, political and organisational setup could be responsible (Godin et al 2008) for a decisional conflict. However, these recognised factors (Godin et al 2008) cannot always influence or dominate patients' decisions and most patients acknowledge use of information that is evidence based to help them surpass their decisional conflict. It has been noticed that patients with proper information tend to be more aware and are able to participate more actively in the consultation process thus promoting shared decision making. Decisional conflict is usually assessed by the Decisional Conflict Scale (Connor 1995). The questionnaire is made up of 3 aspects of decisional difficulty. Decisional uncertainty, factors influencing decisional conflict such as lack of support for decision making or lack of knowledge and perceptions of the effectiveness of the decision making process. It has been well validated. A recently updated Cochrane review of randomised trials in decision aids

found, in the 10 studies where DAs were compared to usual care, patients receiving the DA experienced lower levels of decisional conflict. Only one study out of seven which compared a simple decision aid to a detailed decision aid found an advantage for the detailed decision aid (Connor et al, Cochrane 2009).

Patient satisfaction increased at the same time with decreasing decisional conflict in breast cancer patients on choice of surgery (Jennifer et al, 2007) similar to another randomised controlled trial looking into choice of breast cancer surgery. In this the decisional conflict was less (1.40 vs. 1.62, p= 0.02) in patients using a decision aid compared to those not using one (Whelan et al, 2004). Other studies also using decision aids for different aspects of women health have shown similar results. Another common obstetric related decision is whether to have an elective caesarean in a second pregnancy following caesarean section for a first birth. The decision requires women to balance the medical risks for themselves and their infants and their personal preferences for a vaginal birth or a caesarean section. Shorten et al (2005) found that the decisional conflict decreased significantly ($p<0.05$) in pregnant women with previous caesarean section delivery about the modes of birth options present along with an increase in mean knowledge. A more recent study was carried out of web-based decision aid which gave women who had delivered by CS at their first birth personalised feedback of a recommended delivery method for their second pregnancy (vaginal delivery vs. caesarean section) based on probabilities and their own values (Frost et al, 2009). The intervention was associated with reduced decisional conflict and qualitative data from the study examined the role that the decision aid had played in whether they opted for a vaginal birth after caesarean (VBAS). Most women valued the structured information and balance of risks and benefits of each option, “I thought all the answers I’d given would reflect what I wanted, but of course they didn’t, they take into consideration the risks,

don't they? And the statistics so it's an unbiased opinion so it's different to my opinion… it was good to make me think about it" (p 899).

Reduced decisional conflict seems to have advantages for the doctor-patient relationship. A randomised trial of a satins decision aid found that although the improvement in patient trust in the doctor associated with the doctor's use of the DA just failed to reach significance (P<0.08), for every 5 point reduction in decisional conflict, ratings of trust in the doctor increased by 1.5 (95% CI 1.2-1.9) (Nannenga et al 2009).

Motherhood is a pleasant experience for most women. However, if this pleasant feeling is marred by suspicions of genetic disease it can lead to increased anxiety. Often, it can be daunting for health professionals to give the information to the patient and explain the reason for prenatal genetic diagnosis. The amount of information offered to women contemplating prenatal diagnosis can be vast (Goel et al 1996). There is often a state of confusion among these patients about whether to choose prenatal screening or diagnostic testing and the consequences after a positive result. All these build up to a situation of decisional conflict, which can be a cause of increased anxiety (Marteau et al, 1989). However, Kaiser et al, (2002) found that although decisional conflict reduced significantly (p<0.01) the anxiety level did not show any change after educational intervention about genetic screening. The finding was similar about decisional conflict and anxiety in another random controlled trial about prenatal diagnosis for Down syndrome (Bekker et al 2004).

Anxiety

As mentioned above, although DAs reduce decisional conflict they do not seem to reduce generalised anxiety. DAs in general have not been shown to have any impact on satisfaction level in decision making, however use of a DA has demonstrated a mixed outcome for anxiety level or on quality of life. The actual way forward in making a decision depends on the

condition and the DA used (Connor et al 2009). Similar emotional impact was seen in patients both in breast cancer group and ovarian cancer group (Tiller, 2006). A study done to carry out a randomised controlled trial of a decision aid for women at increased risk of developing ovarian cancer to facilitate decision making regarding risk management options compared the efficacy of customised decision aid to that of a general educational pamphlet in preparing women for decision making. In 131 women with a family history of breast and/or ovarian cancer or of hereditary nonpolyposis colorectal cancer, psychological adjustment was reassessed at 3 time points. Women who were given a DA reported a higher degree of acceptability of use of educational material at both follow-up points compared to the controls that were only given a pamphlet. The study found that neither the intervention group nor the control group experienced any significant increase in psychological distress at either follow-up assessment time points relative to baseline (Tiller, 2006). This suggests that although DAs do not tend to reduce anxiety they do not necessarily cause additional psychological distress.

This is shown in the study carried out by Wong et al, (2006) where the increase in the anxiety level was not linked to the use of decision aid. A study reviewing the use of anxiety as a measure by some studies looking into decision aids found that none of the studies included in the review noticed any effect on the anxiety level with the use of a decision aid (Bekker et al 2003). However, a review of thirteen studies of DAs for patients with prostate cancer found that the use of DAs can decrease levels of anxiety and distress (Lin et al 2009). Davison & Degner (1997) found significantly lower anxiety in the intervention group ($P < 0.005$) and Davison (2003) found statistically significant ($P < .001$) reduction in anxiety level and a significant decrease in depression ($P = .018$) in the intervention group. Decreased distress ($P < .05$) was also found by Flynn et al (2004). The study done by van Tol-Geerdink et al (2006) found that

patients thought that 'hopelessness affects desire to choose.' In the study done by Isebaert et al (2008), 46% of participants found decision aid reassuring, with 73% feeling the decision aid helped them elucidate personal preferences and that a majority (88%) would use a DA again.

5.6 Clinicians' attitudes to Decision Aids

Decisional conflict is highly likely to occur in conditions where there is risk and uncertainty and the stakes are high. Also, the patients and the clinicians who are the decision makers expect to experience regret over the unused options in situations of failure (Janis & Mann 1977). This uncertainty could be the reason for the attitude of the physicians towards a treatment option. Occasionally it can also be that the clinicians' unwillingness to recommend a treatment is a reflection of his or her attitude and sometimes it has been found that even with adequate evidence some clinicians do not easily embrace the change and this can lead to a situation of conflict in decision making for patients (Bhavnani & Fisher. 2010).

Often it is not only patients who experience decisional conflict when making decisions about their treatment options and choices. A Canadian study found that both doctors and patients had decisional conflict about hormone therapy. Responses of 40 doctors and 167 women who participated in the study were analysed. The study found that decisional conflict in patients was higher than the doctors when age of the doctor was greater than 45 years. Women who were undecided about the best choice after the counselling session, women with a university degree and women who said that their doctor usually does not give them control over treatment decision also had higher decisional conflict compared to doctors. Greater decisional conflict was noticed among doctors compared to female patients when the length of the visit was less than 30 minutes, in doctors who were undecided about the quality of the decision and when

women thought that the decision was shared with their doctor. The study realised that there was need for increasing awareness among doctors about shared decision making and this would not only give patients the chance for more participation but also decrease the disparity in decisional conflict between patients and doctors (Legare, et al 2003).

For a decision aid to be effective it has to be used by the clinician. Negative attitudes to using a decision aid, having the patient in treatment or two alternative treatment options could all impact on the utility of the DA in clinical practice. A survey of DA use in a random sample of Ottawa-Carleton family physicians listed in the Canadian Medical Directory as members of the CFPC (n=214), showed a huge gap between their intention to use a DA and their behaviour or actual use of the DA. While the study found that more than 80% of the respondents felt a DA was a useful tool to prepare patients for decision making during treatment options, only less than 60% considered DA a time saving tool. Furthermore, although 54% of the surveyed physicians showed interest in using a decision aid, less than a third actually used it in routine practice (Graham et al, 2003). This attitude was in spite of the fact that the majority of the participants found the decision aid was well developed (86%) and this was highly significant with a P value of ($p=0.007$) and that the DA produced was independent ($p<0.0001$). A significant number of participants that used the DA ($p=0.001$) rated the clarity of the data presented (86%) and felt that the information used in the DA was balanced (87%) ($p=0.023$) and up to date (75%) ($p=<0.0001$). They also found the contents to be acceptable (81% $p=0.063$) and easy to understand for patients (54% $p=0.006$). The participants also found (66%) that the DA would be a reliable tool for helping patients in decision making ($p=0.004$) and would be a tool to help physician's understand issues important to patients ($p=0.033$). At the time of the survey majority, although not a huge (58%) number of the participants found that

introducing the DA in clinical practice would not require major changes (p=0.058), and a lower number (54%) of participants found that it will be easy to experiment with before adopting (p=0.026). Further still a lower number (53%) felt it will improve patient visits (p=0.08) and an equal number (53%) felt it will "increase patient satisfaction with my care" (p=0.015). A highly significant equal number of participants (46%) were not keen to purchase the DA for use in their practice (p=< 0.0001) and a lower number (32%) said that the DA would likely be used by most of their colleagues (p= 0.016) and 27% thought that the use of DA will save time (p=0.088). This was in concordance with the findings of various other studies (Holmes-Rovner et al 2000, Charles et al 2004, and Stapleton et al 2002). This shows that although the participants were happy with the content of the DA and the way it was compiled, the majority felt it will not save time and a highly equal proportion of participants were unwilling to pay for a DA even after accepting that it was a reliable tool for helping patients.

It can be seen that although the agreement and acceptance on the part of the clinicians is low, there are a few who felt that decision aids are a reliable tool and can benefit patients. This has been the trend in modern day practice and more and more clinicians are using evidence based practice to give patients the maximum chance for making informed decision regarding their treatment options and where they get can more benefit and less harm. Particularly in treatments where there is a high level of anxiety such as infertility treatment, it is important that any device which increases the demands made on patients by requiring more involvement in the decision making process does not increase the emotional burden of treatment.

5.7 IVF and DA

Infertility, as mentioned in chapter 1, has different types of treatment. Often it is a very difficult situation to explain the complexity of the problem and the treatment options available. Patients often want instant results which are not very easy to achieve in infertility treatment, which has recently soared to a rate of 1 in 6 couples opting for the treatment. This can lead to increased level of anxiety and stress. In a situation like this, making a decision about the number of embryos to be transferred can be conflicting.

Arguably the decision regarding embryo transfer should be in the realm of effective health services since there is good evidence that twin pregnancies are associated with greater risk (chapter 1) and that single embryo transfer can result in equivalent cumulative conception rates (chapter 1). However, in many countries, including the UK, the decision is influenced by the attitudes of both the clinician and the patient. For example, doctors perceive that a twin birth is valued by infertile patients and patients may perceive that a small increase in the chance of conception outweighs the risk of a multiple birth. The decision is strongly influenced by the patients' own conscience and values and therefore can be comfortably positioned under the "Preference sensitive" category. For each woman the importance of the outcome (i.e. conceiving a child) has to be weighed against perceptions of the risks and disadvantages of a twin birth. For women with good financial means and strong support networks the impact of a twin birth may be less. As previous research has suggested (chapter 1) patients may not have accurate perceptions about risks to twin infants. However, there could be a shift in future due to the advances in IVF treatment around the world, changes in the financing of IVF treatment and with proper educational aids to help the women understand the situation.

In the example of single embryo transfer a decision to replace one embryo might acknowledge the importance to the woman of being able to return to work. The second objective is to highlight to patients that a decision needs to be made and thus to involve the patient in the decision making process. This is particularly relevant to IVF treatment where many patients have two embryos replaced because they assume that they are following standard procedures (Glazebrook et al 2007).

5.8 Development of the Decision Aid leaflet

Introduction

In recent days medical practice has moved mostly to evidence and knowledge based practice and shared decision making between clinicians and patients. Often sharing of this knowledge is done with the aid of a decision aid. As mentioned earlier in the chapter, a decision aid can be in many forms such as a leaflet, a CD or a DVD or a booklet. We decided on the leaflet model because it would be simple and easy to use. Decision aid (DA) can be used as a tool when deciding how many embryos to transfer during IVF treatment. The piloted DA prepared by Van Peperstraten (2010) presented information in text, summaries, tables, figures and through an interactive worksheet and was reviewed positively and was acceptable for use in clinical practice both by patients and professionals.

Contents/ Layout

Our decision aid leaflet is for couples undergoing IVF treatment. It aims to highlight the benefits of single embryo transfer to help patients make a choice that meets their own values and preferences rather than focus on the negative aspects of a multiple birth. This is line with the decision to be made which is whether to have a single embryo transfer or double embryo transfer. The leaflet “Making your choice about embryo transfer” (Appendix 8) contains features associated with an effective DA. It has

been found that to change health-related behaviour by changing attitudes, the most effective way to do it is to have persuasive messaging. We chose to positively frame the information about eSET, in that, we focussed on the benefits and gains of a single birth rather than the risks and losses of a twin birth. Research has suggested that loss-framed messages are more effective in encouraging behaviours that detect presence of disease (e.g. cervical screening) but positive, gain-framed messages have been more successful in promoting behaviours that prevent disease or promote health. For example patients entering into a cardiac rehabilitation programme exercised more if they had received gain-framed information (e.g. regular exercise will give you more energy) compared to loss-framed messages (e.g. Your heart disease may get worse if you don't exercise). This shows that providing information in a positive way, works for a patient population. Similarly our leaflet is informative and presents evidence from relevant previous reserach [(De Sutter,et al. (2006); Veleva,. et al. (2006); Thurin,. et al. (2004); Glazebrook, et al. (2004)] which were selected for the leaflet on recommendations from experts from the two big fertility clinics in Nottingham, one private (Care fertility) and the other NHS (NURTURE) and because they illustrated the important points in the DA.

It includes a graphical demonstration of pregnancy rates following single and double embryo transfer (decision tree) and information on the benefits of a single birth. Use of the flow diagram with different colour schemes for different treatment modalities makes the interpretation easier. Our leaflet is simple but depicts real facts and figures**.** There is a balance between the pictures and the text present in the leaflet which catches the attention of the readers from beginning to end. The recommendation for readability of a DA by experts of health communication (Butow et al 1998) and the International Patient Decision Aid Standards (IPDAS) collaboration is at 8th grade (Elwyn et al 2009) which corresponds to 12 years and on testing the readability on the Online Readability Software we found that the score for

our leaflet is that of 12 year old. The leaflet was also piloted for readability among colleagues. Once the flow of the language looked satisfactory, the leaflet was subject to expert review by senior consultants working for NURTURE and CARE fertility. They looked at the studies used, the content and also compared it with the existing leaflet provided by the HFEA to compare the efficacy of the new leaflet. The leaflet was submitted to the research ethics committee for their evaluation and to check for patient suitability, and they felt that the leaflet was good, giving us the permission to use it in patient groups.

Criteria for development of the DA

The IPDAS instrument had not been published at the time this leaflet was developed. Therefore it could not be tested on the IPADS instrument. However, at the time in the latest Cochrane review (Connor et al 2003) a DA was suggested to be effective if its outcome fulfilled the IPDAS criteria (Elwyn 2006). It had set primary and secondary outcomes. We tried to work on these criteria, focussing specially on the primary outcomes. These primary outcomes were ; 1) 'Attributes of the decision making': taking this into context we developed the DA with matters that would a matter most to the patients using it such as increasing the knowledge about the subject, giving them the ability for correct risk awareness and of feeling informed and clear about values and the other primary outcome set was 2) 'Attributes of the decision process'- it should help the patient recognise that a decision has to be made, know the features and options, also understand that principles that affect the decision and which matter the most, should have the opportunity to discuss their decision with their clinician and be involved in decision making. Elwyn et al (2006) identified 12 criteria with which to judge a decision aid. The decision aid scored well on 9 of the criteria – 1) systematic development process; (2) providing information about options; (3) presenting probabilities; (4) clarifying and

expressing values; (5) guiding or coaching in deliberation and communication; (6) disclosing conflicts of interest (7) balancing the presentation of options; (8) using plain language; (9) basing information on up to date scientific evidence. The DA did not use patient stories and was not available on the internet. The final criterion was “evaluation of effectiveness” and a randomised controlled trial was set up to carry that out.

Effectiveness

Pilot testing a DA before a randomised controlled trial can give an insight into the pitfalls and the probability and space for improvement. Pilot testing also brings to the forefront valuable feedback about the design of the DA, the amount of information and the layout (Claire et al 2007). On this basis after preparing the DA on the recommendations of the experts and focusing on the IPDAS criteria, the initial leaflet was given to a target group. These were women, some of whom have had IVF treatment before and had conceived twins as a result, others were trying to conceive. In all 5 women were selected. After the leaflet was shown to them separately, each of these women discussed the contents actively. They all brought up ideas and also commented on the ease of reading. At least one woman who had conceived twins with great difficulty after few failed cycles was not very optimistic about promoting SET for IVF patients because of the low success rate. It is fair to say that these women were highly qualified and therefore, may not represent the true diversity of our clinics. After the target group the DA leaflet was piloted among colleagues and clinicians who had the option of reading the other DA that is used by the clinics and prepared by the HFEA. It has been found that until recently there were no trials evaluating the IPDAS decision process criteria relating to helping patients recognise that a decision is to be made, understanding that principles have an effect on the choice, or converse values with the

practitioner (Connor et al 2009). Looking retrospectively into our DA development, it can be seen that our DA does reflect the important dimensions referred above in the IPDAS 47 itemed instrument. Our leaflet is informative and tries to deliver succinctly the information required. It also allows the user to compare outcome probabilities across options using the same denominator and time period by giving them examples where patients are able to see for themselves the like for like comparisons. With pictorial and graphic representation of the outcomes, the users have the option to make a choice of the most important thing that matters most to the patient. The explanation provides clear-cut information to the patients on the decision making process. Our leaflet had the opportunity to be reviewed by experts in the area who were not involved in making the decision aid and has citations from one of the largest and most robust RCTs. We have included logos of both the University of Nottingham and the Infertility Research Trust on the leaflet and the readability score is 12 years which is the set criteria for IPDAS meaning that the language is very simple.

According to Connor et al (2009) a DA is affective if it achieves at least one of the two key objectives. The first objective is to improve the treatment choice coordination and reduce the decisional conflict. The second objective is to emphasize that a decision is to be made and thus involve the patient in the decision making process. We think both of these objectives have been catered to in our DA development.

We can see that our decision aid was built around evidence based medicine to help patients make a choice of treatment after making them aware of the consequences and the information and as recommended by Graham et al (2007) is an impactful decision aid that has strongly brought forward the benefits, harms, the scientific uncertainties and options of treatment available for IVF patients. It can be confidently concluded that

our DA not only fulfilled the IPDAS criteria on which it was made but it has also been able to fulfil the 8 most important criteria of the latest IPDAS instrument for assessing a DA.

5.9 Conclusion

Various studies have found that understanding the risks reduces the desire for a multiple birth (chapter 3). The barriers to change include "insufficient information to the couple on the risks of multiple gestations" (Gerris, 2001). Although decision aids have found to assist choice in pregnancy terminations (Wong et al 2006) they have not been used to help infertile couples to make treatment related choices. Routinely an information sheet which details about the complications of multiple births is given to all IVF patients coming for IVF treatment. This information sheet is very exhaustive and focuses on negative consequences of a twin birth, which could induce fear and denial, at a time which in itself is so stressful because of the IVF treatment. It has been in use for some time and surely there has not been much effect on the attitudes of clinicians who explain it to their patients and the patients who read through the document before making a decision about embryo transfer. The reason for this failure could either be the method of delivery or the content of the leaflet.

The need for further investigation into the information needs, knowledge and attitudes of patients and their partners is clearly needed. This will help the patients in decision making about embryo transfer and the clinicians in helping their patients to make informed decision about their embryo transfer. This is extremely important in view of the recent support for strategies to significantly reduce multiple births, including restricting embryo transfer to one embryo per treatment (elective single embryo transfer) for some women (Strandell, et al, 2000; Hazekamp, et al, 2000).

The various studies mentioned above reflect the conflicting attitude of practising physicians in decision making and this is true for IVF patients as well. The remarkable fact that the clinicians were unwilling to pay for the DA can hold significance for IVF patients in the UK too. Although an information leaflet is being used routinely during IVF treatment around the UK, there does not seem to be enough evidence that patients are involved in decision making about the number of embryo transfer at the time of their treatment. It is also possible that any change to this routine might not be easily acceptable and this is reflected from the attitude of the clinicians' during the development the Attitude to twin IVF pregnancies and single embryo transfer (ATIPS) scale.

It can be concluded that a Decision Aid has proved to be a very useful tool in almost all reported studies from the various fields of medicine, and most recently IVF (Van Peperstraten, 2010). Some formats, like the detailed ones, seem to be more useful than the simple ones. The audio-visual with a step by step guide was better received than the simple text only version in breast cancer patients. It has shown to increase awareness, knowledge and the expectation of a treatment. It reduces the decision conflict and uncertainty in conditions like breast cancer, prostate cancer and medical termination of pregnancy. It is important to evaluate the impact of the decision aid on decisional conflict and actual decision regarding embryo transfer.

A RANDOMISED CONTROLLED TRIAL OF A DECISION AID LEAFLET TO PROMOTE SINGLE EMBRYO TRANSFER IN IVF PATIENTS

6.1 Introduction

One study which explored the impact of provision of information about the risks of a twin birth (Ryan et al 2007) found that the proportion of women who preferred a singleton birth increased from 69% to 86% but choices about eSET were heavily influenced by the chances of conception. It may therefore be that the overriding desire for a child outweighs concerns about birth outcomes. In a recent study, done by Scotland and colleagues (2007), found that women waiting to undergo IVF treatment viewed the birth of a child with severe disability as a preferred outcome compared to no child at all. In this study 74 participants were asked to rate five negative birth outcomes associated with twin pregnancy (e.g. giving birth to a child with physical impairments, premature birth). A gambling task was then used to compare their preference values for the negative outcomes to treatment failure (i.e. no birth at all) (Scotland et al, 2007). Women were asked to choose between a definite risky outcome (e.g. giving birth to a child with a cognitive impairment) and options which would either give them a positive outcome (a healthy child) or a very negative outcome (perinatal death followed by no subsequent pregnancy). By varying the probability of the very negative outcome the authors established relative preferences for the different negative outcomes. Treatment failure was valued significantly lower than having a child with cognitive, physical or perceptual impairments. The authors concluded that women undergoing IVF treatment are likely to be more strongly influenced by information about treatment success than by information about negative outcomes associated with a twin birth. However, a limitation of the study was its poor response rate as only 36% of the 226 women approached agreed to participate. A further 7 women failed to complete the measures.

Evidence suggests that most patients choose to replace a minimum of two embryos because of their perception that transferring two embryos will give them a better chance to become pregnant. There is some evidence that couples prefer multiple pregnancies to singleton pregnancies even though they are aware of the medical, social and psychological risks associated with multiple pregnancies (Pinborg et al 2003) (see chapter 3 for further discussion about attitudes to multiple births).

Studies have found that most patients coming for treatment lack information about the risk of multiple pregnancies (Grobman et al 2001) or the benefits of single embryo transfer. In a study of women attending for an initial consultation for IVF treatment it was found that less than 50% were aware of the increased risk of cerebral palsy and infant mortality associated with twin pregnancy (Ryan et al, 2004). Various studies have found that understanding the risks reduces the desire for a multiple birth. The barriers to change include “insufficient information to the couple on the risks of multiple gestation” and the “emotional and financial burden of ART treatment, pushing patients and doctors alike to improve the results at the expense of an increased risk of multiple gestation” (Gerris, 2001). Direct and targeted information has shown to be effective and helpful for people to form precise judgements about risks (Natter & Berry 2005). A study showed that women made better and more knowledgeable decisions when they were provided with an evidence-based decision-aid leaflet prior to a scheduled consultation about choices of termination method (Wong et al, 2006) (see chapter 5 for a more detailed discussion about decision aids).

Further investigation into the information needs, knowledge and attitudes of patients and their partners is clearly needed. This will help the patients in decision making about embryo transfer and the clinicians in helping their patients to make informed decision about their embryo transfer. This is extremely important in view of the recent support for strategies to significantly reduce multiple births (HFEA

2008), including restricting embryo transfer to one embryo per treatment (elective single embryo transfer) for some women. (Strandell, et al, 2000; Hazekamp, et al, 2000).

Ideally, the expected outcome in decision making would be to select a service that increases the chances of quality health outcomes while simultaneously decreasing the undesired outcome. Increasingly clinicians are using evidence based practice to give their patients maximum chances for making informed decisions for their treatment options (Connor, et al 2005).

Often decisional conflict in choosing a treatment method may arise from incorrect or insufficient knowledge (Connor, et al 2009). Decisional conflict can also arise with a physician when there is lack of convincing evidence of the effectiveness of a treatment method. Decisional conflict can affect the patient decision making in many ways such as not making the right choice for them, or not being able to make a clear choice of a treatment process (Connor, et al 2009). Decisions about how many embryos to transfer have the potential to cause decisional conflict. There is a risk of reducing the chance of pregnancy or increasing the risk of twins. It is important therefore to consider the most effective way of delivering information to support patients' choices around embryo transfer. A randomised trial of different methods of informing couples about the risks associated with a twin pregnancy found no impact of information or type of information (leaflet versus discussion) on attitudes to eSET. However, when asked how many embryos they would like transferred in their own treatment, 13% of couples (8/61) randomised to the discussion group said that they would prefer 1 embryo replaced compared to fewer than 1% in the information leaflet group (1/66) and 4 out of 62 in the control condition (Murray et al, 2004). Contrary to the conclusions of the authors this provides some evidence that the quality of information may impact on decisions about embryo transfer.

A randomised trial of an educational DVD found that 82% of the 62 participants randomised to information delivered via the DVD were in favour of eSET at follow-up compared to 67% in the leaflet group. This was a significant difference (p=.014). The DVD was 12 minutes in length and featured interviews with experts (e.g. embryologist) comparing conception rates and multiple birth rates between eSET and DET and outlining risks associated with a twin birth. It also had interviews with 2 mothers of twins (one uncomplicated birth and one mother of twins born 25 weeks preterm) talking about the experience of caring for twins. The leaflet included identical information in written form.

Both brochure and DVD were described as decision aids but it was not clear that they conformed to the principles of a decision aid. For example it was not clear that they included supporting evidence, required participants to think about outcomes that they valued or highlighted that a decision needed to be made. Both the brochure and the DVD increased knowledge about the risks associated with a multiple birth but, compared to the brochure group, the DVD group had stronger agreement with items describing the risks of a twin birth including that twins are smaller (p=0.01), more likely to have learning difficulties (p=0.003), less likely to have been breastfed (p=0.003), more likely to have heart defects (p=0.004) and more likely to be admitted to neonatal care (p=0.044). Participants viewing the DVD also agreed more strongly that parents of twins have less sleep (p=0.002) and greater financial burden (p=0.009). Of the 29 participants in the leaflet group with more than one embryo available for transfer, 20 (69%) chose single embryo transfer compared to 34/39 (87%) in the DVD group. Though this difference failed to reach significance (p=0.078) it was in the predicted direction. Couples said that the information received (either DVD or leaflet) and doctor's advice was the most important influences on their decisions concerning embryo transfer (Hope & Rombauts 2010). A limitation of the study was that

instead of using an intention to treat analysis, the authors excluded couples who had not used the information from the study.

Although these studies suggest that patient information can be effective in increasing knowledge about the risks associated with a twin birth and increasing acceptability of eSET, no study has explored the impact of a decision aid on decisional conflict and anxiety associated with decisions regarding embryo transfer.

This study will evaluate the impact of a decision aid leaflet (see chapter 5 for description of development) on attitudes to single embryo transfer, decisional conflict and satisfaction with the decision making process, compared to HFEA leaflet alone.

6.2 Aims

The study has a primary and secondary aims.

Primary

To conduct an exploratory randomised trial to examine the impact of a decision aid leaflet on patient decisions about embryo transfer, patient anxiety during embryo transfer, patient attitudes to single embryo transfer and multiple IVF pregnancies, satisfaction with the decision and decisional conflict.

Secondary

To examine factors influencing attitudes to single embryo transfer and multiple IVF pregnancies in patients undergoing IVF treatment and to examine the relationship between patient attitudes and decisions about embryo transfer.

End points

The study had two end points: Primary end point was the decisional conflict scores whereas the secondary endpoints included state anxiety

scores, attitudes to twin IVF pregnancies and participation in decision rating.

Study design

The study design was a randomised, controlled trial of a decision aid leaflet for patients undergoing transfer and their partners. Participants were randomised to standard informational care (HFEA leaflet- Appendix 7) or HFEA leaflet plus decision aid (Appendix 8). Researchers were blinded to group allocation and the intended analysis was to be on an intention to treat basis.

6.3 Method

Participants

Patients and their partners attending the Nottingham University Research and Treatment Unit (NURTURE) for IVF treatment were recruited to the study. There were no inclusion / exclusion criteria.

Recruitment and informed consent (Appendix 5)

Patients attending the first appointment for their IVF treatment were sent an invitation letter along with the patient information sheet to participate in the study. Patients had the opportunity to ask any further information at this point. Patients and their partners were approached by nurses in the clinic who checked that they had received the participant information sheet and obtained signed consent

Measures

Demographic questionnaire (Appendix 5) included: Age of patient, marital status, occupation, education level, years to conceive, previous children, age of partner, partner's previous children, and first IVF cycle. Occupational status was coded using the standard occupational classification 2000.

Attitudes to Twin IVF Pregnancy (ATIPS-R) (Rai & Glazebrook, 2007) (Appendix 5).

This is a self report questionnaire that was developed for the study and comprises attitudinal statements that were derived from literature and expert consultation (see chapters 3 and 4 for development of ATIPS-R). Participants rated each statement from 1 (strongly agree) to 7 (strongly disagree). The original 44 items were piloted with a large sample (n=411) and reduced to a short 18 item scale using item analysis. Scores are recoded as appropriate and totalled with higher scores indicating more positive attitudes to twin IVF pregnancies. The questionnaire had good face validity with a reading age of less than 12 years (Flesch reading ease score= 68, 5).

The ATIPS-R comprises 2 subscales.

Attitudes to Risks and Benefits of a Twin Birth (A-TWIN) subscale consist of 12 items and focuses on the advantages and costs of a twin birth. The scale has good face validity with a balance of positive and negative statements. A good internal consistency with a Cronbach's alpha of 0.88 (Bowling 2002) was found. Possible scores for the scale range from 12 to 84 with higher scores indicating more positive attitudes to twin IVF births.

Attitudes to Single Embryo Transfer (A-SET) Subscale: comprises 6 items assessing attitudes to elective single embryo transfer (eSET). This subscale scale had a satisfactory Cronbach's alpha of 0.81 (Bowling 2002). Possible scores range from 6 to 42 with higher scores indicating less positive attitudes to single embryo transfer. The scale discriminated between health professionals involved in IVF treatment and patients.

Spielberger State-Trait Anxiety Inventory (SSTAI) (Short form) (Marteau & Bekker, 1992) (Appendix2b). This is a six-item shorter version of the 20-item instrument. It is a reliable, well validated and

easy to use measure of the state of anxiety. Both the short form and the long form scale have similar reliability and validity scores. It correlates well with the full form (r = 0.95), producing similar scores to the full version across subject groups manifesting both normal and raised anxiety levels. The items on the SSTAI also correlate well with each other, producing a high internal reliability (Cronbach's alpha = 0.82). It is also sensitive to the fluctuations in the state of anxiety. The short scale has comparable results to the long form of SSTAI and has the added benefit of being shorter. This helps to maximise the response rate.

Decisional conflict scale (DCS) (Connor, 1995) (Appendix 5).

Decisional conflict occurs when the patient is unsure of the choice that has to be made. Feelings of uncertainty are likely to be increased when the decision has risky consequences, for example failure to conceive or the increased risks associated with a twin birth. These sorts of decisions often involve a trade-off of values and may involve potential regret about unselected options. The decisional conflict scale assesses the extent to which patients feel uncertainty regarding the decision that they have made (This decision was hard for me to make), the extent to which they felt informed about the decision (I needed more information), the level of support they felt for the decision (I had the right amount of support in making this decision), the extent to which the decision matched their values (It was hard to decide if the benefits are more important to me than the risks or if the risks are more important than the benefits) and the perceived effectiveness of the decision (I feel I have made an informed choice). The DCS has been shown to be a reliable method of measuring the decisional process. The Decision uncertainty subscale has 12 items rated on a Likert scale from 1 (strongly agree) to 5 (strongly disagree). Ratings are summed with possible scores ranging from 12 to 60, so that higher scores equate to more decisional conflict. The DCS was developed specifically to assess the decision making process in the health care consumer.

The test- retest reliability of this scale in individuals for influenza immunisation or breast cancer screening was 0.81, and internal consistency co-efficient ranged from 0.78 to 0.92. The DCS is able to discriminate between strong intentions and uncertainty ($p<0.0002$). It seems to be easy to administer.

Participation in the decision process scale

A 5 point rating scale assessing the extent to which the patient felt they had participated in the decision process concerning embryo transfer (1= decision entirely made by patient, 2= decision mostly made by patient, 3= shared decision, 4= decision mostly made by doctor, 5= decision entirely made by doctor).

Clinical proforma

Included questions about type of infertility, quality of embryos available for transfer, number of embryos available for transfer, number of frozen embryos.

Randomisation

Participants were randomised to one of two groups using numbered packs. A random number sequence was generated using Excel with odd numbers allocated to one group and even numbers allocated to the other group. The random sequence was then matched to the study number on the spreadsheet. A secretary in the Division of Psychiatry was asked to insert the information (decision aid or control) into envelopes labelled with the study number so that researchers were blind to group allocation. The control group information included an additional blank folded sheet to ensure that group could not be identified by envelope size. Group 1 was intervention leaflet plus HFEA leaflet or 2) standard HFEA leaflet alone. Clinical staff was, however, not blind since the intervention leaflet encouraged patients to discuss their decision with their doctor.

Procedure

All patients at NURTURE were sent a letter explaining the study. Patients attending NURTURE between February 2008 and January 2010 were approached by nurses and asked if they had received the patient information about the study. Nurses gave the patients and their partner the pack containing the consent form, the ATIPS-R for the patient and partner and a sealed envelope containing either the Decision aid plus standard leaflet or the standard leaflet alone plus a blank sheet. Patients and their partners (if applicable) returning the baseline questionnaires and consent form were sent the Spielberg State-Trait Anxiety Inventory (SSTAI), the decisional conflict scale (DCS) and the ATIPS-R to complete immediately after embryo transfer, together with a freepost envelope for return. They also rated their participation in the decision process. Information about the embryo transfer procedure was recorded from the patient notes by one of the researchers (VR).

6.4 Ethics approval (Appendix 4)

The study received ethics approval from the Nottingham Research Ethics Committee 1 and Research & Development approval from the University Hospital Trust.

Power calculation

The study was powered using the efficacy sub-scale of the Decisional Conflict Scale. Based on a mean of 7.6 and a standard deviation of 2.4 it is estimated that a sample size of 64 people in each group was needed to detect a difference of 1.2 points between intervention and control ($p<0.05$, 80% power). The calculation was conducted using an online-facility http://www.dssresearch.com/KnowledgeCenter/toolkitcalculators/samplesizecalculators.aspxed.

6.5 Statistical analysis

Data were analysed using SPSS (version 16). Shapiro-Wilks tests showed that all outcome variables were normally distributed so parametric tests were used. The probability level was $p<0.05$.

Response rates

In the study period an estimated 41 study packs were distributed of which 8 patients (7 partners) returned consent forms (19.5%). Of those who returned the consent form 7 patients (6 partners) returned follow-up forms. So the overall response rate for complete returns was 17.1%.

Demographic details are shown in Table 6.1. The mean age of the patients was 34.5 years and 36.43 years for their partners. The majority of the patients (75%) were between 33 and 40 years, for 25 % (2 couples) of the participants it was not their first IVF cycle and one couple had a previous child. Most participants were white European. The majority of the patients were educated either to degree level or above and had intermediate jobs, whereas their partners were mostly with postgraduate degree and in managerial or professional jobs.

6.6 Results

Baseline scores showed that patients were more positive towards twins than their partners but this difference was not significant when comparing patients and partners using paired t-test. Patient and partner attitudes to eSET were similar at both time points. Comparing patients and their partners also showed no significant differences in anxiety and decisional conflict (Table 6.2).

Table 6.1 Demographic details of participants – patients and partners

	Female patients (n=8)	Partners (n=7)
Study condition		
Leaflet	7 (88%)	6 (86%)
Control	1 (12%)	1 (14%)
Mean age SD (±)	34.50 (4.34)	36.43 (2.21)
Age in years		
28-36	6	3
37-42	2	4
Ethnicity		
White European	7	5
Asian/Asian British	1	1
Other	0	1
Occupation		
Managerial/Professional	2	4
Intermediate	5	1
Routine/manual	1	2
Education		
GCSE	1	1
A level	1	1
Degree	3	1
PG Degree	2	3
Other	1	1
First IVF cycle		
Yes	6	5
No	2	2
Previous child		
Yes	1	1
No	7	6

Table 6.2: Outcome variables in the whole group

	Patients (n=8)	Partners (n=7)
Mean A-TWIN scores(±SD)	40.63 (12.34)	37.43 (7.44)
Mean A-SET scores (±SD)	27.50 (3.70)	27.14 (3.98)
Mean A-Twin scores post embryo transfer (±SD)	37.71 (15.76)	38.33 (8.55)
Mean A-SET post embryo transfer (±SD)	27.71 (5,15)	26.17 (2.86)
Mean decisional conflict(±SD)	25.29 (9.38)	28.00 (5.48)
Mean anxiety (±SD)	16.00 (4.29)	14.5 (3.94)

Factors associated with attitudes at baseline

There was a positive relationship between patients' attitudes to twins and their partners' attitudes to twins (r=0.66, n=7, p=0.107) but this was not significant. There was no relationship between patients' and partners' attitudes to single embryo transfer (r=0.156, n=7, p=0.738). Older women were less positive about twins (r=-0.75, n=8, p.031) and more positive about eSET (r=-0.68, n=8, p=0.066). There was no relationship between educational level and attitudes to twins in women (r=0.12, n=8, p=0.977) or attitudes to eSET (r=0.282, n=8, p=0.498). In partners, older men were more positive about eSET (r=-0.881, n=7, p.009). There was also an association between higher educational level in partners and more positive attitudes to eSET (r=-0.593, n=7, p=0.161) and less positive attitudes to twins (r=-0.63, n=7, p=0.129) but these both failed to reach significance.

Relationship between baseline attitudes and anxiety and decision difficulty at embryo transfer (Table 6.3).

Lower levels of decisional conflict in patients at embryo transfer were associated with more positive attitudes to twins at baseline (r=-0.819, n=7, p=0.024) and less positive attitudes to eSET at baseline (r=-0.777, n=7, p=0.040). Increased anxiety at embryo transfer was associated with more positive attitudes to twins (r= 0.59, n=6, p=0.21) but this failed to reach significance. There was no relationship between attitudes to eSET and anxiety at embryo transfer. Higher anxiety at embryo transfer was associated with lower decisional conflict (-0.416, n=6, p=0.412) but this was not significant.

Table: 6.3 Relationship between baseline attitudes and anxiety and decision difficulty at embryo transfer

	Attitude eSET	Attitudes twin	Anxiety
Decision conflict	R=-0.777	R=-0.819	R=-416
	N=7	N=7	N=6
	P=0.040	P=0.024	ns
Anxiety	R=0.166	R=0.596	_
	N=6	N=6	
	Ns	Ns	

In partners more positive attitudes to twins at baseline (r=-0.618, n=5, p=0.27) were associated with less decision difficulty but this was not significant. Baseline attitudes in partners were unrelated to anxiety at embryo transfer. Ratings of patient's contribution to the decision concerning embryo transfer were available for 7/8 patients and 6/7 partners. Four of the patients (57%) felt that they had made the decision about number of embryos to transfer entirely by themselves but only 1 (17%) of the partners felt that the decision had been made entirely by the patient. Three of the partners (50%) felt the decision

had been shared equally between patient and doctor compared to only 1 (14%) of the patients. Two patients and two partners felt the decision had been made mostly by the patient.

Since only 1 patient was in control group it was not possible to compare the control and study group as planned. Follow-up data was available for 7 patients and 6 partners. Selecting only those women (n=7) who had had the decision aid leaflet; there was no significant change in patients' attitudes scores over time. Partners' A-Twin scores did not change over time but partners did become more positive about single embryo transfer over time (t=3.539, df=4, p=0.024) (Table 6.4).

Table 6.4: Change in attitude scores before and after embryo transfer in participants receiving the decision aid leaflet

	Time 1 (baseline) (n=7)	Time 2 (at embryo transfer) (n=7)	P value
Mean women's attitudes to twins (SD)	39.83 (14.27)	37.67 (17.26)	ns
Mean women's attitudes to eSET (SD)	26.83 (4.12)	27.67 (5.65)	ns
Mean partners' attitudes to twins (SD)*	37.0 (9.00)	38.2 (9.55)	ns
Mean partners' attitudes to eSET(SD)*	28.4 (3.51)	26.0 (3.16)	p=0.024

*n=6

Clinical proforma

Out of the total 8 patients who responded and agreed to participate in the study clinical files were only available for 5 patients. Details about type of infertility, number of cycles taken, quality of embryos available for transfer, number of embryos available for transfer, number of embryos transferred, number of frozen embryos and outcome of the treatment is shown in (Table 6.5A and B).

Table 6.5A: Table showing clinical details about participants

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5
Age in yrs	39	40	35	28	30
Type of infertility	Primary	Secondary 4 years	Primary	Primary 3yrs	Primary 5 yrs
Cause of infertility	Azoospermia	Male factor-retrograde ejaculation	Female factor endometriosis	Male factor	Oligospermia
No. of cycles	One	Two	Two	One	Two
No. of eggs retrieved	10	10 10	12 14	15	22 8
No of cleavage embryos	5	8 6	6 8	9	7 3

Table 6.5B: Table showing clinical details about participants

	PT-1	PT-2		PT-3		PT-4	PT-5	
No of blastocysts transferred	2	2	2	2	2	2 Cl	2	2
No of embryos frozen	0	0	0	0	5	3	0	
Outcome	Single	nil	Single	Nil	Twins M&F	Twins 2M	Nil	Twins M&F
Type of delivery	CS	-	E CS	-	Forceps	E CS		ND
Gestation age in wks	40	-	40+4	-	33	38 ½		32
Birth wt. in Kg	3.68	-	3.630		M-3.27 F-1.36*	1st - 3.06 2nd - 3.09		M-1.59 F-1.50

*No complications but still sent to special care for 18 days, Cl- cleavage stage embryo, ECS- Emergency caesarean section, M- male child, F- female child

All patients had 2 embryo transferred. The majority of patients (60%) had a successful outcome after 2 cycles of embryo transfer. All of the patients had fresh cycle embryo transfer even for the second cycle.

Most patients (60%) had twins as the outcome of their treatment and their birth weight was less than the singletons and they also needed special care unlike singletons.

6.7 Discussion

Contrary to some previous research (Gleicher et al 1995) younger women in this sample were more positive about twins and less positive about eSET. Studies by Højgaard et al (2007), Child et al (2004) and Pinborg et al 's (2003) found no effect of age on attitudes towards twins. However, Ryan et al, (2004; 2007) found younger women were more likely to underestimate the demands associated with raising multiples and consequently were less concerned about the possibility of a multiple birth. Older men were also more positive about eSET as were better educated men. This may reflect a lack of awareness of the effectiveness of eSET in younger couples. As is typical in an IVF population (e.g. Glazebrook et al 2004) participants tended to be well educated with more middle class professions. However there was little relationship between educational level and attitudes in women, either to twins or eSET. There was positive relationship between patients' attitudes to twins and their partners' attitudes to twins. However, there was no relationship between patients' and partners' attitudes to single embryo transfer, similar to Kalra, et al (2003).

For majority of the participants in our study it was their first IVF cycle and like other studies most participants were negative about SET (Højgaard et al 2007). Other studies have also found that even twin prone couples, chose DET in their first IVF/ICSI cycle (Van Peperstraten et al, 2008). However, for at least 25% (2 couples) participants it was not their first IVF cycle and failure to conceive from a previous IVF cycle can lead to patients becoming less positive to eSET (Van Peperstraten et al, 2008). However, others have found previous failed cycle had no effect on preference of twins or decision about eSET (Højgaard et al 2007). Child et al (2004) found that history of

assisted reproductive treatment was associated with a significant increase in desire for multiple births.

The scale seems to be a useful tool in assessing the participants' attitudes. In patients positive attitudes to twins and negative attitudes to eSET were strongly predictive of lower levels of decisional conflict. This may reflect the fact that all women for whom information was available had double embryo transfer. Decisional conflict was definitely low in this patient group with a mean of 25 out of a possible high of 60 in patients.

Anxiety levels at embryo transfer were high in patients and their partners and increased stress associated with IVF has been noted in other studies (e.g. Højgaard et al, 2007). At baseline women were more positive about twins than their partners similar to other studies (Højgaard et al 2007; Child et al., 2004; Ryan et al., 2004; Pinborg et al., 2003) but this difference was not significant due to the small sample size. This study found that with the use of the DA, although the patients became less positive towards twins they also become less positive about elective single embryo transfer, although this was not a significant change. Thus it was not found that increasing the level of information significantly changed patients' attitudes towards twin pregnancies and the choice of eSET unlike Newton and colleagues (2007), who found that the desirability of elective single-embryo transfer increased and the desirability of twin pregnancy decreased, among both men and women by providing them with risk information.

A longer period of infertility (Child et al 2004) and cost of treatment (Kalra et al., 2003) could be a contributing factor along with the desire to complete their family at one go because of the uncertainties of the treatment available and decreasing success rate with age could be other reasons for positive attitudes to twins, although these factors were not analysed. However, Højgaard et al (2007) found no association of length of infertility to desire of twins. Desire for a

successful pregnancy at any cost looks as the influencing factor and other studies have found that despite evidence that eSET reduces risks of a twin birth and can be associated with comparable cumulative pregnancy rates, couples perceive that replacing more embryos will increase the chance of success (Glazebrook et al 2007; Newton, et al, 2007).

Inadequate knowledge of neonatal complications among fertility specialists and insufficient information provided to fertility patients have been argued as one of the most important factor in the rise of twin pregnancies (D'Alton, 2004). Additional information in the form of a bespoke, piloted decision aid did not significantly change attitudes to twins over time in either patients or partners similar to Murray et al. (2004). Other studies like ours have also shown that infertility patients seem to be rather unaffected by perceptions of a high risk associated with twins (Kalra et al., 2003).

Some patients may face decisional conflict or difficulty in decision making (Whitlock et al, 2002) because of the difficulty in understanding about the benefits and risks accompanied with the confusion involved with the actual process. Other factors like increased knowledge with better information, help in climbing the decision making ladder, are factors that are adaptable. Although these modifiable factors reduce decisional conflict they do not seem to change the more intrinsic factors associated with the scientific suspicions of the process (Connor et al 2003). This is similar to our findings in this study where patients' attitudes risks and benefits perception about twins and single embryo transfer do not significantly change over time with the use of a decision aid. However this is not true for their partners who became significantly more positive about eSET over time.

All patients for whom information was available had double embryo transfer. The majority of women felt the choice had been entirely their own but only one partner felt the clinician had not been involved in the

decision. It is interesting that partners became more positive about eSET after embryo transfer compared to baseline and were also more likely to feel that the decision about embryo transfer had been shared.

The fact that that the patients receiving the decision aid felt that they had made a strong contribution to the decision about embryo transfer is encouraging. Clinicians have recommended involving patients in decision making process by increasing their knowledge (D'Alton, 2004). However previous research has suggested that patients perceive that decisions about embryo transfer are strongly influenced by medical advice (Glazebrook et al, 2007).

It could be that clinicians are already working closely with patients in the decision making process and indeed there is pressure on clinics from the HFEA to reduce rates of multiple births. Also the current HFEA leaflet has clear information about the risks of multiple births. It could also be that the attitudes towards elective SET were independent of methods of information provision similar to Murray et al (2004) who reported that, in a randomised study, attitudes towards elective SET were not dependent on how the information was provided. Providing intervention group participants with both leaflet and the standard HFEA leaflet could have been another deterrent in changing the attitudes to HFEA, because participants are fully aware of the HFEA and its role. However it is not really possible to judge the effectiveness of the decision aid in the present study due to small sample size and lack of control group.

Strength and weakness of the study

The main weakness of the study was the poor response rate which was due to the failure of the recruitment process. Although the clinical staff agreed to take consent from patients, in practice they could have been very busy with their job demands and therefore the recruitment failed. The nurses were too busy to do more than just hand out study packs. The target of 64 patients in each group was not met. Since the

majority of responders were in the intervention group it seems that the control groups were less likely to participate. This is a failure of the study design. A researcher in the unit would have been able to obtain consent and then allocate to condition. Not only would this have increased the participation rate but it would have been possible to construct a consort diagram to show the flow of patients. In effect this study could be considered a feasibility study as it has been able to show that the measures are acceptable and appropriate for this type of study and the findings could be use to help develop a full randomised trial of a decision aid for patients undergoing embryo transfer. Clinical staffs were not blind since the intervention leaflet encouraged patients to discuss their decision with their doctor which may have been another methodological drawback of the study. However we do not think that not blinding the staff would have been a problem in recruitment of patients.

We think there was enough blinding and concealment in the allocation process and labelling. However the disparity on response rates suggests that people allocated to control may not have returned questionnaires. Ideally it would have been better to gain consent before allocation to condition. The study was not able to assess the effectiveness of the leaflet because of the poor recruitment. In order to improve recruitment it would have been better to have a designated researcher in the unit. The Decision aid itself has met most of the criteria for effective design. For example, one of the recommendations of the IPDAS criteria for a good patient decision aid is to encourage patients for discussion with their clinicians and surely our leaflet did indicate that, however we cannot say for certain that the patients discussed with their clinicians.

We selected our ATIPS-R measures which were validated previously as part of this research (Chapters 3 and 4) and the others from previous published and validated, Spielberger State-Trait Anxiety

Inventory (SSTAI) (Short form) (Marteau & Bekker, 1992) and the Decisional conflict scale (DCS) (Connor, 1995).

Although there was no direct question asking about the duration of infertility, in study 3 we found that although not significant, older women had less positive attitudes towards eSET but women who were having their first IVF cycle were significantly more positive about single embryo transfer and the experience of fewer previous cycles of IVF was also associated with significantly more positive attitudes towards eSET. This shows that the scales were able to differentiate between the attitudes of patients depending upon their length of infertility. However, one study looking into length of infertility did not find any association of length of infertility to desire of twins (Højgaard et al 2007).

One of the items 'If IVF treatment was government funded patients would choose single embryo transfer' which is part of the A-SET scale, although it talks about funding there are no indication as to the number of cycles and other associated costs i.e. it is not very explicit about the cost and this can be confusing for patients.

Although we did have an item "A twin pregnancy avoids the need for further IVF treatment" relating to the desire to complete family in one go, there were no direct items pertaining to this concept. However, analysis of this item showed that there was poor correlation between the items when this item was included and therefore for better inter-item correlation this item was removed from the analysis.

The decision aid had pictorial representation of the risk and benefits of twin birth and the benefit of elective single embryo transfer, these were true figures from literatures in the area. The pictorial representation in a bar chart and a Consort diagram meant it was not intimidating and also easy to catch the eye. This would have helped them make their decision with ease.

Conclusion

The result of the study showed that majority of the patients were positive about twins and even after use of a customised decision aid their preference for twins did not change. Partners did become more positive about eSET. Unfortunately the sample size was too small to make any judgement about the effectiveness of the decision aid. However the fact that a 100% of participants had double embryo transfer and 60% of participants in the study for whom information is available had twins suggests that there is a need to help patients make informed choices about single embryo transfer. The study provides further evidence of the validity of the ATIPS-R scale as baseline scores predicted decisional conflict. As the group was very small it will be interesting to evaluate further and find whether or not, age and desire for twins actually only influence less cautious patients as found by Newton et al, (2007). Only time will show if a law is forcefully used, like Sweden, or a process of informed choice, like Netherlands, really works for our patients in UK.

DISCUSSION

7.1 Introduction

This PhD, through the four stages of the research, found that twin and singletons born very premature had similar mental and psychomotor development at two years of age even though twins had older mothers from higher social class and so might be expected to experience a more stimulating environment compared to children of less mature and less educated mothers. Despite their social advantage, 27% of the premature twins had at least mild cognitive delay and twins were statistically more likely to have a serious abnormality compared to singletons.

Study 2 developed an evidence-based, reliable scale (ATIPS) to assess attitudes to a twin birth which was reduced to two reliable short sub-scales following item analysis. One scale (A-twin) assessed perceptions of the risks and benefits of a twin birth and the second subscale (A-SET) assessed attitudes to elective single embryo transfer. There was some evidence for validity as the scales were able to distinguish between attitudes of medical students and those of clinicians. In study three IVF patients and clinicians involved in IVF treatment completed the ATIPS. Two further items were removed from the A-SET scale to improve internal consistency to form the revised ATIPS-R scale. Clinicians were less positive than patients about a twin birth and more positive about eSET, supporting the validity of the scale. Despite the established risks of a twin birth for mothers and infants we found evidence that many patients undergoing IVF treatment and clinicians involved in treatment had positive attitudes towards twins and negative attitudes towards eSET. In particular both clinicians and patients underestimated the risks of a twin birth to the infant. First cycle IVF patients were significantly more positive about eSET than women undergoing repeated cycles, signifying the variations in

attitudes. The results of the study have been published in a peer-reviewed medical journal (Rai et al, 2011).

The final part of the research was to develop an evidence-based decision aid. The DA conformed to established criteria for good communication about treatment choice (Appendix 8) and was acceptable for use in a patient population. The randomised controlled trial failed due to poor recruitment but did produce some useful pilot data. We found that patients with less positive attitudes to eSET and more positive attitudes to twins experienced less decisional conflict at embryo transfer. There was also some evidence that the decision aid was effective in improving partners' attitudes to eSET. Patients using the DA at the point of embryo transfer showed less decisional conflict in choosing twins as their preferred outcome even after been given additional illustrative material depicting the risks with twins and the rates of twins with DET.

Overall, it can be said that this research has created an important tool for assessing the variability in attitude towards twins and SET and should be used at a time when there is no universal method of measuring the attitude of either the clinician or the patient group. It has also produced a useful decision aid tool which could be used in clinical practice to help health professionals communicate with patients about the advantages of single embryo transfer. This can be important universally also as not all countries are very keen on bringing a legislation for elective single embryo transfer.

7.2 Role of regulation on embryo transfer

The HFEA's recent recommendation, based on the evidence provided by a review done by Cutting et al, (2008), to limit the multiple birth rates to 24% (2005 level) in year 1 (2009) and to 20% in year 2 (2010) and 10% in year 3 (2011), was taken after the data for 2007 showed that ART (IVF

and donor insemination) in 2007 accounted for 1.5% of all births in the UK and 1.8% of all infants were result of IVF or donor insemination (HFEA 2009). The number of cycles of IVF treatment carried out in the UK is increasing each year and the most recent available figures show a 5.8% increase between 2006 and 2007 which corresponds to an 8.3% increase in births and an 8.5% increase in babies born as a result of IVF (HFEA 2009). In the same time period the birth rate increased by a much smaller margin (0.6%) from 23.1% live birth rate for cycles in 2006 to 23.7% for cycles in 2007. The comparable rate for 2005 was 21.6%, 15% in 1995 and 8.5% in 1985, suggesting a slow but steady increase. Despite pressure from the HFEA to reduce the rates of multiple births, 23% of IVF cycles in 2007 resulted in a multiple birth, an increase of 0.3% on 2006 figures. UK has had one of the lowest rates of eSET in Europe until the 2009 intervention. This is because eSET is not compulsory here, and choosing patients for eSET lies entirely in the hands of the treating clinicians. Clinicians' unwillingness and attitude to embrace eSET is compounded by patient's attitudes to eSET and their desperation to conceive. The additional costs associated with repeat cycles could be seen as a barrier to single embryo transfer as suggested by the Health Belief model. However, HFEA is increasingly recognising the importance of removing financial disincentives to eSET. For example, from October 2010 the HFEA will only charge clinics a flat rate of £104.50 for a patient's first cycle of IVF. If initial treatment fails there will be no subsequent charge. A recent review of international differences in the uptake of single embryo transfer concluded that vast disparity in rates of eSET uptake in different health care systems will remain unless there are changes in the way IVF treatment is funded and regulated (Maheshwari et al 2010).

At this stage, using this validated and reliable scale to get a perception of the thoughts of healthcare professionals involved in IVF treatment and after care and patient groups could prove to be very useful. This could

also be an opportunity to introduce the DA leaflet as well. Measuring the attitudes could be helpful for the health services. It would enable them to get an understanding about the problems and dilemma faced by the clinicians and patients and the reluctance in acceptance of eSET in these groups. Most of which, NHS is obviously aware of, but it has not been measured on a valid and reliable scale. It might also be that over time, with targets already set by the HFEA, the attitudes of both healthcare professionals and patients have changed and there could be a possibility of bringing a legislation to promote eSET.

7.3 IVF practise around the world

Most countries mentioned in Table 1.5 demonstrate that they do not have legislation on embryos transfer. At the European Society of Human Reproduction and Embryology (ESHRE) consensus meeting in 2002, it was agreed that the preferred ART outcome should be the birth of one child and that a twin pregnancy should be considered a complication (Land et al 2003). European countries are far ahead of other developed nations in promoting SET, however, some feel that the increase in rates of eSET is still very modest (12% in 2001 versus 13.5% in 2002, 15.7% in 2003 and 19.1% in 2004) (Anderson et al 2008). Twin deliveries after IVF/ICSI are still close to 22% (2004) in Europe (Anderson et al 2008).

Often research on SET has reflected the mood of the healthcare setup in which it is carried out. Private funded clinics favour DET to eSET. Chapter 3 demonstrate that in those European countries where eSET is practised routinely, (nearly 50% eSET) such as Sweden and Finland, multiple birth rate is below 15%, but the pregnancy rate per embryo transfer is between 31 and 35 %. Whereas in countries like Iceland where eSET rate is only 10.5%, the multiple birth rates is 26.5% and the pregnancy rate per transfer is 40.5% (Bergh et al, 2007). This shows that there is not much difference in pregnancy rates between the countries using eSET or DET.

As mentioned earlier, focus should also be on the funding system of countries, like Sweden and Finland, for a better evaluation of the practise of eSET in these countries.

Recently, a study was reported by Veleva et al, (2009) from Finland, who compared eSET use at two time periods. First period was between 1995-1999 when eSET rate was 4.2% and DET was more common ("DET period"), and the second period was 2000 to 2004 when eSET rate was 46.2% ("eSET period"). Over this ten-year period 1510 women, younger than 40 years were treated at the infertility unit at Oulu University Hospital. In total they had 2,386 cycles of fresh embryos, followed by 1,272 cycles when frozen-thawed embryos were transferred (FET). About 90% of deliveries in both periods occurred within the first four treatment cycles and they suggested it was similar to that achieved by DET. The study found that the cumulative pregnancy rate per ovum pickup was 38.2% (eSET) versus 33.1% (DET), cumulative live birth rate per ovum pickup was 28% versus 22.5%, and cumulative live birth rate per woman was 41.7% versus 36.6% suggesting that all figures were better in the eSET group compared to DET. In addition, the cumulative multiple birth rate was significantly lower in the eSET period (8.9% versus 19.6% in the DET period). Total treatment cost per woman in the eSET period, on average, was five per cent less than in the DET period (ranging from 2-20% less). In terms of Euros, the total treatment cost per woman decreased by an average of 275 Euros (ranging between 164-1184 Euros) from the DET to the eSET period. When the researchers calculated the incremental cost-effectiveness ratio (ICER) (Fiddelers et al 2009) they found that 19,889 Euros were saved per live baby born at term (after 37 weeks) in the eSET period compared with the DET period (ESHRE, 2009). This further confirms similar findings reported by other studies (Tiitinen et al 2001; Gerris et al 2004; Thurin et al 2006; Fiddelers et al 2006) that eSET is more economical than randomised DET in the long run.

IVF is costly and different countries have different models of funding this treatment. In countries like France and Belgium, where IVF costs are fully covered under the public health programme, the use of IVF does not differ according to women's socioeconomic position (Tain 2003) unlike countries like

USA, where IVF is offered mostly by the private sector, its availability depends on a couple's ability to pay (Neumann, 1997; Stephen & Chandra 2000). Countries like Sweden (Table 1.5) reimburse 6 cycles and eSET is compulsory in first cycle for only women younger than 35 yrs.

In countries like Finland and UK IVF services are offered both in the public and the private sector and it will be worth evaluating the Finland funding system. It is claimed that in Finland wealthy couples can shorten their waiting times by using services in both sectors (Klemetti et al, 2004; Klemetti et al 2007). Like UK, Finland dose not have legislation on eSET but it has been in use since ten years and the rate of multiple births is at 10% (Table 1.5). As a result of this huge surge in use of eSET in Finland the latest study suggests advocating single embryo transfer for all women <40 years of age (Veleva et al, 2009). In Finland, although the private sector is the most important IVF provider and over 60% of all IVF treatments are provided by private clinics, the cost of IVF treatment is partly covered by the National Health Insurance based on fixed scale of charges which includes 60% of doctor’s fees and part of examination cost. Patients getting treatment under the public sector, pay a small user charge for their clinic visits. For both private and public sector patients the Social Insurance Institution reimburse about 50% of the drug costs.

The study found that on a population based calculation; public expenditure was mostly allocated to young women and women from the highest socioeconomic position. About 25% of white-collar women aged less than 30 years of age succeeded in achieving a live-birth, but only 19% of blue-

collar women after the mean 1.5 year treatment period succeeded while the number of needed cycles per live birth among blue-collar women was higher. Due to the higher use of IVF, in every age group, the public expenditure was about two-fold for upper white-collar women compared to blue-collar women. Women treated in the private sector received more cycles than women in the public sector, and the women treated both in the public and in the private sector ('both sector users') received the most cycles. Success was poorest among the “both sector users” and their live births were the most costly (Klemetti et al 2007). This study reflects that with this kind of funding set-up where there is provision for reimbursement, those higher in the socio economic system benefit the most and also the disbursement of fund is not fair, e.g. younger patients had more allocation of fund and so was the case with women in white-collar jobs. I was therefore reported that women who were better financially had more funds allocated.

This could be the situation in UK if NHS funding is removed. Restriction to one cycle, which is the current practise, drives patients to select DET in the hope of a better chance of pregnancy because currently there is no funding available for freezing the embryos. Our study echoed this attitude of patients where our participants in the RCT, even after use of a bespoke leaflet, still choose DET as their treatment preference. Some of the factors influencing this preference for DET has been reflected during this research and is worth evaluating.

7.4 Risks for mother and child

Taking into consideration the infertility characteristics and the undetected abortions after natural conception, the abortion risk is not higher for IVF pregnancies in comparison to the general population (Tummers et al. 2003) as claimed by some (Schenker & Ezra 1994). However, perinatal mortality rate for twins was 46.8 compared to 8.8 for singletons and an

overall rate for all IVF pregnancies at 22.6 (Lieberman 1998). The figures reflect that mortality increases more than 5 times for twins and is a real risk to both mother and the foetus/child. Studies have shown that twins have worse outcomes than singletons with long term neurological problems, higher rates of perinatal mortality and neonatal morbidity (Blondel & Kaminski, 2002).

Our study found that in the sample as a whole, after controlling for infant health at birth (days ventilated and gender), socio demographic factors (index of material deprivation and maternal level of education) were associated with better cognitive outcomes, thus social class acts as a resilience factor. This is true for a high proportion of IVF children where mostly couples are from high socioeconomic class as found by Klemetti et al (2007) where they found from the Finnish database that the highest number of IVF participants were from the higher socioeconomic class. These home environments, in general, would also be healthy for cognitive development of a twin, although twin births are at greater risk. In our very small sample RCT study we found that three of six IVF twin infants were very low birth weight and two were born very premature. However, our study on premature infants also found that very premature twins were at the same risk for cognitive delay as singletons and this was similar to what a review done on 7693 extremely low birth weight infants found (Adams-Chapman, 2008). In general these low birth weight infants had a significantly higher risk of neurodevelopment problems. When these infants were studied at 18 months of adjusted age they showed decreased motor and cognitive ability (Adams- Chapman et al 2008). Generally, a significantly high number (30-60%) of very preterm children develop cognitive deficits and learning disabilities (Holsti et al 2002). Our study did not find better MDI or PDI index score at 24 month corrected age in twins even though they had some protective factors at baseline including higher maternal age and higher maternal educational level. A study carried out by

the National Institute of Child Health and Human Development Neonatal Research Network between May 1991 and December 1994 found that the mortality risk for very low birth weight (VLBW) in twins was same as singletons (Donovan. et al, 1998) and when controlled for gestational age, the rate of major handicaps was similar between twins and singletons weighing less than 1000g (Gardner et al, 1995).

Baseline characteristics such as mean birth weight, mean cord arterial pH, mean days on NICU to discharge, gestation age <29 weeks at birth of participant singletons and twins were not significantly different in our study of premature infants, pointing to the fact that prematurity in itself is a risk, whether it is singleton or twin does not matter and so is the mortality risk. Being a premature twin however, asks more in terms of caring from the parents compared to singletons. Our study did find that 4.4% of twins had serious malformation compared to none in the singleton group. Cochrane (2009) has also reported that the higher percentages of malformations noticed in the IVF/ICSI births is due to the multiple births (Sebire et al 2000; Wennerholm et al 2000).

Our study on premature infants also found that though not significant, more singleton mothers were hypertensive, which could be a cause for preterm birth leading to prematurity and low birth weight in singletons similar to the findings of Ochsenkhun et al (2003) who found that significant decrease in birth weight of singletons was associated with pregnancy induced hypertension but not in twins.

Psychological condition such as depression is another problem which is faced by twin mothers because of inability to return to work for long time and also because of caring for twins (Glazebrook et al, 2004), however some studies found that mothers were very enthusiastic about twins and used phrases such as “twins are a joy to each other” (Pinborg et al 2003). Researches have found that twin births are associated with a higher risk of

divorce rates (Nielsen et al 1986; Pinborg et al 2005). However, when the divorce rate, 4 years after delivery of IVF twins were compared to IVF singletons, the divorce rates were similar (7.3% for IVF twins and 6.9% for IVF singletons). This however, was not true for couples with spontaneous twins where the rate was 13.3% which was almost twice as high. It could be because of stronger marital relationships in IVF/ICSI parents and probably because IVF/ICSI parents cope better with the increased marital stress and therefore have lower rates of divorce in them, thus avoiding divorce or separation. However, the same study found that in general, couples with twins experienced higher marital strain and less marital benefit compared to couples with singletons (Pinborg et al., 2003b). Another study found that parents of a VLBW infant have twofold higher odds of chance of getting divorced compared with parents of a child with birth weight greater than1500 grams (Shailender et al 2006), signaling that caring for a VLBW infant can be very demanding for parents.

Earlier in chapter 1 we have shown that twins are at a risk of low birth weight similar to the small sample in study 4 (chapter 6) similar to Ombelet et al, (2006), but unlike our premature infant study (chapter 2) where singletons had slight lower mean birth weight compared to twins. These twins still had low birth weight, just not significantly different from singletons. Most RCTs also reflect the big gap in the birth weight between twins and singletons and it can be seen that twins carry higher survival risk than singletons. Also it can be that the similarity in the divorce rates between IVF singleton couples and the IVF twins' couples could be due to insufficient amount of researches done on this subject. Furthermore, despite arguments about good outcomes associated with twin birth the fact remains that twins are more susceptible to be born premature with lower birth weight and that IVF twins have poorer outcomes than IVF singletons. This was also found in our randomised control trial. The 2006 figures for England and Wales show that 41% of multiple live births born

from IVF were classified as low birth weight (below 2.5 kg), compared with 56% of all live multiple births in England and Wales and 51% of multiple live births following IVF in 2006 were born preterm compared with 53% of all live multiple births (55% of multiple live births following frozen embryo IVF in 2006 were born preterm compared with 53% of all live multiple births). These figures are alarmingly high and cannot be evaluated in isolation, so it will be incorrect to judge 'what a greater risk- IVF is or prematurity?' However, it has been found that in a natural pregnancy chances of twins is 1 in 100 and recent ratio is 1 in 80, which shows the rise in the rates of twins due to ART treatments and mostly IVF and this in itself answers the question whether IVF is a risk or not. In 2006, 10.9% of singleton live births following IVF were born preterm compared with 6.2% of all live singleton births in England and Wales and 9.7% of singleton live births were born with a low birth weight compared with 6.0% of all live singleton births in England and Wales (Moser et al, 2007). This has also been seen in our very small response rate sample of study 4.

It can be seen from the studies cited in various chapters of this thesis and our own studies that preterm, prematurity, twins and IVF have become more and more intertwined. If we look IVF in isolation we find that apart from the risks of twins and multiple, there is a weak relationship between IVF and drug treated ADHD (Källén et al 2011). Two reviews that follow have been done by the same authors and they report elaborately on the risks of IVF and ICSI in particular. Although out of the scope of this research we thought it was important to highlight these in a summary form. The first review done by Tosti et al (2006) on the impact of IVF on the health of the mother and the child found that the mother suffered from obstetric complications such as placenta previa, gestational diabetes, preeclampsia, and foetal heart rate variability. The majority of the studies included in this review showed no obvious problems in children born after conventional IVF or ICSI, but there was increased risk to both mother and

child due to the multiple gestations due to the transfer of multiple embryos. However, due to ICSI, a specific risk was found, with an excess of malformations in the male urogenital tract and increased incidence of hypospadias. There were few cases of histiocytosis and retinoblastoma also found. The review also reported that that the studies in it reported that specific syndromes such as omphalocoele, Beckwith–Wiedeman, Prader–Willi, Angelman and retinoblastoma observed in IVF babies may be associated with epigenetic alterations probably induced by IVF procedures (e.g. gamete and embryo culture). It also found that a new link between major and minor birth defects and epigenetic changes reported in *in vitro* conceived children had been found.

A more recent review building on the previous review by the same author found that (Fortunato & Tosti, 2010) during ICSI the reactive oxygen species (ROS) have a heavily deleterious impact on the DNA of the sperm and the oocyte, however, has some ability to repair fragmented DNA although incomplete repair may lead to long-term pathology and studies on animals indicate that the use of sperm with fragmented DNA in ICSI can produce genetic and epigenetic changes during preimplantation embryo development. This in turn could alter foetal/placental development and, as a result generate offspring with abnormal growth and behaviour, early aging, and tumours. In the same review, follow up studies showed that even though not significant, ICSI was associated with a higher number of malformations (11.0% vs. 5.6%). One of the studies included in the review which was done at Cornell University in New York, found that in a sample of 5891 neonates although there was no increased incidence of '*de-novo'* chromosomal abnormalities in a small sample of ICSI-born offspring, however, the rates of malformation in these babies ranged from 3.5% to 6.2% and at three years of age (n = 811), 10.4% in ICSI and 10.7% in IVF singletons were at risk of developmental delays. Although not huge, it is still worth consideration. A more alarming finding was in the

group who required ICSI with testicular sperm extraction (ICSI-TESE), in which 80% of the cases were abnormal, with 50% showing triploid/tetraploid karyotypes. the incidence of *de novo* Y-chromosome microdeletions in male children conceived through ICSI or IVF was observed to be statistically significantly higher than in male children conceived naturally (10.8% vs. 0), indicating that the risk of gene mutation may be increased in ART offspring. The earlier reported higher rates of hypospadias in ICSI born male babies compared to the general population still holds relevance. Examination of singleton children at 5.5 years age found out that a history of undescended testicles was found significantly more commonly in boys born after ICSI (5.4% vs. 0.7%), with the result that they had a significantly higher incidence of urogenital surgery (19.2% vs. 8.9%). Other studies have found that among ART singletons, have septal heart defects, and cleft lip with or without cleft palate, oesophageal atresia and anorectal atresia. It also reported from another study that children born after ICSI had reduced number of central retinal branching points and therefore abnormal retinal vascularisation, as compared with the control group (P = 0.0002). Ultrasonographic examination of the foetal heart at 22nd week of gestation in IVF/ICSI conceived babies found that 6% of the foetuses had cardiovascular anomalies. Two cases, one each of atrioventricular septal defect and ventricular septal defect was also found but each was associated with trisomy of chromosome pairs 21 and 18 respectively and there was one case of urinary system also. The review reported that these structural defects slightly exceeded the population risk. Comparing IVF- and ICSI-produced embryos before and after thawing showed that even though statistically non significant, there was an increased rate of *de novo* chromosomal anomalies in cryo ICSI foetuses/children compared with the fresh ICSI group and also major malformations were more commonly noticed in cryo ICSI live borns than in cryo IVF live borns. They also found many rare syndromes such as

Goldenhar syndrome and Rubinstein-Taybi syndrome (RTS) apart from psychological problems for both mother and child similar to that reported by us due to multiple births (Fortunato & Tosti, 2010).

We did not find any extra developmental benefit of being a singleton but other studies have reported contrary to our findings of the first study. These studies have definitely shown that risks from IVF/ICSI increases more so due to the multiplicity so it may be that having singletons could decrease the rates of these complications which are coming forth more frequently now on observation of IVF/ICSI children as the use of the technique increases day by day. Even though our fourth study was very small due to low response it showed more twins had low birth weight. There may be a time in research when it could be possible to separate the risks between the two groups. However, in this current research we have to look into the problems from both these (IVF and multiple birth) with the same spectacle.

Beyond doubt IVF/ICSI has more benefits than complications and is certainly not the problem if it is helping so many sub fertility couples around the world to conceive and start or complete their family as they have every right to do that. It is a scientific and medical process and like many other healthcare processes has risks and side effects; for example, doing even a minor surgery on a patient carries risks of bleeding, anaesthesia, infection, etc. however, this does not deter us from carrying out the procedure because it is important for the wellbeing of the patient. Similarly, IVF is a healthcare process used for the treatment of infertility which has been recognised by the World Health Organisation as an ailment. It therefore implies that IVF will be carried out in the foreseeable future but obviously, like surgeries, we need to be better prepared to tackle the side effects before it gets to epidemic level. Undoubtedly, risk of prematurity has become integral to multiple births, although higher for

triplets and beyond, but still a higher risk for twins than singletons from IVF. In a natural twin birth, due to genetic disposition, the body has the capability to cope with carrying a twin, but because IVF is artificially induced the risks are greater. Although there has been links to placental insufficiency and malnutrition apart from preterm birth, which is the main cause of IVF prematurity, more research is definitely needed to find other causes of prematurity other than IVF.

Studies detailed in Chapter 1 have shown that both IVF singletons (Koivurova et al , 2005) and IVF twins (Ombelet, et al, 2006) are at greater medical risks than spontaneously conceived singletons and twins. Furthermore, IVF twins are at more risk than IVF singletons and details in chap1 have suggested that the complications in IVF births are due to the reason of more frequent incidence of multiples (Olivennes et al, 2005; Bonduelle et al, 2003). The risk of death around the time of birth is 3-6 times higher for twins and 9 times higher for triplets compared to singletons (HFEA 2010).

The very premature twins in study 1 spent an average of 11 days in the NICU with no significant difference to NICU admissions between very premature singletons and twins and the apparent reduction in days ventilated was a non significant difference. However, our RCT study did show that twins were taken to NICU and not the singletons. This has also been suggested by the HFEA's latest figures. The latest figures published by HFEA that show that 40–60% of IVF twins needed to be transferred to the intensive care unit when they are born compared to only 20% of singleton IVF babies and 8% required assisted ventilation compared to 1.5% of singletons (HFEA 2010). The findings in this thesis provide no support for that argument that twins born very premature are at less risk than singletons born very premature so these HFEA figures are of genuine concern. There are few more points that should be considered when

considering the UK IVF population, such as the age of the patient and if that has any influence on the risks of pregnancy on the mother and the child.

In UK, the average age of women being treated for IVF has changed from 34.9 yrs in 2005 to 35.2 yrs in 2007, compared to 30 years in Finland. This late conception age also makes female patients seek more IVF treatment because of the decreasing fertility with age in women. It is now well known that health risks for the woman and baby increases with age and the IVF success rate decreases with age from 22 live births per 100 cycles among younger women compared to 6 per 100 among older women (Klemetti et al 2007). It is difficult to determine an optimal and equal age to stop the resource allocation for IVF. IVF treatment of selected women aged 40–43 has been found to be quite successful (Broekmans & Klinkert, 2004; Klipstein et al, 2005) and natural pregnancies also occur for women in their forties. However, a given age-limit could be an indicator and can encourage women to attempt to start family life (getting pregnant) during the normal fertile age. The responsibility also lies on the society and the family and social and family policy should promote an environment for childbearing at a young age (Klemetti et al 2007). As Chavkin & Johnson (2007) and Stillman (2007) have pointed out this is a big challenge especially in countries that do not have policies supporting parents who both work.

7.5 Elective single embryo transfer

Beyond doubt it has been established by researches around the world that a fresh cycle with SET has a lower implantation rate compared to a fresh cycle of

DET (Gerris et al 1999; Martikainen et al, 2001; Thurin et al 2004; Lukassen et al 2005; van Montfoort et al 2006; Pandian et al 2009; Baruffi

et al 2009). Using a statistical model of live birth and twin outcomes Roberts et al. (2009) demonstrated that in unselected cycles, the live birth rate would be reduced by up to 20–30% (from 21% to 17% live birth rate) in order to achieve a 10% twin rate which is the current target of the HFEA if rate of SET is 55%. Double embryo transfer was standard treatment in the unit but the twinning rate was only 18.5%, much lower than the national average. The study shows that patients who can get pregnant with fresh DET may have their chances decreased with fresh eSET.

However, apart from excluding the possibility of cryopreservation the study assumes no attempt to select patients for single embryo transfer. Selection of patients for SET, on the basis of twin risk, at rate of SET at 20%, the conception rate would have only increased to 18.5% (Roberts et al. 2009). However, even in selected patients with probability of better outcomes, a decrease in live birth rate with SET compared to DET has been reported by some studies (Gerris et al 2005). Furthermore the unit on which the figures are modeled (Roberts et al 2009) cannot be considered typical as it included only couples without a previous live birth and with a minimum of 3 years infertility.

Often in eSET trials a second IVF cycle with frozen embryo achieves rates very close to DET and therefore supporters of DET would argue that cryopreservation is also an option in DET and that it is unclear how many eSET IVF cycles would be needed to give conceptions rates which equate to the rates found in DET (van Wely et al 2006). The study done by Veleva et al (2009) found out that in the DET period, 826 women had 1359 fresh and 589 frozen embryo transfer compared to the eSET period where 684 women had 1027 fresh and 683 had FET cycles. This shows that more cycles were needed per patient in the eSET period. However, when Veleva et al (2009) compared outcomes in periods with low eSET to subsequent periods with eSET and concluded that eSET with

cryopreservation was associated with a higher cumulative birth rate per woman (41.7% vs. 36.6%) and lower twinning rates (8.9% vs. 19.6%) compared to DET periods. This is indeed an encouraging sign when considering the efficacy of eSET.

Similar encouraging results have been reported by many other studies; such as Saldeen & Sundstrom (2005) showed that the twinning rates declined from 22.6% to 6.2% when eSET was used for IVF patients in Sweden but the clinical pregnancy rate did not vary significantly and remained at a level comparable with DET; another study found that the rate of twins after DET was 34 % compared to 0% after SET even though the cumulative live birth rates following the transfer of fresh and frozen embryos was similar between SET (43%) and DET (45%) groups (Le Lannou et al, 2006); Styer et al, (2008) found that single blastocyst transfer showed equal rates of pregnancy to double blastocyst transfer but it had the benefit of decreased twin rate and Veleva et al (2006) showed in their retrospective study that eSET can be equally effective in women between 36 and 39 years as in younger women undergoing IVF treatment. A more detailed evaluation of these studies is mentioned in chapter 1.

These contradicting evidences often pose dilemma with the licensing authorities, clinicians and patients alike and illustrate the importance of patient information that allows patients to participate in the decision process.

7.6 Importance of health professionals in decision making

Health professionals were the most important source of information for many IVF (Blennborn et al 2005) patients. Clinicians, besides partners, had the biggest influence on patients when making choices of number of embryo transfers (Glazebrook et al 2007; Blennborn et al 2005). Our RCT with patients and their partners found that the majority, 57% of the patients

felt that they had made the decision about number of embryos to transfer entirely by themselves and only 14% of the patients felt that the decision had been shared equally between patient and doctor. This view was not supported by partners' responses, where 17 % felt that the decision had been made entirely by the patient and 50% felt the decision had been shared equally between patient and doctor.

Clinicians are concerned about their patients' chances of conceiving, the reimbursement plan and therefore not many IVF clinicians perceive twins as a complication. The attitudes of clinicians differ from clinic to clinic and country to country. Clinicians in a public healthcare setup prefer more SET and than DET and often follow the legislation. A study looking into attitudes of clinicians towards SET and twin pregnancy found that the majority of the participating doctors (51%) were from public IVF clinics and only 30% participants came from private IVF centres (Bergh et al 2007). Van Peperstraten et al (2008) found that participant doctors thought legislation would be good for implementation of eSET and lack of it is an important factor in influencing the attitudes of the clinicians and equally the patients. This reflects that there is a need to assess the attitude of both clinicians and patients towards the risks of a twin birth and the use of eSET. A universal platform where this can be measured would be a useful tool and this has been reflected in our validation of the ATIPS-R scale (chapter 4) developed (Chapter 3) as part of this research.

Our literature review in chapter 1 has shown that at least two studies reported on cumulative birth rates with eSET (Thurin et al, 2004 and Lukassen et al 2005) and one of the studies has been very robust in its trial conduction (Thurin et al, 2004). It was multicentre based and with a good number of patients. This trial is therefore particularly very significant and for that reason it has been used in the leaflet (DA) developed during this research. It was probably after this study that Sweden now has

legislation for eSET and has one of the highest rates of eSET in the whole world. This rate rose from nearly 55% in 2003 to 70% in 2005 (Maheshwari et al, 2010). The results of these trials can not only demonstrate the effectiveness of eSET but can also exhibit the usefulness or failure of legislation for eSET use. However, scenario is different in different countries and therefore a similar research in UK based clinics could reflect a more realistic picture of the outcome of eSET use in UK patients.

7.7 Need for intervention

There is a clear need for intervention between clinicians and patients to measure the attitude of both clinicians and patients at a time when NHS funding is only limited to 1 IVF cycle even though NICE recommends 3 IVF cycles for women aged 23-39 years when the chances of success are more than 10% (NICE 2004). To measure this attitude and to identify the places for intervention the ATIP scale was developed (Chapter 3). The study showed that a scale (ATIP) originally developed for use with health professionals was acceptable to both IVF patients and clinicians in terms of ease of use and understanding and was able to detect differences within and between the two groups.

Our study 2 (Chapter 3) found that nearly 50% of the IVF health professionals disagreed with this statement that a twin pregnancy increased the chance of a premature birth (X^2=4.38, df=1, p=0.036) and 39% of IVF professionals agreed that the best outcome of IVF treatment is a twin pregnancy unlike only 27% of non-IVF health professionals (Table 3.7). However, more than 40% of both IVF and non-IVF group of health professionals agreed that the rewards of a twin birth are worth any risks to the baby (Table 3.7).

Interestingly, study 3 (Chap 4) found that IVF clinicians' scores on the A-Twin are low (mean A-Twin= 27.94, SD=7.96) suggesting that, as a group, they recognise the risks associated with a twin birth. Unlike study 2 (Chap 3), 100% IVF clinicians agreeing the best outcome of IVF treatment is a single pregnancy, but similar to study 2 (Chap 3) 17.6% agreed that the rewards of a twin birth are worth any risks to the baby and 23.5% agreed that the risks associated with a twin pregnancy are not so great. This clearly demonstrates their attitude towards twins like many other studies which have argued that a twin birth should not be seen as an adverse outcome (van Wely et al. 2006, Gleicher, et al, 2009.). The study also found that neither the age of the clinicians nor their years of experience in the IVF world were in any way associated with their attitudes towards twins and eSET.

The attitude of IVF clinician's towards eSET is further demonstrated by the fact that they are not very expressive of the positive attitudes towards eSET (mean A-eSET= 25.88, SD=6.36). The majority (82.4%) of the clinicians are against universal application of SET, although majority (64.7%) do agree that younger patients should have eSET but 58.8% think it is better to risk a twin birth than have more IVF cycles. Majority of the participant IVF clinicians demonstrated peer pressure and perceived their colleagues as not favouring SET with only 23.5% agreeing doctors involved with IVF favour SET. They also regard patients as strongly against single embryo transfer with only 11.8% agreeing patients favour eSET. This study (Chapter 4) has indeed been able to reflect many of the factors influencing the clinicians' attitudes towards eSET such as professionals' negative attitude towards eSET, doubts about consequences of full implementation of eSET, lack of negative experience with twins, lack of responsibility for the couple, for the unborn child, lack of knowledge of patients about essential eSET aspects, bad financial situation/social economic status of patients, lack of responsibility on part of

patients for the consequences of the choice eSET/DET, lack of legislation about eSET, competition between hospitals, peer standards, absence of protocol and bad performance publicly available similarly as identified by Van Peperstraten et al, (2008) which is also mentioned in detail in chapter 4.

A retrospective study looked into the live birth rates in 760 couples referred in 1994 who had waited for up to 4 years for IVF treatment and compared with the live birth rates of 199 couples referred at a similar time to Manchester Fertility Services, a fee-paying unit, where they received IVF treatment shortly after referral. The study found that the waiting time was advantageous in that 17.8% (135 of 760) of the couples referred to St Mary's Hospital conceived without IVF treatment and 60% of these patients within one year of referral. It also found that the waiting time was disadvantageous to women aged 30-34, in whom treatment was delayed by 3-4 years because of the waiting time to get the treatment. A low figure of only 26.8% (204 of 760) of couples originally referred eventually received NHS-funded IVF treatment at that hospital. The researchers recommend that a waiting time of a maximum of 18 months would be adequate to adjust the spontaneous conceptions and at the same time also reduce the adverse effect of long waiting times to get a single cycle of free IVF and this could give better success for older women (Horne et al, 2003). This study reflects the frustrations of the health professionals because of the long waiting times and therefore the reluctance for eSET and positive attitude towards twins.

Our study 3 (Chapter 4) unlike study 4 (Chapter 6) found that female IVF patients did hold quite favourable attitudes towards a twin birth as many other studies (Pinborg et al 2003; Blennborn et al, 2005). Although some earlier studies have reported finding a more favourable attitude towards a multiple birth was associated with increased age in female IVF patients

(Gleicher et al. 1995; Grobman, et al. 2001), our study found that older women were less positive about twins (r=-0.75, n=8, p=.031) and more positive about eSET (r=-0.68, n=8, p=0.066) and even in partners, older men were more positive about eSET (r=-0.881, n=7, p=.009).

Our study 3 (Chapter 4) found very unfavourable attitudes towards single embryo transfer (mean = 32.04/42, SD=6.04). This attitude is clearly revealed in the responses to individual statements with only 5% agreeing that patients favour single embryo transfer and only 2% agreed that all IVF patients should have single embryo transfer.

In accordance with previous studies (Gleicher, et al. 1995; Grobman, et al. 2001; Child et al 2004, Henderson et al. 2004; Ryan, et al. 2004) our study 3 (Chapter 4) also found that parity and previous cycles of IVF were associated with a more favourable attitude towards twins. This can be a reflection of the desire for an instant family in these infertility patients. Although not significant, these findings are further supported by responses to the statement “the best outcome of IVF treatment is a twin pregnancy” with 65.7% of women without children agreeing compared to 45.5% of those with children. Women with no previous children were significantly more positive about twins than women with previous children (t=2.21, n=100, p=0.031) unlike women who were having their first IVF cycle who were significantly more positive about single embryo transfer (z=3.94, n=100, p=<0.001). Also women having their first cycle of IVF were significantly less positive about twins than women on their second or subsequent cycle of IVF (t=2.52, n=100, p=0.013), (Table 4.2). Experience of fewer previous cycles of IVF was also associated with significantly more positive attitudes towards eSET (r=0.31), n=100, p=0.002). Parents with children were significantly more likely to recognise that a twin birth would make it harder for them to return to work (57.5% vs. 28.4%; X^2= 8.1, df=2, p=0.017). Study 4 (Chap 6) demonstrated lower

levels of decisional conflict in patients at embryo transfer were associated with more positive attitudes to twins at baseline (r=-0.819, n=7, p=0.024) and less positive attitudes to eSET at baseline (r=-0.777, n=7, p=0.040). We also found that although statistically insignificant, at the start of the treatment, patients undergoing embryo transfer had higher anxiety level similar to Højgaard et al (2007) and this was associated with more positive attitude towards twins than their partners similarly found by many other studies (Højgaard et al 2007; Child et al., 2004; Ryan et al., 2004; Pinborg et al., 2003).

Study4 (Chapter 6) found that although not significant, there was a positive relationship between patients' attitudes to twins and their partners' attitudes to twins but there was no relationship between patients and partners attitudes to single embryo transfer, similar to Kalra, et al (2003). There was no relationship between educational level and attitudes to twins in women or attitudes to eSET but although statistically insignificant, there was an association between higher educational levels in partners and more positive attitudes to eSET and less positive attitudes to twins. This difference in attitude in educated partners demonstrate that if properly briefed with facts, partners can play a massive role in influencing their female partners decision in making a choice about SET.

This study is the only work to use a valid and reliable measure to assess attitudes to twin IVF pregnancies and single embryo transfer. A limitation is that it sampled clinicians and patients in only one infertility service. However, this group is one of the leading providers of IVF treatment in UK with 11 clinics spread across England.

ATIPS-R seems to be a reliable scale that can be used internally and externally to measure attitudes towards risks and benefits of twin IVF births and also attitudes to single embryo transfer in IVF treatment. There is no other validated scale like ATIPS-R that can be used universally in

assessing attitudes towards twins and single embryo transfer and ATIPS could prove a useful tool for evaluating interventions to promote single embryo transfer and for evaluating service factors associated with high rates of twin IVF conceptions. This is demonstrated in our study four (Chapter 6), where, although the sample size was small the scale was able to detect a change in partners' attitudes to eSET. The results clearly demonstrate the usefulness of a reliable method to access IVF patients' and clinicians' attitudes. It may be that rather than provide information about the risks of twins as previous studies have done, it may be more helpful to emphasise the benefits of a single birth and provide evidence about eSET and involve active participation of the patients in the decision making process. A meta-analysis of the effectiveness of the HBM in predicting health behaviour (Christopher & Carpenter, 2010) found that perceived benefits and barriers were good predictors of health behaviour, particularly health protective behaviours. Since eSET could be considered to be a health protective behaviour this is very relevant to the development of health education materials for patients undergoing IVF treatment. Promoting a sense of threat was less effective in changing people's behaviour, suggesting that the strategy of simply informing people about the risks associated with a twin birth is not appropriate. The same meta-analysis also found that it was important to measure perceived barriers and benefits close in time to the behaviour. This suggests that the ATIPS-R could be very useful. It is quick to complete and could give a reliable assessment of people's perceptions of the benefits a single birth and barriers to eSET. The ATIPS-R could also assess responsiveness to information.

7.8 Use of decision aid

It was thought that providing couples with more information about the potential risks to the babies may be an effective strategy to change their

attitudes towards a twin birth as they appear knowledgeable about the risks for the mother and prepared to accept these. Patient education and helping them to make an informed choice could be a way forward. Evidence based medicine is in use in also branches of medicine from psychiatry to surgery, obstetrics and gynaecology and many others. This gives patients the opportunity to understand about the condition they are suffering and then make a choice which is knowledge driven. This not only reduces the decisional conflict, anxiety and stress in patients but it also gives them the satisfaction that they were able to choose the treatment option for themselves. Often this approach brings the desired good results in the best interest of the patients.

IVF patients in UK are given (Appendix 7) a detailed leaflet containing information about multiple births. Apart from being exhaustive, the layout is not very eye catching. Our study4 (Chapter 6) found that even having a bespoke DA could not change the attitude of the participants, but the sample size was very small and should be further looked into. Van Peperstraten et al (2010) have piloted a leaflet for IVF patients for intervention and many other researches have used information sheets in their studies. Four previous studies have used information provision in an attempt to increase the uptake of SET (Hope & Rombauts, 2010; Murray et al, 2004; Ryan et al 2007 & Newton et al, 2007). Our leaflet (Appendix 8) is informative but not exhaustive. With bar charts and graphs it gives the figures from important studies in a colourful and pictorial format. However, patients often find face to face discussion with staff members as the most useful tool (HFEA, 2010; Blennborn et al 2005). A key feature of decision aids should be to encourage discussion between patients and doctors.

Many studies before that have looked into the decision-making process have mainly focused on two issues, either couples' desire for twins or their

inadequate knowledge about the complications of twins (Blennborn et al, 2005; Newton et al, 2007; Child et al, 2004; Ryan et al, 2004; Kalra et al, 2003; Pinborg et al, 2003; Grobman et al, 2001). However, the recent HFEA survey has shown that the important factor for the patients not choosing eSET was the fear of not conceiving (Blennborn et al 2005; 2007; Van Peperstraten., 2008) and low implantation rate with SET and this can cause a situation of decisional conflict while deciding about eSET. For example, Ryan et al (2007) found that when the chance of pregnancy was equal to DET, 75% chose eSET, this fell to 7% when the chance of preganacy was reduced by 30%.

Our study 4 (Chapter 6) found that attitudes to choice of eSET and twin pregnancies did not change by increasing information unlike (Newton et al, 2007) who found that the desirability of elective single-embryo transfer increased and the desirability of twin pregnancy decreased, among both men and women by providing them with risk information. Likewise, additional information in the form of a bespoke, piloted decision aid did not increase the acceptability of SET in female patients similar to Murray et al (2004). However, without a comparison group it is difficult to know if patients might have become more negative towards eSET closer to the point of treatment. Decision difficulty scores did not change much after information like Højgaard et al (2007) and there was no association between opting for twins and having received information and feeling well informed. In our study, where all patients had double embryo transfer, more positive attitudes to eSET and less positive attitudes to twins were associated with more decisional conflict suggesting that attitudes did impact on the decision process. Few studies have used a theoretical framework for developing information for infertile couples. We used the Health Belief Model to guide the development of the information. This usefulness of this model as a framework for health information has been acknowledged in a study exploring women's perceptions of late fertility

with a view to preventing involuntary childlessness (Hashiloni-Dolev et al 2011).

7.9 Limitations of this study

This whole research has been a very ambitious project and as with any research there are always limitations to healthcare and patient related projects. It takes time and proper funding to carry on a project like this. However we have been able to achieve with the limitations around. This research can become a basis for further research which other researchers cans carry it further.

We have already highlighted our strengths and weaknesses in our individual research chapters. To summaries our limitations, in our first study which was a retrospective analysis of data of a large controlled randomised trial on premature births. As this was a retrospective study we could add anything to the data collection to increase our sample size and therefore had to work on what was available. As mentioned earlier in Chapter 2 the sample size of twins was also very small (which may have led to type two errors) compared to singletons and therefore a more or less homogeneous sample and there was also no record of any IVF births. Therefore we could not comment or differentiate natural premature children with IVF babies. Therefore this study is not robust enough to paint the right comparative picture of cognitive development of a twin, and especially an IVF twin, compared to an IVF singleton.

Still the study's good initial response rate, the excellent follow-up rate and the prospective study design (which avoids selection bias at 2 year assessment) was good and the two year assessment by trained teachers using a valid and reliable scale was the strength of this study.

Our study 2 was an anonymous survey, using the ATIPS 44 item scale. It had large sample size (Kline, 2000) although a moderate response rate of

above 50%. As it was an anonymous survey the chances of biased reports are less unlike focus group interviews and one to one interview where the chances of leading and prompting the participants are quite high. The aim of this study was to develop a measure that had reliability and was valid. This measure seems to be a reliable method of measuring the attitudes in the Risk and benefits subscale which had a good Cronbach's alpha 0.7 and also the Single embryo transfer subscale with a satisfactory Cronbach's alpha of 0.53 (Bowling, 2005). The scales have a good spread of scores and an absence of floor and ceiling effects suggesting that the scale would be useful outcome measure to detect changes in attitudes and to compare groups.

Our third study is the only work to use a valid and reliable measure to assess attitudes to twin IVF pregnancies and single embryo transfer. A limitation is that it sampled clinicians and patients from only one infertility service provider. However, this group is one of the leading providers of IVF treatment in UK with 11 clinics spread across England. Both the clinical pregnancy rate (42.4 % vs. 35.7%) and live births (42.1% vs. 32%) at this centre are above the national average rate in women below 35 years of age. This trend is reflected in other groups of patients as well.

The questionnaire was anonymous which is likely to have enhanced the validity of the responses; however it also meant that it was not possible to determine how representative the sample was. We were also not able to get the participant women to comment on the feasibility of this measure because the Clinic's ethics committee had not given us the permission to talk to any patients. Another limitation of the study was its cross-sectional design. In order to further evaluate the validity of the measure it would be useful to use the measure to predict patient choices or clinical decisions.

Finally, our fourth study was not a success with a very poor response rate which could not be estimated, for reasons beyond my control, but had it

been successful we would have had very good results on many aspects of IVF treatment, including attitudes to risks and benefits of twins and the use of single embryo transfer. Clinical staff was not blinded since the intervention leaflet encouraged patients to discuss their decision with their doctor. However we do not think that not blinding the staff would have been a problem in recruitment patients. The study included only patients coming for their first IVF treatment and this could have been a problem for recruitment but we do not have any data about how many first time IVF patients came to the clinic during our period of study.

7.10 Clinical implications of the thesis

Advances in IVF treatment have improved outcomes for many infertile couples. Whilst increasing the implantation rate through transplantation of more developed embryos and better selection of embryos will improve the chances of a live birth, such developments could also potentially increase rates of multiple births unless clinical services adjust their practices to accommodate these developments (Gibbons et al 2009). Stillman et al. (2009) did a retrospective study at Shady Grove Fertility Reproductive Science Center in USA and looked into elective embryo transfer and the payment of the IVF treatment which has noted an overall rise in singleton pregnancy rates and decreased twin rates overtime. In all 784 eSET was performed during the 6 year study period from 2002 to 2007. All women had at least two high quality embryos available for transfer. Patient using their own embryos had similar pregnancy rate whether they had SET or DET (65% vs. 63%), but the twin rates was really much lower with SET (1% vs. 44%) compared to DET. Women using donor eggs had a lower pregnancy rate with eSET (63% vs. 74%), but yet again the twin rates were very low (2% vs. 54%). The rise in eSET use was mostly seen in patients with insurance or participants of the shared risk money-back guarantee program of the centre. This yet again reflects the earlier

argument in the beginning of this chapter that funding plays a very important role in changing attitudes and decision making.

The results of studies demonstrating superior outcomes for eSET suggest that it is time to move away from education that focuses on the risks associated with multiple births and towards an education process that allows patients to make informed decisions about embryo transfer. In circumstances where financial barriers are removed and conception rates comparable patients are more likely to choose eSET.

This thesis has demonstrated a need for patient and clinician education. Health professionals involved in IVF were no more aware of the risks associated with a twin birth than other health professionals. In particular there was evidence that the health risks for twin infants were under estimated. Twins are at an increased risk of premature birth and this thesis has demonstrated that twins have no less risk of the negative sequel associated with very premature birth, including poor neurodevelopmental outcomes. There was also evidence that although health professionals and patients were not, as a group, positive about twins, they were negative about eSET. An evidence-based decision aid which highlights the benefits of eSET, including reduced risk to infants, could make a strong contribution to the promotion of eSET. It is important that such information reflects the most recent research and such developments should be accompanied by clinician training and such a programme could be evaluated using the ATIPS which has proved valid and reliable in both patients and health professionals.

7.11 Conclusion

The literature review demonstrated that though the live birth rate following IVF treatment is lower with a single cycle of eSET compared to a single cycle with DET, the cumulative live birth rate is similar, emphasising the

importance of funding for repeated cycles and cryopreservation of embryos. The review also demonstrated that DET was associated with high rates of twin birth in comparison to eSET where the twin birth rate was virtually nil. This is an important clinical outcome given the increased risks of preterm birth and low birth weight in a twin pregnancy. Analysis of data from a follow-up of a representative sample of very preterm infants demonstrated that twins had similar neurobehavioural outcome at two years corrected age even though born into a better socioeconomic environment with older, and therefore more mature, mothers than singletons in the study. Twins also had statistically higher rates of severe malformation compared to singletons.

Despite this evidence, patients and clinicians had rather negative attitudes to eSET as measured by the ATIPS developed in chapters 3 and 4. Although health professionals were less positive about twins than in previous studies there was evidence that, like patients, they underestimated the risks to the infant of being a twin. The two subscales (A-SET & A-TWIN) proved to be reliable measures of attitudes to a twin birth and to eSET, in health professionals and patients, with good internal consistency. The scales discriminated between patients having their first cycle of treatment and those with previous cycles and patients with previous children were less positive about twins than those without children as predicted. The decision aid leaflet developed in chapter 5 conformed to recommended standards for an effective decision aid tool. It also used the Health Belief Model to support the strategy of highlighting the benefits of a single IVF birth. Although it was not possible to evaluate the leaflet in a randomised controlled trial as planned, the study provided a useful basis for future research and provided further validation for the ATIPS. Female IVF patients who were more positive about twins and less positive about eSET at recruitment to the study experienced less decisional conflict about the number of embryos to transfer in an

environment where DET appeared to be common. Results also showed that in a very small group of male patients who had received a decision aid leaflet to help them make a choice about embryo transfer, attitudes to eSET became more positive over time. Further research is needed to explore the use of a DA in the context of IVF treatment and decisions about embryo transfer. The ATIPS is a useful outcome measure to explore the effectiveness of educational interventions to promote the uptake of eSET in a choice-based health system.

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APPENDICES

APPENDIX 1

Information sheet study 2

APPENDIX 2

Demographic questionnaire for different participant groups of study 2 with the long (44 questionnaire) ATIP scale

APPENDIX 3

Short (20 questionnaire) ATIPS-R

APPENDIX 4

Study 4 Ethics approval

APPENDIX 5

Study 4 details

- Patient/ Partner information pack
- Consent form
- Patient/ Partner demographic and ATIPS-R questionnaire

APPENDIX 6

Study 4 follow-up questionnaire

- Anxiety scale
- Decision conflict scale
- ATIPS-R
- Free post envelope

APPENDIX 7

HFEA leaflet

APPENDIX 8

Study 4 Decision Aid leaflet

Publications

- Presented at the International conference on “Controversies in Reproductive Medicine” 2006 Development and preliminary validation of the Attitudes to Twin IVF Pregnancies scale

- Abstract accepted as Poster in Society for Reproductive and Infant Psychology (SRIP) Conference 2007 St Anne's College, Oxford-Validation of the Attitudes to Twin IVF Pregnancies scale in a patient population

- Presented at infertility conference at Middlesex university, UK 2008, Validation of the shorter Attitudes to Twin IVF Pregnancies scale in patient and IVF specialist groups

- Abstract published in Journal of Reproductive and Infant Psychology -2008

- Paper published in Journal of Assisted Reproduction and Genetics- 2011