Chapter 8
Multiple Pregnancy Update: Issues Following Assisted Reproductive Techniques

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Introduction

It is estimated that infertility affects 1 in 7 couples of reproductive age in the United Kingdom [1]. Births following in vitro fertilisation (IVF) techniques are said to account for 2 % of all births in the UK [2]. Approximately 13,000 IVF babies are born each year, with one in five IVF pregnancies resulting in multiple gestation compared with one in 80 from natural conceptions [2]. However, overall the trend is downwards, dropping from 26.6 % in 2008 to 16.3 % in 2014 [3] (Fig. 8.1). Multifetal conceptions are the single most important determinant of pregnancy and long-term outcomes for both the mother and baby and these risks increase exponentially with the number of fetuses. There is good evidence that IVF conceived pregnancies, even if a singleton pregnancy, are at increased risk of adverse outcomes for the majority of pregnancy complications and these risks increase further with multiple pregnancy [4]. Monozygosity (MZ) is associated with higher risks of adverse outcomes. While the majority of MZ twins are spontaneously conceived (22 % compared with 2 % of IVF twins), there are some technologies, which increase the risk of MZ twins with IVF [5]. Assisted conception technologies such as IVF increase the risk of these pregnancies by twofold, although overall incidence remains low [6].

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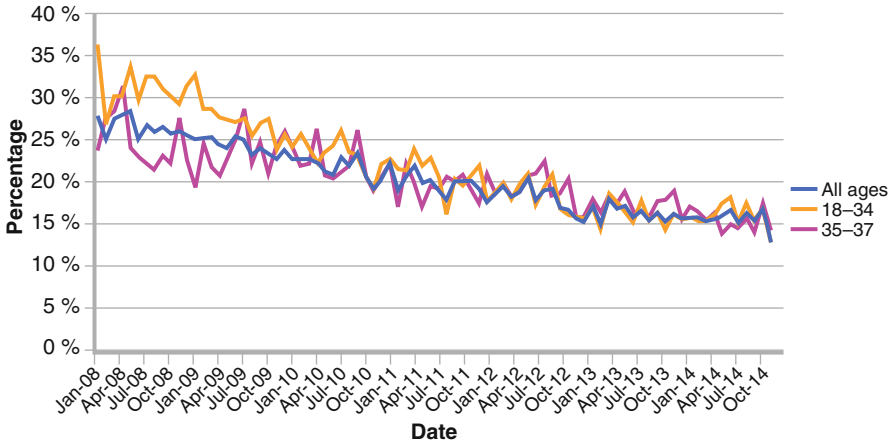

Fig. 8.1 Monthly multiple pregnancy rate (% of pregnancies) 2008–2014 (Source: Human Fertilisation and Embryology Authority (HFEA) [3])

What Are the Maternal, Fetal and Neonatal Risks Associated with Multiple Pregnancies?

Multiple pregnancy is considered to be the most common adverse outcome and largest health risk associated with assisted reproductive technologies (ARTs) [2]. Perinatal mortality rates are higher for multiple pregnancies. In 2009 the stillbirth rate was 12.3 per 1000 twin births and 31.1 per 1000 triplet and higher-order multiple births, compared with the singleton perinatal mortality rate, which is 5 per 1000 births [7, 8]. In multiple pregnancies 66 % of stillbirths are associated with growth restriction and birth weight less than 10th centile [7]. Approximately half of twin pregnancies will result in prematurity [2, 7]. Preterm birth is associated with an increased risk of long-term mental and physical handicap including cerebral palsy, mental disability, long-term learning difficulties and chronic lung disease [2]. The risks of producing a child with cerebral palsy are eight-times greater in twins and forty to fifty-times greater in triplets compared with singleton pregnancies [8]. Triplet pregnancies are associated with preterm birth before 37 weeks gestation in over 90 % of cases, leading to significant neonatal morbidity and mortality. Major congenital anomalies are 4.9 % more common in multiple pregnancies than in singletons [7].

These risks were highlighted in the 2006 Human Fertilisation and Embryology Authority (HFEA) report led by Professor Braude: “One Child at a Time” [9]. This investigation group was set up in response to growing concerns regarding the increasing rates of multiple pregnancies following ARTs as clinics often transferred more than one optimal embryo in order to increase pregnancy rates. As well as neonatal mortality, it also identified maternal risks, which include higher risks of miscarriage, gestational diabetes, pregnancy-induced hypertension, pre-eclampsia, impaired fetal growth and stillbirth, and problems during labour including

Table 8.1 Summary of the risks of multiple pregnancies to mother and baby

	Risk
Mother	Higher rates of **miscarriage**.
	Higher chance of **pregnancy induced hypertension**: 20 % in women pregnant with twins compared with 1–5 % in women pregnant with a singleton.
	Higher risk of **pre-eclampsia**: up to 30 % for twin pregnancies compared with 2–10 % in singleton pregnancies.
	Higher risk of **gestational diabetes**: up to 12 % in twin pregnancies compared with around 4 % for singleton pregnancies.
	Higher chance of **intervention in delivery**: elective and emergency caesarean section rates are higher for mothers of twins.
	Maternal mortality associated with multiple births is 2.5 times greater than with singletons.
Baby	**Premature Birth**. Preterm delivery rate is increased by 50 % compared with singleton pregnancies. 10 % twin births take place before 32/40 compared with 1.6 % singletons.
	Perinatal Mortality. Five times higher in twins in 2013 than singletons
	Neonatal Care/Admission to NICU. 40–60 % twins will be transferred to NICU when they are born, compared with 20 % IVF singletons
	Additional Health Complications:
	Respiratory distress
	Cerebral Palsy
	Delay in Language Development
	Disability
	Congenital malformations

Data from Braude [9]

intrapartum hypoxia, obstetric haemorrhage and increased need for elective and emergency caesarean section [6, 9] (Table 8.1).

The Barker Hypothesis predicts that adverse antenatal conditions can lead to long term consequences in the adult. Certainly the increased risks of multiple pregnancies with or without ARTs, such as hypertension and diabetes may lead to cardiac and metabolic disturbances in later life, which cannot be ignored. Epidemiological data are needed in IVF adolescents and adults [6].

Assisted Reproductive Technologies and Multiple Pregnancies: How Does It Happen?

Assisted reproduction technologies (ART) aim to approximate male and female gametes in order to create an embryo with the hope of subsequent embryo implantation leading to a clinical pregnancy. Techniques include intrauterine insemination (IUI) where motile sperm are placed in the uterine cavity close to the fundus in a woman with confirmed tubal patency or in-vitro fertilization (IVF) where embryos are created outside the body and subsequently replaced in the uterine cavity. Both

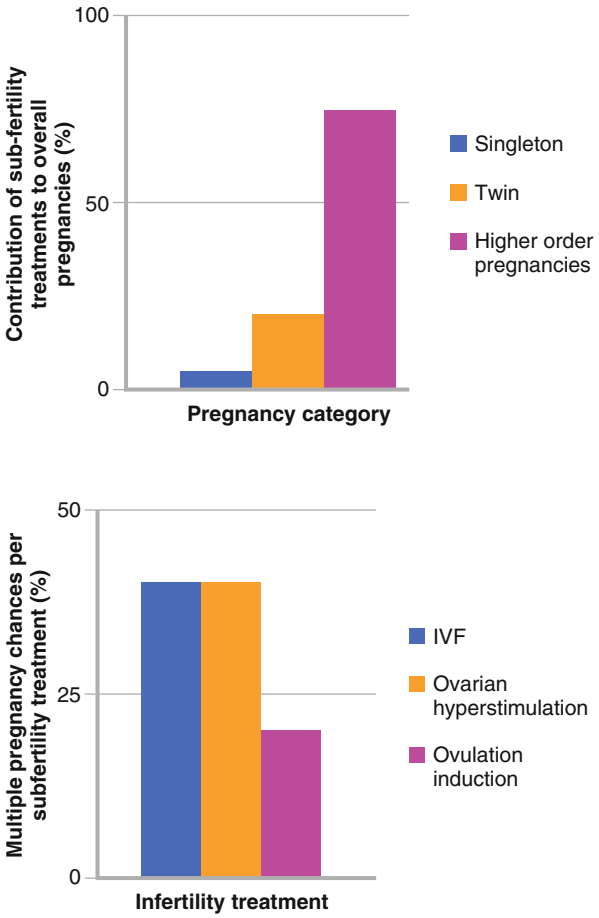

Fig. 8.2 Contribution of sub-fertility treatments to overall pregnancies (*upper graph*) and reported frequency of multiple pregnancies in relation to IVF, ovarian hyperstimulation and ovulation induction (*lower graph*) (Used with permission of Elsevier from Fauser et al. [11])

IUI and IVF treatments can be carried out in natural cycles but have disappointingly low results so that almost all treatments (97.6 % [3]) now include an element of ovulation induction to improve pregnancy rates. Gonadotrophins are the most common method of ovulation induction (OI) for ART inducing multi-follicular development. In IUI treatment, development of multiple follicles increases the risk of multiple pregnancy [10]. Methods to reduce the risk of multiple pregnancy with IUI include abandoning treatment, conversion to IVF, switching to oral estrogen antagonists and accepting lower success rates or considering fetal reduction in an established multi-fetal pregnancy. In IVF treatment the HFE Act permits the transfer of more than one embryo which also increases the risk of multiple pregnancy in selected groups. Strategies to reduce the risk include elective single embryo transfer (eSET) and blastocyst culture. Births resulting from infertility treatments account for around 1–3 % of all singleton births, 30–50 % of twin births and greater than 50 % of higher order multiples (Fig. 8.2) [11].

Ovulation Induction

The aim of OI is to use the lowest effective dose of fertility drug in order to achieve monofollicular ovulation for patients with anovulatory infertility [12]. This is then repeated monthly until pregnancy is achieved for up to six to nine cycles. The method of ovulation induction depends on the ovulatory disorder, classified by the World Health Organization [13]. The two groups that would benefit from ovulation induction are those with hypothalamic pituitary failure (Group I: hypothalamic amenorrhoea or hypogonadotrophic hypogonadism) and hypothalamic pituitary dysfunction (Group II: normogonadotrophic, predominantly polycystic ovary syndrome).

In WHO Group I, women may have low or normal serum FSH and LH, with low estradiol concentrations and normal or low testosterone. They do not have a withdrawal bleed with a progesterone challenge test [13]. Ovulation is induced either with pulsatile gonadotrophin-releasing hormone via a pump or with urinary (FSH and LH) or recombinant gonadotrophin (FSH) therapy. The aim is to support the growth of a single follicle until it reaches 16–18 mm size when hCG is administered to trigger ovulation. Usually a low-dose step up regime of gonadotrophins is used to minimise multifollicular development, reducing rates of multiple pregnancy and ovarian hyperstimulation [12]. If the trigger of hCG is administered in the presence of more than one large follicle the rates of multiple pregnancies exponentially increase, with reported rates of 50 % with greater than 3 large pre-ovulatory follicles [10]. It is therefore recommended to cancel the hCG trigger and to advise the couple to avoid unprotected sexual intercourse in that cycle if there are >3 pre-ovulatory follicles developed.

In WHO Group II disorders, clomifene citrate is used for stimulation of ovulation by blocking the estrogen receptors in the hypothalamus and blocking the negative feedback effect of estradiol [12], leading to increased endogenous FSH secretion and stimulating follicular development. Again the aim is to use the lowest necessary dose of clomifene in order to nurture one follicle. The risk of multiple pregnancy rises from the background rate of 1 in 80 to 1 in 10–20 with clomifene use, becoming more common with the use of higher doses of clomifene in those with PCOS [14]. Side effects of clomifene include Ovarian Hyperstimulation Syndrome (OHSS) (1–6 %) [12], visual disturbances, nausea, vomiting, dizziness and in some cases seizure activity.

In this same group of ovulation disorders, FSH can be used for women resistant to clomifene to achieve ovulation. As for the Group I disorders a low-dose step up regime is employed to reduce the risks of multiple pregnancy and OHSS. In some cases aromatase inhibitors such as letrozole have been used. They work by decreasing the aromatization of androgens to estrogens, decreasing the negative feedback cycle of estradiol and increasing follicular growth [12]. Pregnancy rates are promising with a lower incidence of multiple pregnancies, and a more favorable effect on the endometrium compared with clomifene [15].

Gonadotrophin Stimulation in Intrauterine Insemination (IUI)

IUI with controlled ovarian stimulation is widely used in cases of unexplained subfertility and mild male-factor infertility before resorting to more invasive options like IVF [16]. In contrast to older studies, more recent evidence has suggested that using IUI with gonadotrophin stimulation may correct subtle ovulation issues, leading to a greater number of oocytes and consequently a higher live pregnancy rate. The offset is of course multiple pregnancies, rates of which have been reported as high as 20–30 % in some centres regardless of the infertility cause [10, 11]. Reduction of the risk of a multiple pregnancy can be obtained by either avoiding any gonadotrophic stimulation (a 'natural cycle'), using strict cancellation regimes or using a low-dose step up regime similar to that described in the last section of this chapter. This can result in a reduction to 10 % multiple pregnancy rate without an overall impact on live birth rates [17]. Recent NICE guidelines [1] do not support using this method in those with unexplained infertility and instead suggest that it is restricted to those who are unable to have vaginal intercourse due to a disability or psychosexual problem, those in whom sperm washing is appropriate (such as HIV positive men) or those in same sex relationships. However, NICE are currently reviewing this recommendation which is therefore likely to change at the next update.

IVF/ICSI

In IVF procedures, controlled ovarian hyperstimulation can also be employed to generate the follicles for embryo creation *in vitro*. It is the *number* of embryos transferred which has a direct bearing on the chance of a multiple pregnancy. The risk of twins after double embryo transfer (DET) is 23.5 % for cleavage stage embryos (day 2–3 of development) and 36.4 % for blastocysts (day 5 of development). Elective single embryo transfer (eSET) in selected patient groups has shown promising success with clinical and live pregnancy rates, which are not dissimilar to those for double or higher order embryo transfers.

IVF itself appears to increase the risk of monozygotic twins by twofold compared with natural conception (0.8 % vs 0.4 %) although the overall incidence is low [6, 18]. The HFEA routinely collects outcome data from all IVF/ICSI treatment cycles across the UK and have reported that the incidence of twin pregnancy after eSET of a cleavage stage embryo is 0.6 %, identical to natural conception whereas eSET of a blastocyst embryo results in a more than doubling of the twin pregnancy rate to 1.9 % [3]. These are presumed to be monozygous pregnancies as the chance of simultaneous natural conception is thought to be very low.

Monozygosity itself is associated with higher adverse outcomes as two thirds of monozygous twins are monochorionic [7]. A twin pregnancy with a shared chorion is at increased risk of complications due to the vascular placental anastomoses that

connect the umbilical circulations of both twins, leading to twin-to-twin transfusion syndrome (TTTS), which complicates 10–15 % of monochorionic pregnancies. This leads to haemodynamic and liquor discordance in the "donor" and "recipient" twin and in severe cases death of the recipient twin due to high output cardiac failure. In these cases death of the surviving twin can be as high as 12 % with the risk of neurological abnormalities in those that do survive being approximately 18 % [19]. Monochorionic pregnancies also have a higher chance of fetal loss greater than 24 weeks of gestation (3.3 % fetuses) compared with dichorionic pregnancies [19]. Overall these babies may also be more at risk of neurodevelopmental abnormalities.

IVF twins also seem to have a small but statistically significant increase in the risk of preterm labour, approximately by 23 % [6] compared with spontaneously conceived twins. Early fetal loss of one twin can lead to premature delivery of the remaining twin. Similarly IVF twins have shown an increased risk of low birth weight in IVF twins [6]. Rates of congenital anomalies are known to be 30–40 % higher in IVF pregnancies (septal heart defects, cleft lip, oesophageal atresia, anorectal atresia). The risk of anomalies after conventional ART is the same as natural conception but is higher after ICSI. This is much like a "chicken and egg" problem with ICSI. It is not completely clear if it is the process of ICSI (i.e., stripping cumulus cells and longer exposure to light and oxygen, which causes the anomalies) or if it is due to the underlying sperm dysfunction which provokes the need for ICSI in the first place. Most severe sperm dysfunction (<5 million sperm/ml) is probably genetic involving the Y chromosome, although there is no evidence to suggest that in multiple pregnancies this rate would be higher, especially for hypospadias [20, 21]. The risk of congenital heart disease in monochorionic twins has been shown to be higher [19, 22].

Overall, it should be acknowledged that factors that predispose to infertility are also linked with adverse perinatal outcomes. To determine whether a particular ART is leading to an adverse outcome or whether it is a consequence of other infertility causes and complex factors between the couple needs further investigation [6, 7].

The HFEA and Elective Single Embryo Transfers (eSET)

High multiple pregnancy rates are preventable. A recent publication from the HFEA examined the national picture of multiple pregnancies and births after fertility treatment [2]. In 2008 almost a quarter of births resulting from IVF treatment were multiple [2]. The HFEA mandated a target goal of reducing the multiple pregnancy rate to 10 % of all live births. Although the mandate was removed after a legal challenge, the HFEA continues to advise clinics to reduce multiple pregnancy rates. There has been a decrease in multiple pregnancy rates from 26.6 % in 2008 to 15.9 % in 2014 [3], which begs the question, why did this happen?

One of the goals set by Professor Braude's report, was for clinics to move from double embryo transfer (DET) to elective single embryo transfer (eSET) even if

more than one embryo is available as a result of IVF preparation. This was quite a changing of the tide in reproductive medicine given the firmly held belief among professionals and the public that the number of embryos transferred positively equates to successful pregnancy outcomes. Couples who are in a desperate position to achieve a pregnancy balance the benefits of having two or more babies against the cost of repeating fertility treatment both financially and psychologically. The NHS funds approximately 40 % of IVF treatment cycles so the majority of the financial burden of treatment falls on the couples themselves. The HFEA publishes the results of the pregnancy rates for each fertility clinic in the UK, which becomes *de facto* a league table that produces a perverse incentive to maximise pregnancy rates by transfer of one or more embryo. In a competitive market the motivation of clinics to maximise pregnancy rates mirrors the desires of the couple and all of these motivations are not sufficiently offset by the known dangers of multiple pregnancy for the mother and her babies.

All the available evidence shows that increasing the number of embryos transferred increases pregnancy rates. Other countries in the world have less stringent laws on the number of embryos that may be transferred and consistently show higher pregnancy rates than the average in the UK [23]. The HFE Act restricts the number of embryos transferred to two in women under 40 years of age and three for older women. With restrictions on number of embryos to transfer, other strategies have been developed to maximise the chance of pregnancy. There is convincing evidence that for women aged less than 36 years with more than one optimal quality embryo, the chance of conception is almost the same with eSET as with DET of sub-optimal embryos. In women over 40 years of age there is reassuring evidence that eSET of an optimal embryo maintains pregnancy rates (21.7 %) similar to women having DET (21 %) where in most cases DET will have been chosen due not having an optimal embryo to transfer [3]. There is further evidence that blastocyst transfer increases pregnancy rates; however, this belies the fact that not all embryos have the potential to survive to day 5 in culture and therefore this option may not be suitable to all patients.

There has been encouraging data released by the HFEA in recent months. There has been a rise in eSET from 5 to 29 % overall, with a specific rise from 7 to 38 % in the 18–34 age range [2]. Despite the rise in eSET, pregnancy and birth rates have been maintained and have recently started to rise [2] (Fig. **8.3**). The average multiple birth rate in the fertility sector is now 15.9 % [3], closer to the 10 % target set by the HFEA than ever before. With eSET the risk of twins is only 1 in 50 pregnancies.

Fetal Reduction

The ethical rationale in relation to fetal reduction is that of a “consequentialist” approach, in which the parents and the clinician weigh the benefits and risks of the pregnancy continuing and make a “best interest” decision for the remaining fetus(es) and for the mother’s health [24, 25].

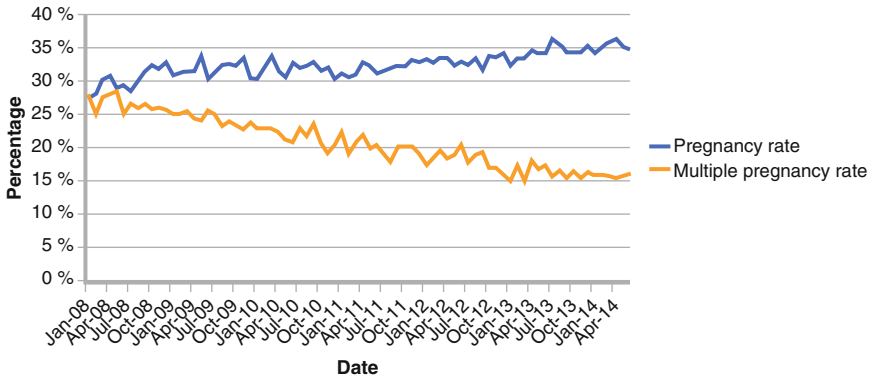

Fig. 8.3 Pregnancy rate (per embryo transfer) and multiple pregnancy rate (per pregnancy), fresh and frozen transfers: 2008 to mid-2014 (Source: Human Fertilisation and Embryology Authority (HFEA) [2])

Multifetal pregnancy reduction (MFPR) attempts to ameliorate the maternal and fetal risks of higher order pregnancies by reducing the number of fetuses to a more manageable number [8]. Epidemiological studies have shown that twin pregnancies produced a child with cerebral palsy 8 times more often than singletons and for triplet pregnancies this rate was 47 times higher [26]. For example, 8–12 % of triplet pregnancies will experience some kind of neurodevelopmental sequelae compared with twin pregnancies. This is likely to be even higher if the triplet pregnancy contains a monoamniotic pair [19]. Reducing the triplet pregnancy to twins significantly reduces the risk of preterm delivery without an increase in miscarriage rates [27]. Full fetal medicine assessment should be carried out before deciding on which fetus(es) to terminate. This is best carried out between 11 and 14 weeks gestation when the risk of spontaneous reduction has passed and in order to identify features of aneuploidy (i.e., nuchal translucency) [27]. Fetuses at lowest risk of aneuploidy, determined by nuchal translucency should be left intact as should those implanted closest to the cervix so as not to increase the risk of miscarriage of the entire pregnancy should the fetus closest to the cervix miscarry following MFPR. Studies to date do have major limitations, however, as many do not differentiate between trichorionic and non-trichorionic pregnancies, the latter in which a monochorionic pair exists, which of course will have a bearing on fetal outcomes (which will be discussed below). However, despite the controversies, reducing triplets to twins suggests that the chance of preterm labour before 32 weeks gestation drops by around 55 %, with very little increase in miscarriage [27], and the potential to take a live born baby home increases from 80 to 90 % [8]. However, it is clear that expectant management of a trichorionic triplet pregnancy does have a reasonable perinatal outcome.

MFPR does have a significant psychological impact on parents, most reporting acute stress, pain and fear [28]. The ethical dilemma of the parents must be taken into account, encompassing the emotional journey already experienced through the ART process balanced against their own ethical and religious beliefs.

Recommendations for Birth Choices and Intrapartum Care

When multiple pregnancy is diagnosed in a fertility unit, referral to specialist multidisciplinary team should be made, consisting of a specialist obstetrician, midwives and ultrasonographers, all of whom have experience of managing twin and triplet pregnancies. Within the clinic, the woman and her partner will receive specialist prenatal screening and diagnosis as well as initial counseling regarding selective fetal reduction if she has triplets or a higher order pregnancy [6]. She will also receive advice regarding nutrition, the antenatal course including frequency of scans and antenatal clinic appointments, information regarding the risks, signs and symptoms of preterm labour, advice regarding the likely timing and optional modes of delivery [7]. An enhanced support program should offer psychological, parenting and breastfeeding from those with the experience and knowledge relevant to twin and triplet pregnancies.

A study from Australia of IVF conceived twins compared perinatal adverse outcomes with spontaneously conceived (SC) twins and in particular dizygotic twins [5]. This showed clearly that IVF conceived twins have a greater risk of adverse events including preterm birth, low birth weight and death than SC twins. Obstetricians caring for women with IVF conceived twins should take this into consideration when developing management plans for these pregnancies.

Zygosity, Chorionicity, and Amnionicity

Risks to the fetuses in multiple pregnancies depend partly on amnionicity and chorionicity [7]. Zygosity refers to the genetic makeup of the twins. When a single zygote splits into two equal zygotes they share the same genetic material (monozygotic) and if two separate zygotes are simultaneously fertilized by two sperm they are genetically different (dizygotic). Chorionicity refers to the placentation and amnionicity refers to the relation of the amniotic membranes between the twins. Two amnions and two chorions lead to dichorionic, diamniotic pregnancies (DCDA). Dizygous twins are always DCDA. These are the most common types of twinning occurring in approximately two-thirds of multiple pregnancies and carry the lowest risks for the fetus and mother due to the complete separation of the placentas.

Monozygous twins can become DCDA twins if cleavage of the single zygote happens before day 3. This happens in 25–30 % of monozygous twinning. More commonly cleavage occurs after day 3 and before day 8 when the blastocyst has already formed, resulting in a monochorionic diamniotic (MCDA) pairing. Here each twin has its own amniotic sac but shares a placenta and occurs in 75 % cases. Much more rarely, cleavage of the blastocyst will occur after day 8 and before day 13. These twins will share both the placenta and amniotic sac in monochorionic

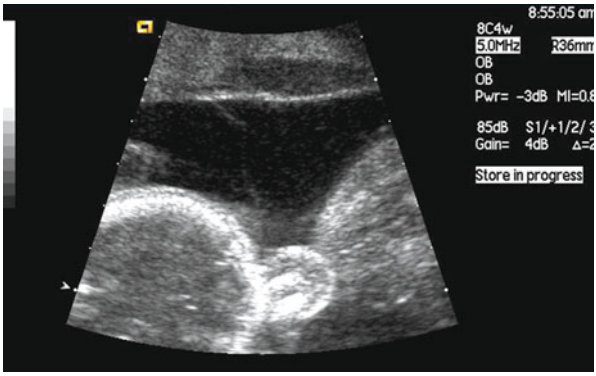

Fig. 8.4 "T sign" in Monochorionic Twins (Reproduced with permission of John Wiley and Sons from Taylor and Fisk [8])

monoamniotic pregnancy (MCMA). This type of twinning occurs in <2 % cases and is high risk for cord entanglement and stillbirth. Cleavage after day 13 results in conjoined twins. This is extremely rare and beyond the scope of this chapter. Around a third of twin pregnancies are monochorionic and can also occur in higher order multiples as well. Twin-twin transfusion syndrome (TTTS) is a condition associated with monochorionic twins and occurs in around 10–15 % of these pregnancies [19] and is associated with a 20 % risk of stillbirth [7]. This is discussed in more detail below.

Antenatal Care

First trimester screening in twin pregnancies allows accurate dating, screening for Downs Syndrome, determination of fetal number, amnionicity and chorionicity. The most accurate and reliable time is between 11^{+0} and 13^{+6} weeks gestation [7]. Ultrasound reveals either a "T sign" for monochorionic (Fig. 8.4) or a "lambda or twin peak" sign in dichorionic pregnancies (Fig. 8.5).

Twin-Twin Transfusion Syndrome

Determining chorionicity is the most important indicator of fetal outcome in twins and guides the antenatal management. A monochorionic placenta contains unique vascular architecture which include superficial arterio-arterial or veno-venous communications allowing bi-directional flow between the fetuses but also deep arterio-venous communications allowing only uni-directional flow. Thus intertwin transfusion is a normal event in MC twins – and is usually balanced. TTTS occurs

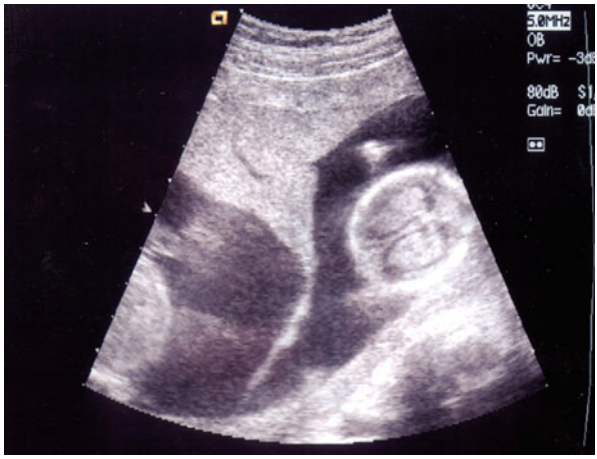

Fig. 8.5 "Twin peak" or "lambda" sign (Reproduced with permission of John Wiley and Sons from Taylor and Fisk [8])

when haemodynamic imbalance arises as a result of the particular arrangement of deep anastomoses, which overwhelms any compensation afforded by superficial anastomoses. Consequently the vascular abnormalities lead to hypovolaemia in one twin (the donor), which is thought to cause activation of the renin-angiotensin system leading to oligohydramnios and oliguria. Conversely in the recipient twin there may be increased secretion of atrial naturietic peptide leading to polyuria and polyhydramnios. Volume overload leads to cardiac hypertrophy, fetal hydrops, outflow tract obstruction and eventually death [8, 29]. TTTS occurs in 15 % of MCDA twins, affecting some 1600 pregnancies [30]. Scanning begins at 16 weeks and is carried out fortnightly until 24 weeks gestation, aiming to pick up the early signs of TTTS. Quintero staging [31] below (Table **8.2**) outlines the different stages of TTTS and what the defining ultrasound features are [29, 30].

In addition, screening for Downs Syndrome is an important point of discussion with parents, since there is a greater likelihood of Down's Syndrome with a twin or triplet pregnancy [7]. The likelihood of a false positive result is higher than in a singleton pregnancy, however, and as a consequence the offer of invasive testing is also increased. The risk is calculated based on nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A at 11^{+0} to 13^{+6} weeks gestation. A risk per baby is calculated in a dichorionic pregnancy compared with a risk for the pregnancy in monochorionic twins. Second trimester screening has limitations in dichorionic pregnancies as a risk per baby cannot be established accurately and therefore the rate of invasive testing is higher. Second trimester screening should not be used in triplet pregnancies [7]. Non-invasive prenatal testing (NIPT) of cell free fetal DNA can be used. However, any positive result will need confirming with invasive karyotyping, not least to determine with certainty, which, if any, is the affected fetus.

Table 8.2 Quintero staging for twin-twin transfusion syndrome

Stage	TOPS (O < 2 cm, P > 8 cm)	Absent bladder visualisation	Critical arterial Doppler (absent/reversed end diastolic flow)	Hydrops	Demise
I	+	–	–	–	–
II	+	+	–	–	–
III	+	+	+	–	–
IV	+	+	+	+	–
V	+	+	+	+	+

Data from Taylor and Fisk [29]
TOPS twin oligo-polyhydramnios (values refer to amniotic fluid pocket), *O* oligohydramnios, *P* polyhydramnios

With regard to IVF pregnancies and antenatal screening, it should be noted that PAPP-A levels are significantly lower in fresh transfer IVF pregnancies, hence potentially leading to a false positive result and increased risk of having CVS or amniocentesis [6].

Growth Restriction

The incidence of growth restriction in twin pregnancies has been reportedly as high as 29 % (4 % concordant and 25 % discordant) occurring in up to 42 % of monochorionic twins and 25 % of dichorionic twins [8]. Therefore standard antenatal care of twins employs regular growth scans in DCDA twins every 4 weeks and every 2–3 weeks in MCDA twins. Twenty-five percent growth discordancy or more between twins or triplets is considered to be a clinically significant measure of intrauterine growth restriction [7]. Management of discordant growth including timing of delivery is complex, and is a multi-disciplinary decision. Identification of IUGR at the extreme of prematurity, for example in DCDA twins, may warrant discussion with the parents to allow the pregnancy to continue in order to optimize the health of the larger twin, albeit potentially at the expense of the smaller twin [8].

In terms of screening for the maternal complications of multiple pregnancy, blood pressure and urine analysis is carried out at each antenatal visit to screen for the development of hypertension. Predicting preterm birth is less straightforward. Some studies have reported that cervical length measurements could be helpful. In twin pregnancies the mean cervical length at 24 weeks is similar to that of singletons, but one that is less than 25 mm (compared with 15 mm in singletons) may be predictive of preterm labour before 30 weeks gestation [8]. Progesterone supplementation has not been shown to be effective at preventing preterm labour in twin pregnancies [32]. Fetal fibronectin has also not been shown to be able to accurately provide a quantifiable risk of preterm labour as it has done in singletons and therefore is not recommended as a sole predictor of preterm labour [7].

Timing and Mode of Delivery

It is becoming common practice to consider an induction of labour at 40 weeks for those pregnancies resulting from assisted reproductive techniques, particularly IVF. However, these discussions are redundant with twins in light of the evidence stating the optimal safe timing of birth. Existing evidence has identified that in twin pregnancies that progressing beyond 38 weeks gestation leads to an increased rate of perinatal morbidity and mortality [33].

The Twins Timing of Birth Trial [34] randomised women with twin pregnancies to either elective birth at 37 weeks gestation or standard care/expectant management from 38 weeks gestation. An elective birth at 37 weeks was associated with a significant reduction in the serious adverse outcomes for the twins compared with expectant management allowing labour to progress beyond 38 weeks. Currently NICE recommendations [7] state that in DCDA twin pregnancies, labour should be induced between 37 and 38 weeks gestation and from 36 weeks gestation in MCDA twins, with steroid cover to aid lung maturity in preparation for delivery [7]. Most monochorionic monoamniotic twins (MCMA) have some degree of cord entanglement which can have significant implications for antenatal and intrapartum morbidity and mortality. Delivery is usually recommended by caesarean section from 32 weeks gestation [19]. In triplet and higher order pregnancies delivery decisions are taken on an individual basis and will be mostly driven by the growth and wellbeing of each of the fetuses. Triplet pregnancies containing a monochorionic pair have higher fetal loss rates than trichorionic triplets [19]. The general recommendation is that labour should not progress beyond 36 weeks in triplet pregnancies due to a higher risk of fetal death [7]. Elective birth is usually offered from 35 weeks gestation following a course of antenatal steroids.

Mode of delivery in twin pregnancies is based on the principles of the presentation of the first twin (cephalic being preferred), fetal growth and wellbeing [8]. The Twin Birth Study Collaborative Group [35] randomized uncomplicated twin pregnancies between 32^{+0} and 38^{+6} weeks gestation to a trial of planned caesarean section or vaginal delivery between 37^{+5} and 38^{+6} weeks delivery and compared the maternal and fetal outcomes. Findings concluded that an elective caesarean birth does not significantly increase or decrease perinatal complications and mortality compared with vaginal birth. However, it is worth noting that there was a high intrapartum caesarean section rate in the vaginal delivery group of around 39.6 % for both twins and 4.2 % for combined vaginal-caesarean delivery [35]. The twin birth study did, however, exclude pregnancies with a significant size discrepancy between twins. A consensus hasn't been reached regarding the timing of delivery in these twins. In general the current authors would consider a growth discrepancy of around 20 % to indicate that growth restriction is evident, which is echoed in the current literature, though NICE guidance recommends 25 % discordance as the best indicator of selective growth restriction [36]. In a recent multi-centre, prospective trial of 1000 women in Ireland, the Evaluation of Sonographic Predictors of Restricted Growth in Twins (ESPRiT) trial revealed that a difference of 18 % or

more in twin birth weights is associated with an increased risk of fetal or neonatal death, bowel complications, breathing difficulties, infection and admission to the neonatal intensive care unit [37]. Taking into account additional measures of fetal wellbeing (e.g., gestation, middle cerebral arterial doppler and ductus venosus Doppler measurements of each twin, liquor volumes and presentation of twin 1, the presence of any obstetric complications and whether steroids have been administered), a discussion can take place between the obstetrician and the mother regarding the appropriate mode of delivery.

It is appropriate to aim for a vaginal birth in uncomplicated monochorionic twin pregnancies providing there is no clinical indication for Caesarean section such as twin one presenting breech or a previous caesarean section [19]. Evidence of acute transfusion in labour is reported in the literature, and has been described as high as 10 % therefore continuous monitoring of the fetuses should be employed in labour [19]. In higher order pregnancies caesarean section is usually recommended to avoid the challenges of intrapartum monitoring and potential birth trauma from internal podalic versions and breech extraction procedures that may be required [19].

Strategies to Promote Single Embryo Transfer

Now the focus of research is on selecting the best quality embryo for transfer using techniques such as time-lapse imaging of embryo growth, extended culture to blastocyst, metabolomics or controversial pre-implantation screening.

The challenge for IVF clinics is to move away from the focus on their position in the HFEA leagues tables in terms of pregnancy rates and to move towards a holistic approach to creating a family that isn't burdened by bereavement or long-term health problems of their ART-conceived children. In order to do this, strategies could include increasing conception rates with eSET or changing funding arrangements.

Research into increasing pregnancy rates with eSET has focused on better selection of embryos and methods of improving the chance of implantation of the embryo. Using the technique of blastocyst culture has continually shown potential in research studies to improve clinical pregnancy rates [38, 39]. Blastocyst culture involves extended culture of the embryos from the traditional day 2 cleavage stage to day 5 (blastocyst stage) [38]. Cochrane reviews have shown that the live birth rate is as much as 40 % higher in favour of the blastocyst stage culture [39]. However, blastocyst eSET doubles the risk of monozygotic twins compared to cleavage stage embryos and the risk of congenital malformations and preterm birth are significantly higher [6]. There is a lack of long-term safety data and of the long term health effects of prolonged embryo culture. Blastocyst culture reduces the number of additional embryos available for freezing meaning that women face a further episode of ovarian stimulation. Given the concerns about an increased risk of borderline ovarian tumours with repeated cycles of OI [40], the long term consequences of a wholesale move to blastocyst transfer are unknown.

In vivo maturation involves the maturation of immature oocytes from antral follicles with minimal or no gonadotrophin stimulation followed by maturation and fertilization in the laboratory [41]. Avoiding gonadotrophins has the additional benefit of reducing the risk of ovarian hyperstimulation mentioned earlier in this chapter and therefore reducing the multiple pregnancy rate. Its use would be particularly beneficial for those at risk of hyperstimulation and hence multiple conceptions, such as polycystic ovarian syndrome patients and those with a high antral follicle count. The advantages aside from multiple pregnancy reduction are that it is less costly, safe and convenient. The main disadvantage is that, at present, the live birth rate is lower [41]. However, it may be that this could be improved in the future with optimized protocols and laboratory training. Follow-up developmental studies in children have thus far been promising [41, 42].

Time lapse photography without removing the embryos from the incubator has been proposed as a better method of assessing normal development of embryos than the traditional approach of intermittent microscopy when embryos are removed from the incubator and assessed by an embryologist [43]. It is suggested that closer analysis of stages of cleavage will result in better embryo selection and increase pregnancy rates but the evidence to support this is yet to be sufficiently convincing to justify the additional costs in changing laboratory equipment given those costs will drive up costs to the patients even further. Since most IVF cycles in the UK are funded by the couple, an unintended consequence of time lapse photography may be to push up DET rates.

It has been suggested that investigating the metabolomics of the embryos will improve embryo selection. This involves analyzing metabolites in the culture medium in which the embryos have developed with the suggestion that this will identify the optimum embryo for eSET but results to date have been disappointing [44].

It is recognized that embryo implantation is an immunological process involving cross-talk between the secretory phase endometrium and the hatching day six embryo. Focusing on improving implantation rates after transfer of a single optimal embryo has centred on these immunological processes but use of steroids has not resulted in significant improvements in pregnancy rates apart from in women with antiphospholipid syndrome [45]. An alternative approach has been to cause damage to the endometrium to provoke a healing response with a migration of natural killer cells, which alters the immune environment in the uterine cavity. There is some evidence of increased pregnancy rates for women with recurrent implantation failure (more than two failed IVF treatments after transfer of optimal embryos) but this has not provided a solution to improving pregnancy rates after eSET for all other patients.

The alternative approach adopted by Sweden, Finland and Belgium is to increase state funding of IVF eSET cycles. In Belgium couples can now have up to 6 eSET cycles funded by the health service [5]. A liberal approach to funded IVF combined with eSET in Sweden and Finland has resulted in a reduction for IVF twins to 6% of cycles [6]. The increased costs of providing more IVF treatment has been offset by a significant reduction in the obstetric, neonatal, pediatric and long-term costs of dealing with the consequences of complications linked with multiple pregnancy.

Conclusion

In 1984, Baroness Warnock produced a report assessing the Human Fertilisation and Embryology Association following the birth of Louise Brown, the first IVF baby in 1978 [46]. In her report she discussed the ethical, social and spiritual aspects of assisted reproductive techniques. She concluded that "childlessness is a source of stress to even those who have chosen it… it can disrupt the picture of the whole future of their lives… unable to fulfill their own and other people's expectations." She explained that infertility is a condition meriting treatment and that it should not be limited to the private sector and should be offered within the NHS. Achieving a family is incredibly important to many people and should be supported in as safe a way as possible. The long term outcomes for the majority of children born from IVF are reassuring once prematurity and multiple gestations are taken out of the equation.

From this chapter it would be safe to conclude that the burden on society, the parents and the children themselves from iatrogenic, avoidable multiple pregnancies is too high [38]. Financial pressures for the NHS are worsening and the costs of neonatal and postnatal resources are high for those children born prematurely or with neurodevelopmental morbidities. Measures need to be continued in reproductive medicine clinics to drive the multiple pregnancy rates down, such as elective single embryo transfers. We now have the evidence to demonstrate that live pregnancy rates are not reduced by eSET in the under 36 year old age group. It remains to be seen from audit figures whether those in the advanced maternal age category would also benefit from this approach with a similar reassuring improvement in live birth rates. Promotion of singleton birth as the 'norm' in IVF clinics is already in progress and we hope will continue.

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