Chapter 3

Judicious Fertility Treatment to Minimise the Risk of Multiple Pregnancy

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Additional information is available at the end of the chapter

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Abstract

Pregnancies resulting from fertility treatment are associated with higher rates of multiple pregnancy and have higher rates of pregnancy complications than spontaneously conceived pregnancies. Methods exist to make fertility treatment safer and less likely to result in multiple pregnancy and practitioners should be practicing fertility treatment with the aim to produce a healthy, term, singleton pregnancy. Approaches to minimising the risk of multiple pregnancy include carefully monitoring ovulation induction (OI) cycles to produce mono-follicular ovulation. Identifying patients at risk of excessive response to ovulation induction and treating them with low dose therapies and close monitoring is a critical step in practicing safe OI treatment. Performing single embryo transfer in all but exceptional cases of in-vitro fertilisation (IVF), and never transferring more than two embryos, is the single, most successful way to reduce the multiple pregnancy rate with IVF. An appreciation of the increased risk of mono-chorionic twinning with IVF is also important. This chapter will explore ways to minimise the risk of multiple pregnancy with a variety of fertility treatments.

Keywords: ART, multiple pregnancy, ovulation induction, single embryo transfer

1. Introduction

Assisted Reproductive Technology (ART) has, since its inception, been associated with increased rates of multiple pregnancy as the treating doctors struggled to balance an acceptable live birth rate with the risk of multiple pregnancy. A multiple pregnancy results in increased rates of both maternal and neonatal morbidity compared with a singleton pregnancy. Further, multiple pregnancy is associated with increased rates of prematurity, especially an increased

rate of severe prematurity, low birth weight, neonatal death and longer term developmental concerns [1]. Women with a multiple pregnancy are at risk of nearly every complication of pregnancy in comparison to women pregnant with a singleton pregnancy. Pre-eclampsia, gestational diabetes and operative delivery are all associated with significant increased maternal morbidity in multiple pregnancies.

A multiple pregnancy, for patients who have suffered through months or years of infertility and treatment, can often be seen as a "double blessing" and may indeed result in a successful outcome for many patients. For many years rates of multiple pregnancy for women undergoing ART were accepted as a necessary part of treatment. With ongoing development of fertility treatment, employing better processes and therapies, the success rate of ART has improved, and thus the impetus for using methods that also run the risk of high rates of multiple pregnancy are no longer warranted or accepted. Now when determining the success of an ART technique or an ART service provider, the rate of singleton, term, live birth should be seen as the gold standard of measurement and the aim of successful treatment [2]. Strategies to achieve this are now the cornerstone in research, development and guidelines in ART techniques and stricter regulations and protocols are in place to implement safer methods.

This chapter will explore ways in which ART, in particular ovulation induction, super-ovulation and intra-uterine insemination (IUI) and in-vitro fertilisation (IVF), can be delivered to ensure low rates of multiple pregnancy and make ART and the pregnancy that results safer for mother and baby.

2. Ovulation induction

Ovulation induction involves stimulating the ovary with the aim to induce mono-follicular-ovulation in a sub-fertile woman who is anovulatory. A trigger injection, to mimic the mid-cycle luteinising hormone (LH) surge, is given to initiate release of the ovum and timed intercourse is advised.

Multiple pregnancy may occur with ovulation induction secondary to unintended over-stimulation of the ovary and the development of more than one follicle and the release and subsequent fertilisation of more than one oocyte. Rates of multiple pregnancy with ovarian stimulation depend greatly on the treatment protocol used, but for all methods has been approximated at up to 9 times the rate of natural conception in fertile women [3].

A recent 5-year review of multiple pregnancy rates in the United States revealed 22% of the nation's twin pregnancies were due to ovulation induction and 40% of triplet pregnancies were as a result of ovulation induction treatment [4]. The rates of multiple pregnancy secondary to ovulation induction are falling as better techniques and practices are introduced however, not as quickly as is being seen with more invasive ART techniques such as IVF. Stricter controls and more stringent regulations are being enforced in many countries towards IVF treatments in the hope of stalling the multiple pregnancy rate, however this has not been replicated in the field of ovulation induction, as this is often performed outside of large fertility clinics, or

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without strict tracking protocols. Hence it is believed that ovulation induction accounts for up to 65% of the world's higher order multiple pregnancies [5].

Ovulation induction agents are usually divided into oral and injectable agents with the historical belief being that injectable agents, usually recombinant or urinary derived follicular stimulating hormone (FSH), being associated with higher rates of both multiple pregnancy and ovarian hyper-stimulation syndrome.

2.1. Clomiphene citrate

Clomiphene citrate was until recently the first line fertility treatment for anovulatory women undergoing ovulation induction [6]. Clomiphene is a selective oestrogen receptor modulator that blocks negative feedback of rising oestrogen levels at the level of the hypothalamus thereby resulting in ongoing FSH secretion and follicular development. Clomiphene citrate has historically had rates of multiple pregnancy quoted at 7%, with higher order multiple pregnancies rates occurring in less than 1% of confirmed pregnancies. [7] Newer data however suggests that multiple pregnancy rates with the use of clomiphene may be as high as 9% and higher order multiple pregnancy rates closer to 2%, as often ultrasound monitoring of the stimulated cycles is not performed [8]. Clomiphene, unlike other ovulation induction agents, does not have a higher rate of multiple pregnancy rates with higher dosing. The anti-oestrogenic properties exhibited by clomiphene on both the cervical mucus and endometrial lining with increased dosing have a negative impact on the rate of conception and implantation. Hence, although ovulation rates may increase, successful pregnancy, including multiple pregnancy, are not necessarily increased. Thus, for clomiphene, unlike other ovulation induction agents, simply prescribing lower doses of the agent will do little to reduce multiple pregnancy rates.

2.2. Letrozole

Letrozole is an aromatase inhibitor that is now recommended as a first line ovulation induction agent [6]. It is associated with higher rates of mono-ovulation than clomiphene and thus lower rates of multiple pregnancy, at around 3.5% [9], but with overall similar if not higher live birth rates [10]. It has a shorter half-life than clomiphene and, unlike clomiphene, during treatment endogenous FSH is suppressed by rising oestrogen levels thus reducing the risk of multiple follicles developing. Due to the benefit of increased live birth rates and a reduction in the rates of multiple pregnancy letrozole should be the oral agent for first line use in anovulatory women undergoing ovulation induction. However, letrozole must be used under informed consent as ovulation induction is not an approved indication for the drug.

2.3. Metformin

Metformin has, over the last few years, been increasingly used for the management of women with PCOS, having potential benefits with regard to its metabolic consequences [11] and androgenic side-effects [12]. However, with respect to anovulatory infertility as a sole agent the benefit of increasing the chance of a live birth is not clear, other than perhaps as an adjuvant to clomiphene citrate in overweight women [13], or as an adjuvant to FSH ovulation induction [14].

2.4. Follicular stimulation hormone (FSH)

Injectable agents, usually recombinant FSH, have historically been associated with higher rates of multiple pregnancy. When first described dosing regimes in the realm of 225 IU of FSH were used to induce ovulation in anovulatory women with multiple pregnancy rates of around 25% [15]. As greater experience was gained using FSH and with a clear distinction being made between dosing for the aim of mono-ovulation in ovulation induction, versus ovarian hyper-stimulation for IVF cycles initial dosages fell dramatically. Low dose, step up protocols are now the recommended regime with close monitoring to observe response [16]. Unlike oral agents that are given for a limited number of days in the early follicular phase, FSH can be given for an extended period until follicular development is seen. With this method rates of multiple pregnancy can be as low, or lower, than with oral agents and can be achieved with higher live birth rates. In countries with good health insurance and state funding for fertility treatments out of pocket costs to patients are comparable to oral agents and are thus often used as a first line treatment due to their increased success rates.

In our unit, after exclusion of other potential infertility factors, we aim to induce mono-ovulation with a low dose step up protocol. We start all women on a low dose of gonadotropin, on average 25 IU FSH, and monitor women with oestrogen levels and ultrasound tracking of developing follicles. Dosing is increased if no response is seen after 10 days, with dose increments of 12.5 IU, until a threshold is reached whereby mono-follicular development occurs and the dose is not increased further. If more than 2 follicles of 10 mm are noted the cycle is cancelled, and in patients under 35 years consideration is given to cancelling with two follicles. Review of our data has showed that our rate of multiple pregnancy using this method for ovulation induction is below 4% [17]. This is with a cumulative live birth rate of close to 50% over 3 cycles and a cycle cancellation rate of around 10%. After 3 cycles the live birth rate per cycle falls significantly as the patients with additional reproductive pathology start to make up a greater percentage of remaining patients. If after 3 cycles a successful pregnancy has not occurred we give consideration to switching to IVF treatment. This allows a low rate of multiple pregnancy and a close to 50% rate of successful pregnancy for our patients without exposing them to the increased risk of IVF unless it is warranted.

The hallmark of reducing rates of multiple pregnancy with ovulation induction is to closely monitor follicular development both with hormone levels and ultrasound tracking to ensure only a single dominant follicle, or a maximum of two, will develop and ultimately ovulate. It would be assumed that with close monitoring a clinician could predict when a patient was at risk of releasing more than one oocyte and could act prudently to avoid conception in such cases. Existing guidelines surrounding risk adverse practice in regard to tracking are sparse and not overly cautious. The American College of Obstetricians and Gynaecologists (ACOG) guideline recommends abandoning an ovulation induction cycle if there are more than 3 follicles measuring more than 15 mm [18]. Studies have shown that follicles as small as 7 mm at time of trigger can result in successful ovulation and impact the multiple pregnancy rate, although it is generally believed that follicles of 14 mm in size or greater will have a mature oocyte [19]. Capping the recommended maximum number of follicles before cancellation of the cycle at more than 3 is doing little to reduce the rate of multiple pregnancy and indeed risks, not just a multiple pregnancy but a higher order multiple pregnancy.

More judicious care can be taken to actively avoid multiple pregnancy by ensuring mono-ovulation by very closely monitoring oestrogen levels and follicular development on ultrasound. By cancelling cycles when more than 2 follicles of greater than 10 mm are present has been shown to actively reduce multiple pregnancy rates. Oestrogen levels above 600 pg/mL have been associated with increased rates of multiple pregnancy [20] and higher than 2000 pg/mL with higher order multiple pregnancy. [21] Using both ultrasound follicle tracking and serum oestradiol measurements to carefully track cycles is imperative to minimise multiple pregnancy.

As a general rule, younger women, women with a greater antral follicle count or higher anti-mullerian hormone (AMH) levels are more likely to have a greater response to a lower dose of induction agent and thus should be started at a minimum dose on the first cycle and tracked accordingly.

All couples should be worked up prior to embarking on ovulation induction to confirm tubal patency and adequate semen analysis, and to ensure a more invasive form of ART may not be a better first line therapy. The group of women for who ovulation induction is most widely used is those with anovulation secondary to poly-cystic ovarian syndrome (PCOS.) This is often a group of patients that are of a younger age than the average infertility patient and have a high antral follicle count and in reflection of that, often a high AMH. These women may also benefit from the additional use of metformin during their stimulation to improve outcomes [14]. It is critical that these women are identified as high risk for responding excessively to even small doses of ovulation induction agents and should be started on very low doses of ovulation induction agents and very carefully monitored. Being younger also means the rate of fecundity per ovulation is high and therefore every effort should be made to aim for mono-ovulation.

Options available when development of an excessive number of follicles is observed include cancelling the cycle, aspirating the excess follicles or switching to an egg collection and IVF cycle. None of these options are ideal for a patient hoping to achieve a pregnancy but need to be discussed with the patient before embarking on treatment. Cancellation of the cycle can be devastating to the patient from a financial and emotional cost, however a cancelled cycle due to hyper-stimulation of the ovary gives valuable information to the practitioner for management of the next cycle in regard to dosing and monitoring. Follicular aspiration for either reduction in follicle number, or for transfer to an IVF cycle is difficult if it has not been discussed as an option pre-treatment, and has ethical implications in regard to informed consent for a patient who is now being faced with either cancellation of the cycle or conversion to a more complicated and costly treatment. It is imperative that as part of the consent process for ovulation induction the risk of multiple follicle development is discussed and the options and recommendations when an excessive number of follicles develop are considered.

Having an absolute maximum cut off of 2 follicles, and for high risk couples one follicle, will be a huge step forward in reducing the multiple pregnancy rates with ovulation induction. Such an approach has been associated with multiple pregnancy rates below 5% and no higher order multiple pregnancies [22]. This compares with rates up to 30% if no intervention is made until follicular numbers reach more than three [23]. High risk couples, for whom more than one follicle should be the threshold for cancellation include young women undergoing

their first few cycles and who have an expected high fecundity per follicle, but also patients for whom multiple pregnancy would be particularly dangerous. This includes women with an independent risk of pre-term birth and women with underlying medical conditions making them more susceptible to the pregnancy complications of multiple pregnancy.

3. Super ovulation and intra-uterine insemination (IUI)

Super ovulation and IUI involves stimulating the ovary with ovulation induction agents with the aim to produce two follicles, then with ovulation trigger performing IUI to allow the sperm to bypass the cervical environment. It is usually performed in patients with unexplained subfertility or mild male factor subfertility. Consequently, the purpose of the treatment is to increase the chance of a successful pregnancy by increasing the number of oocytes ovulated and the availability of sperm.

Given it is used in women that are already ovulating, prudent use of ovulation induction agents is imperative and careful monitoring of the cycle with ultrasound and oestrogen levels is important, as in ovulation induction, to prevent multiple pregnancy and higher order multiple pregnancy. Unlike ovulation induction, where the aim is to produce a single dominant follicle, super-ovulation is aimed at producing two follicles, with well controlled cycles accepting up to three follicles, but certainly no more. The reason is in this situation there is a potentially as yet unrecognised factor limiting conception, whereas in standard ovulation induction treatment for the anovulatory woman, it is only the absence of ovulation that is limiting conception, hence when that is overcome the woman should conceive. Once four follicles are present there is no increase in the live birth rate, but a significant increase in the multiple pregnancy and higher order multiple pregnancy rate [21].

As the aim is to produce more than one follicle the risk of multiple pregnancy is high, higher than that is seen with IVF or ovulation induction. Overall rates of multiple pregnancy are around 14% in well controlled cycles, involving cancellation when more than three follicles are identified [24]. This is higher than is seen with IVF cycles, even in well controlled ovarian hyperstimulation protocols. Like ovulation induction the discussion regarding switching to an IVF treatment course, or cancellation of the cycle is required to be had with the patient prior to embarking on treatment. Often the decision around opting for IVF, to minimise the risk of a multiple pregnancy, or to adopt the cheaper treatment of super ovulation and IUI, but a greater risk of a multiple, revolve around the costs to the patient. This situation is unfortunate as the cost to the health care system and the family, ultimately, are greater when a multiple pregnancy results.

4. In-vitro fertilisation

In vitro fertilisation resulted in the first live birth in 1978. Since that time the use of IVF technology has changed dramatically and the increased success and its widespread use to treat all manner of subfertility issues has meant currently in Australia 1 in 25 children born are the

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result of an IVF cycle [25]. Like ovulation induction and super ovulation, IVF is associated with increased rates of unintended multiple pregnancy, in comparison to spontaneous conception, plus there is also a greater risk of an embryo splitting and resulting in monozygotic twinning.

While the key to reducing rates of multiple pregnancy with ovulation induction and superovulation and IUI lies with careful monitoring of the cycle and judicious cancellation of cycles when multiple follicles develop, the cornerstone to reducing multiple pregnancy rates in IVF treatment is to ensure single embryo transfer is the norm.

As IVF technology has developed and successful live birth rates have increased the need to transfer more than one embryo has rapidly declined. There is no significant difference in the live birth rate for women aged under 37 years undergoing a single embryo transfer (sET) compared with a double embryo transfer (dET), only an increase in the multiple pregnancy rate and subsequent increased pregnancy complication rate [26]. For women aged under 37 years the rate of multiple pregnancy with a double embryo transfer is as high as 25% [27], compared with less than 6% for women undergoing single embryo transfer [28].

Although implantation rate is not the gold standard by which to measure success of a fertility treatment, when compared with sET, dET has been reported to be associated with lower implantation rates suggesting a deleterious effect on the intrauterine environment when dET is employed [29]. This observation is further supported by the increased rates of poor pregnancy outcome when dET is performed but only one embryo implants. This scenario is associated with increased rates of growth restriction and preterm delivery compared with singleton pregnancies resulting from a single embryo transfer [30]. A review of the American Society for Assisted Reproductive Technology outcomes between 2004 and 2013, of over 180,000 IVF cycles concluded that although the live birth rate may increase with a dET, this is substantially out-weighed by the risk of multiple gestations [31]. They demonstrated that for patients with favourable prognostic factors; including younger maternal age, transfer of a blastocyst, and additional embryos cryopreserved, the gain in the live birth rate from sET to dET was approximately 10–15%, however, the multiple birth rate increased from approximately 2% to almost 50% for both fresh and frozen embryo transfer cycles.

Single embryo transfer is associated with not just a reduction in multiple pregnancy rates, but also a reduction in overall pregnancy complication rates with little effect on the live birth rate compared with double or higher number embryo transfer rates [32]. Double embryo transfer rates are occasionally recommended or supported when a patient has particular barriers to implantation success and thus have a perceived lower rate of risk to multiple pregnancy with dET. These may include advanced maternal age, poor embryo quality or multiple previous unsuccessful attempts at single embryo transfer.

The barrier to implementing universal single embryo transfer appears to lie in the cost of IVF treatment to the patient. In countries or regions where state funded or supported fertility treatment exists, the rates of single embryo transfer are far higher. The factor most influencing the likelihood a patient will undergo a single embryo transfer over a double or greater number embryo transfer is whether or not they have health insurance, a greater influencing

factor than that of maternal age [33]. In Australia where fertility treatment is subsidised by the state and rates of health insurance are high, the rate of single embryo transfer is over 75% and reflected in the multiple pregnancy rate from IVF being below 6% [34]. In comparison, in the United States sET recorded in the same year was less than 25% [35]. This is also a reflection of the strict regulations that exist in Australia governing IVF treatment.

Regulations and policy governing single embryo transfer also exist in many Scandinavian and some European countries, such as Belgium, as well as Australia, with reflective low rates of multiple pregnancy and high rates of cycle success. The transfer of more than two embryos is banned in Australia and double embryo transfer only allowed in the setting of significant advanced maternal age or multiple failed attempts at single embryo transfer [36]. In comparison, other European countries like Greece, Montenegro and Lithuania have few regulations governing IVF protocols and treatment and overall data from Europe show rates of double embryo transfer well over 50% and rates of transfer of three or more embryos as high as 12.5% [37]. The multiple birth rate is reflected in this practice with the multiple birth rate following IVF being 18.7% in Europe compared with 5.6% in Australia and New Zealand [37]. The multiple birth rate following IVF is even higher in the United States at 26.6% [35]. This is despite slightly higher rates of double embryo transfer in Europe, however this is thought to reflect the high rate of fetal reductions that occur in Europe as a management strategy for multiple pregnancy.

Despite implementing a single embryo transfer an IVF cycle may still result in a multiple pregnancy due to monozygotic twinning. Monozygotic twins are at increased risk of significant complications including Twin-Twin Transfusion Syndrome (TTTS) and Twin Anaemia-Polycythaemia Sequence (TAPS), fetal anomalies and perinatal morbidity. The rate of monozygotic twinning is increased in IVF pregnancy by 6 times compared with spontaneously conceived pregnancies [38], occurring at a rate of around 2.5% [39]. The reason for this is likely multifactorial. Culture media, embryo quality, use of gonadotropins and manipulation of the zona pellucida are all thought to play a role in the increased rates of monozygotic twinning following IVF [40].

In natural conception the rate of monozygotic twinning increases with age, likely a reflection of egg quality, however the inverse has been seen in pregnancies conceived with IVF. Women under 35 are twice as likely to have a monochorionic twin pregnancy following IVF treatment compared with women aged over 35 [41]. The mechanism for this may include the zona pellucida experiencing increased thickening with advancing maternal age, resulting in the embryo of an older patient being more robust to the manipulation exerted on it during IVF or Intracytoplasmic Sperm Injection (ICSI), or during embryo biopsy. This is an important observation and further supports the argument for single embryo transfer for younger patients with a good chance of implantation per embryo transfer. If a patient is at increased risk of monozygotic twinning, and has a double embryo transfer the risk of a higher order multiple pregnancy, with the added complication of a monozygotic twin pair develops.

The stress that a developing blastocyst and embryo undergoes during an IVF cycle may rationalise the increased rates of monozygotic twinning. Monozygotic twin pregnancies are more likely in day 5 blastocyst transfer than day 2 or 3 cleavage stage transfer, perhaps reflective of the strain that may be put on the embryo the day of transfer. Monozygotic twinning occurs due

to the embryo splitting anywhere from Day 4 through to Day 8. Transfer in the middle of this time period involves subtle changes to the pH, temperature and nutrient environment that could explain the increased rate during blastocyst transfer. The actual mechanics of the transfer may also play a role in making the embryo more likely to split. Blastocyst transfer is associated with nearly a three times increased chance of embryo splitting and resultant monozygotic twinning compared with cleavage stage transfer [42]. This finding has not lead to a change in practice due to the significantly greater live birth rate seen overall with blastocyst transfer due to the ability to select an embryo that has survived until day 5 of development and also result in transfer at a similar time to when the blastocyst would be reaching the uterine cavity in a natural conception [43].

The increased rate of monozygotic twinning for blastocyst transfer is not replicated, or at least not as pronounced, when the transfer is a result of a frozen cycle, rather than a fresh transfer [41]. An explanation for this is the freezing/thawing cycle may harden the zona pellucida making the blastocyst more robust against the process of embryo transfer and reduce the chance of splitting. A regime of 'freeze all' may be worthwhile to further reduce rates of multiple pregnancy from monozygotic twinning with blastocyst transfer.

Micro-manipulation techniques of the egg and embryo such as ICSI and pre-implantation genetic diagnosis have long been thought to play a role in increased rates of monozygotic twinning through weakening of the zona pellucida making it prone to splitting. Like blastocyst transfer, if this effect exists, it is likely associated with fresh transfers rather than frozen transfers. Because of this it is recommended that conventional IVF be used over ICSI unless significant male factor fertility issues exist.

Embryo quality has an association with the chance of monozygotic twinning. Poorer embryo quality has been shown to increase the rate of monozygotic twinning [44]. An appreciation of this is important when considering double embryo transfer due to poorer embryo quality. An awareness that the resultant pregnancy may develop into a higher order pregnancy, such as a dichorionic-triamniotic triplet pregnancy is crucial.

Not all multiple pregnancies that develop after single embryo transfers are monozygotic. A review of twin pregnancies following single embryo transfer found 18% of twin pregnancies were dizygotic [45]. The explanation for this was likely concurrent spontaneous conception with a frozen transfer or ovulation of uncollected eggs and subsequent fertilisation with fresh transfers. This hypothesis is supported by the fact that unexplained subfertility, with an underlying chance of conception, and obesity, that increases chance of uncollected oocytes due to limitations of ultrasound, was the main risk factors for dizygotic twinning in this scenario. The importance of abstaining from unprotected sexual intercourse at time of transfer is imperative when counselling couples on how to reduce the risk of multiple pregnancy.

5. Conclusion

The rate of multiple pregnancy associated with ART has fallen steadily with the implementations of better practices. As pregnancy success rates have increased the belief that more follicles or more embryos equates to better outcomes has been disproven. Close monitoring of

ovulation stimulation protocols, and a practice of single embryo transfer for IVF has resulted in far lower multiple pregnancy rates and safer practices for women. An awareness of the risk of multiple pregnancy with ART and the ways in which this can be avoided is paramount to the future direction of ART, both for research and regulatory bodies.

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