CHAPTER 23

Pregnancy and neonatal outcome following IVM

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INTRODUCTION

Immature oocyte retrieval and subsequent oocyte maturation in vitro (IVM) without the need for any ovarian stimulation is a promising new development in assisted reproductive technology (ART). Many successful pregnancies have been reported and IVM is successfully performed in many parts of the world[1–5].

IVM gives the benefits of ovarian stimulation – namely more oocytes – without the risks of ovarian stimulation. Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening condition associated with ovarian stimulation. Severe OHSS affects 1–2% of all women undergoing ART and up to 6% of women with polycystic ovaries (PCO) or polycystic ovary syndrome (PCOS)[6]. The only way to avoid OHSS totally is to avoid ovarian stimulation[7].

Any new development in assisted reproduction must also be accompanied by data concerning congenital abnormality, perinatal outcome, and later developmental sequelae.

Early data concerning pregnancies resulting from IVM have been generally reassuring so far[8–10]. This chapter will outline the currently available data, as well as data from the McGill series, concerning congenital abnormality, neonatal outcome, and obstetric outcome following IVM. The importance, as with all ART, of continuing surveillance and ideally centralized data collection will also be highlighted.

CONGENITAL ABNORMALITY

Although the collection of immature oocytes without any ovarian stimulation at all avoids the costs, side-effects, increased monitoring, and short- and possible long-term risks associated with ovarian stimulation, IVM also involves an additional 1 or 2 days' culture of the oocyte in vitro from the immature germinal vesicle, or metaphase I stage, to the metaphase II stage when fertilization can take place. Recent concerns regarding the possible effects of in-vitro gamete and embryo culture on congenital abnormalities in general and of imprinting disorders in particular[11,12] highlight the importance of continued reporting of any congenital abnormalities following IVM. To date, however, data are limited to four published series[8–10,13].

From a total of over 150 babies born following IVM, six major congenital abnormalities have been reported (Table 23.1). This rate – just under 4% – is similar to that reported following other ARTs[14] and slightly higher than that in spontaneously conceived controls. A comparative study[13]

Table 23.1 Major congenital abnormalities following IVM (n = 155)

Omphalocele (n = 1)
Cleft palate (n = 2)
Ventriculo-septal defect (n = 2)
45XO/46XY mosaic (n = 1)

n, number of babies

shows a similar odds ratio when IVM is compared with IVF and with ICSI (Figure 23.1).

Minor congenital abnormalities – those which are not life-threatening, do not impair function, and do not require corrective treatment – are often not reported. However, in the most recent McGill series, these affected 3/55 babies (5.4%) – two cases were unilateral congenital dislocation of the hip and one was a patent ductus arteriosus which closed spontaneously without requiring any corrective treatment.

MULTIPLE PREGNANCY

All ART treatments are associated with a significantly increased risk of multiple pregnancy[15,16]. The major determinant of multiple pregnancy is the number of embryos transferred. National differences in legislation account for the major differences in practice in differing parts of the world. Therefore one would expect lower incidences of multiple pregnancy in many European and Scandinavian countries following IVM compared with countries where many embryos are transferred.

All series report a high incidence of multiple pregnancy following IVM when compared with spontaneously conceived controls. Multiple pregnancy is the single most important factor leading to an increased perinatal risk with all ART. Rates of preterm delivery, stillbirth, neonatal loss, and later developmental sequelae are all more frequent following multiple pregnancy compared with singleton pregnancies.

At McGill, when IVM was compared with IVF and with ICSI, then multiple pregnancy rates were similar. The triplet pregnancy rate was 5% for IVM, 3% for IVF, and 3% for ICSI. The twin pregnancy rate was 21% for IVM, 20% for IVF, and 17% for ICSI – our rate of twin pregnancy is 1.3% in the general population.

There are no significant differences in the multiple pregnancy rates between IVM and other ART pregnancies. Nevertheless, couples undergoing IVM need to be aware of the risks

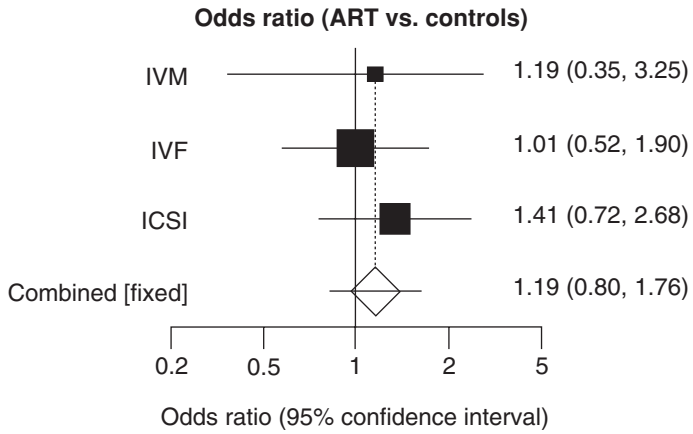

Figure 23.1 Odds ratio (fixed effects model) of any congenital abnormality following conception with IVM, IVF, and ICSI

and consequences of multiple pregnancy when more than one embryo is transferred and to balance these risks against the increased likelihood of live birth associated with two and three embryo transfer compared with single embryo transfer in IVM.

MODE OF DELIVERY

More ART pregnancies are delivered by cesarean section. Although much of this increased intervention is the result of the higher rate of multiple pregnancy, the cesarean section rate is still increased in singleton ART pregnancies. The reasons for this are unclear – although some studies have reported higher incidences of malpresentation and also of placenta praevia in pregnancies conceived as a result of IVF or ICSI[15,17]. Other authors have suggested that the threshold for recourse to cesarean section is lower in women who have conceived following ART[18,19].

The McGill data shows no demonstrable difference in the rates of cesarean section following IVM, IVF, or ICSI conceptions. Overall cesarean section rates are higher following ART (Figure 23.2).

Overall rates of instrumental delivery following IVM are similar to those in the general population at around 10% of deliveries.

BIRTHWEIGHT

Mean birthweight of all babies – singletons and multiples – following ART is lower than spontaneously conceived babies. The major reason for this is the high rate of multiple pregnancy. However, even in singleton pregnancies following ART, there is an increased incidence of lower birthweight babies[16].

Data from IVM are too early to determine whether or not the incidence of low birthweight babies is increased compared with spontaneously conceived babies. Some data suggest it is similar to other ART, whereas other data suggest that birthweight is similar to the general population[13]. That IVM singleton pregnancies are not associated with lower birthweight could either be as a result of the patients undergoing IVM – usually those with PCOS or those with ultrasound-only PCO – or because the number of pregnancies is still too small to demonstrate a difference.

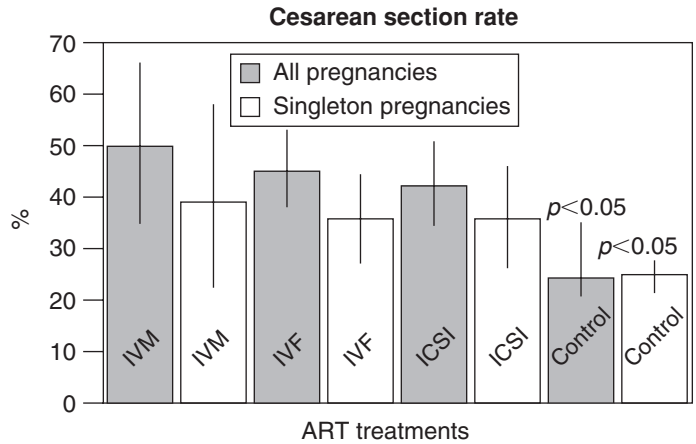

Figure 23.2 Cesarean section rates (95% CI) in all pregnancies (shaded) and singleton pregnancies (clear) following IVM, IVF, and ICSI treatments and spontaneously conceived controls

Similarly, when the proportion of macrosomic babies from singleton pregnancies is compared, there is no significant difference between any of the ART groups. This is important as some animal studies have suggested there may be an increased incidence of large-offspring syndrome following IVM[20].

GESTATIONAL AGE AT DELIVERY

Similarly the mean gestational age at delivery of all babies – singletons and multiples – following ART is lower than in spontaneously conceived pregnancies. As discussed above, the major reason for this is the high rate of multiple pregnancy. However, even in singleton pregnancies following ART, there is an increased incidence of preterm and extreme preterm birth[16].

Data from IVM are too early to determine whether or not the incidence of preterm delivery is increased compared with spontaneously conceived babies. Early data amongst the different ART treatments suggest that there is no significant difference between the proportion of premature deliveries before 37 weeks or before 34 weeks[13].

APGAR SCORES AND CORD pH LEVELS

For babies conceived following IVM compared with gestational age-matched controls, no studies so far have shown any difference in the median Apgar scores at 1 and 5 minutes, the proportion of babies with an Apgar score of 6 or less at 1 and 5 minutes, the mean cord pH, and the proportion of babies with mild acidosis (cord pH <7.2) or severe acidosis (cord pH <7.05).

WEIGHT FOR GESTATIONAL AGE

Weight for gestational age is determined by calculating the ratio between the birthweight at delivery and the standard norm for that gestation. This is an indirect measure of intrauterine growth retardation[21].

Babies conceived following IVF or ICSI have a slightly lower mean birthweight ratio than spontaneously conceived controls[16]. Also the proportion of all babies with a weight for their gestational age below the 5th centile (birthweight ratio <0.8) is higher in babies conceived following IVF or ICSI compared with the general population. Early data suggest that this is the same for babies conceived following IVM[13].

PREGNANCY COMPLICATIONS

The rate of gestational diabetes is higher in pregnancies which resulted from IVM compared with other ART and with spontaneously conceived controls (Figure 23.3).

This is more likely to be a result of the inherent predisposing risk of women undergoing IVM – namely those with PCO/PCOS who already have a higher risk of gestational diabetes[22,23] rather than as a direct result of the IVM treatment modality.

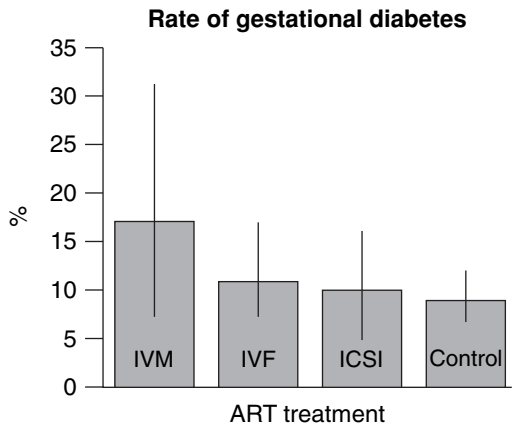

Figure 23.3 Rate of gestational diabetes in pregnancies conceived as a result of IVM, IVF, ICSI, and spontaneously

The rates of other pregnancy complications, including pre-eclampsia, do not appear increased following IVM when compared with other ART or when compared with spontaneously conceived controls.

CONCLUSIONS

The data presented here are generally reassuring for women undergoing IVM. Previously published evidence demonstrates higher rates of multiple pregnancy, earlier delivery, and lower birthweight – even in singleton pregnancies following established ART treatments (IVF or ICSI). The obstetric and perinatal outcomes following IVM are comparable to these established treatments, and may be associated with fewer low birthweight babies, although the data are still early. Continued ongoing surveillance – as with any ART modality – is important so that the risks and benefits of all infertility treatments can be appropriately compared.

Furthermore, all ART treatments show a trend towards a slight increase in the occurrence of any congenital abnormality, and this is most marked for babies conceived following ICSI. This is consistent with increasing evidence from large ART-based studies which show an increased prevalence of major malformations[14,24], chromosomal anomalies[25], and, more recently, imprinting disorders[26]. Whether ART has a direct causative effect, however, is still equivocal owing to the many confounding variables – particularly the effect of infertility per se on the risk of developing congenital abnormalities[27,28]. Similarly, multiple pregnancy – whether spontaneous or following ART – is itself associated with an increase in the incidence of congenital abnormalities, particularly congenital cardiac malformations[29].

In conclusion, when ART is indicated, IVM offers a reduction in the risks of ovarian stimulation and, based on current data, no increased risk of congenital abnormality or perinatal outcome over that already accepted for IVF or ICSI. For an 80% power and a 5% alpha, with a probability of congenital abnormality in the population of 3% and a factor of 1.5, over 1000 IVM babies and over 3000 controls would be needed. The establishment of national and international registries for babies born following IVM, continued data collection and matched studies, and the results from ongoing child development longitudinal studies are essential as the use of IVM as a clinical treatment continues to expand.

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