Chapter 9
Maternal Medical Complications in Pregnancy Following Assisted Reproductive Technology

Margaret Ramsay and Shobhana Parameshwaran

Introduction

There has been an increase in the demand for assisted reproductive technology (ART) in the last 30 years. Assisted reproductive techniques have proved effective in achieving successful conception as well as outstanding live birth rates of 51–72 % after up to 6 treatment cycles; for women younger than 35 years the live birth rates are even better at 65–86 % [1]. Assisted reproductive technology refers not only to In Vitro Fertilization (IVF) but also to several other procedures related to the reason for subfertility, including intrauterine insemination. These procedures are usually paired with drugs to enhance ovulation. Women undergoing ART need it for various reasons: chronic anovulation due to polycystic ovarian syndrome (PCOS), diminishing ovarian function due to advanced age, tubal disease and male factor subfertility. However, these women may also have other significant problems which affect not only their fertility but also their risk for problems occurring should they achieve pregnancy, e.g., raised body mass index (BMI), pre-existing medical conditions including hypertension, diabetes or endocrine problems.

The use of ART has been linked with adverse pregnancy outcomes, including gestational hypertension, pre-eclampsia and gestational diabetes. Maternal medical complications, especially pre-eclampsia, are known to be exaggerated in those who conceive a twin or higher-order multiple pregnancy following ART. [2] In a large prospective study of singleton pregnancies, the pregnancy outcomes for 34,286

M. Ramsay, MA, MB, BChir, MD, MRCP, FRCOG (✉)
Department of Fetomaternal Medicine and Obstetrics, Nottingham University Hospitals, Queen's Medical Centre Campus, Nottingham, UK
e-mail: mmramsay@doctors.org.uk

S. Parameshwaran, MBBS, MS, MRCOG
Department of Obstetrics and Gynaecology, Sheffield Teaching Hospitals, Sheffield, UK
e-mail: pshobhana@hotmail.com

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women who spontaneously conceived were compared with 1222 women who had been given ovulation induction therapy and 554 who had undergone IVF treatment [3]. An increased incidence of gestational hypertension and pre-eclampsia was found in the IVF group as compared to the spontaneous conception group; the adjusted odds ratio for pre-eclampsia was 2.7 (with 95% confidence interval 1.7–4.4), which reached a high degree of statistical significance ($p<0.01$). Ovulation induction was found to be associated with increased risk for gestational diabetes (adjusted odds ratio 1.5 with 95% confidence interval 1.1–2.2). The question raised was whether these pregnancy complications were due to the ART techniques themselves, or to the innate characteristics of the patients undergoing a particular treatment modality [4].

A systematic review concentrating on 15 cohort studies (11 of which were matched) of singleton pregnancies conceived following IVF as compared to spontaneous conceptions concluded that the relative risk for hypertensive complications was 1.49 (95% confidence interval 1.39–1.59) [5]. This review estimated that the absolute increase in risk for hypertensive complications was about 2%. The same review reported the findings of 6 cohort studies (4 of which were matched) regarding risks for gestational diabetes. The findings were of a relative risk for gestational diabetes of 1.48 (95% confidence interval 1.33–1.66) in the IVF group compared to spontaneous conceptions; this was an absolute increase in risk of approximately 1% [5].

Others studies have disagreed and did not find an association between use of ART and higher incidence of gestational hypertension or diabetes [6, 7]. One of these studies was a cohort of 242,715 women in Japan, where 3 study groups divided by the type of ART procedure (ovulation induction alone, intrauterine insemination and IVF) were compared with matched controls to adjust for maternal characteristics including age, parity, BMI, smoking and alcohol consumption and pre-existing medical complications [7]. This study found no differences in hypertensive complications between the groups but did find overall that the ART pregnancies had more adverse outcomes including preterm delivery and low birthweight infants; the incidence of gestational diabetes was not reported. The study concluded that maternal factors associated with infertility contribute to adverse pregnancy outcomes and it is not anything to do with the ART procedures themselves.

Other authors have used Propensity Scoring (a statistical tool to minimise selection bias and confounding factors in observational studies) in their analysis of prospectively recruited subjects, who conceived with or without IVF techniques. They found the association between IVF and pre-eclampsia to be much weaker than previously described [8].

There are, however, some circumstances when maternal medical complications may be anticipated following ART.

Problems Arising due to Advanced Maternal Age

Childbearing at advanced maternal age is becoming increasingly common, especially in affluent countries. Assisted reproductive techniques, including IVF and egg

donation, contribute to an increasing incidence of pregnancies in women outside of the normal reproductive age. In England and Wales the average age at childbearing has increased progressively since the mid-1970s from 26.4 to 29.5 years in 2010, with 48 % of all babies born to mothers aged more than 30 years [9].

Advanced maternal age (more than 35 years) is associated with subfertility, chromosomal abnormalities, miscarriage, multiple gestation, low birth weight, placenta praevia and caesarean delivery [10, 11]. In addition, advanced maternal age is associated with an increased risk of pregnancy complications including gestational diabetes, pregnancy-induced hypertension and pre-eclampsia [10–12]. A national prospective cohort of more than 1.5 million maternities in Sweden found the odds ratios for maternal death in women aged 40–44 years (as compared to the age group 20–29 year) to be 16.2 (with 95 % confidence intervals 6.38–41.2); in the age group >45 years, the odds ratio was even higher (121, with 95 % confidence intervals 27–542) [10]. There are also adverse perinatal outcomes including antepartum stillbirth, intrapartum-related perinatal death, early neonatal death and neonatal unit admission [10, 11]. However, in all these studies it is acknowledged that there are many confounding factors. In a prospective cohort of singleton pregnancies, there were no difference in the incidence of gestational hypertension or pre-eclampsia once race, body mass index, parity, smoking, other medical disorders, previous adverse outcomes and use of ART had been controlled for; only gestational diabetes became more common with advancing maternal age (adjusted odds ratio of 2.4 in women over 40 years, compared to those less than 35 years) [11].

A retrospective cohort study looked at the interaction between maternal age, use of ART and maternal pregnancy complications [13]. There were 330 women aged 40 years or more, of whom 242 had conceived spontaneously (SC) and 88 had conceived with IVF (all with autologous embryos); these were compared with 450 women aged 30–34 years (of whom 422 had conceived spontaneously and 28 following IVF). The respective incidence in these groups of pregnancy induced hypertension was 7.9 % (SC), 20.5 % (IVF) in the older mothers; 2.6 % (SC) and 14.3 % IVF in the younger mothers. Pregnancy induced hypertension was more common in all women who had conceived following IVF, compared to those who had conceived spontaneously; however, it was overall more common in the older mothers, regardless of mode of conception.

Risk Assessment, Identification, and Management of Specific Pregnancy Complications

Hypertensive Complications of Pregnancy

Women should have risk assessment at booking (Table 9.1) and those at high risk of developing pregnancy induced hypertension or pre-eclampsia should be offered low dose aspirin (75 mg daily) [14]. These women should also have a plan

Table 9.1 Pre-eclampsia risk assessment and prevention

Assessment should be made in early pregnancy, to allow for initiation of prophylactic low-dose aspirin treatment from 12 weeks gestation and appropriate surveillance of blood pressure and urinanalysis throughout pregnancy [14].
High Risk
Women with the following conditions are high risk for developing pre-eclampsia. These women should also be started on aspirin 75 mg from 12 weeks until delivery, unless there are contraindications to its use.
Hypertensive disorders during a previous pregnancy
Chronic kidney disease
Autoimmune disease such as Systemic Lupus Erythematosis or Antiphospholipid syndrome
Type 1 or type 2 Diabetes
Chronic Hypertension
Moderate Risks
If a woman has *two* or more of the following risk factors she should be started on aspirin 75 mg from 12 weeks until delivery, unless there are contraindications to its use.
First pregnancy
Age 40 years or older
Pregnancy interval of more than 10 years
Body mass index of 35 kg/m^2 or more at first visit
Family history of pre -eclampsia
Multiple pregnancy

for closer maternal and fetal surveillance especially in the third trimester (Table 9.2) [15].

Gestational Diabetes

Women who are at high risk of developing gestational diabetes (GDM) on the basis of their age, having BMI ≥30 kg/m^2, South Asian ethnicity, previous macrosomic baby of 4.5 kg or more, personal prior history or close family history of diabetes should be screened at 26–28 weeks with a glucose tolerance test (GTT) [16]. If the GTT is abnormal, referral should be made to the multidisciplinary obstetric-diabetic clinic. Dietary assessment and modification, use of oral hypoglycaemic agents (Metformin) and/or insulin may be necessary to ensure normo glycaemia.

Thromboembolism

Women should have a risk assessment early in pregnancy based on their age, parity, family and personal history of thromboembolism, medical history and current health to assess their risk of thrombosis during pregnancy (Table 9.3) [17]. A decision about whether thromboprophylaxis should be offered during or after pregnancy

Table 9.2 Recommended frequency of maternal surveillance for those deemed at high risk of developing pre-eclampsia

24–32 weeks gestation	32 weeks gestation until delivery
No more than 3 week interval between assessments	No more than 2 week interval between assessments
Women to be included in this schedule are those who have one or more of the following factors:	
First pregnancy	
Previous pregnancy complicated by pre-eclampsia	
Interval of ≥10 years since last pregnancy	
Age ≥ 40 years	
BMI ≥ 35 kg/m^2	
Family history of pre-eclampsia (in mother or sister)	
Diastolic blood pressure at booking ≥80 mmHg	
Proteinuria at booking visit	
Multiple pregnancy	
Medical conditions (pre-existing hypertension, renal disease, diabetes, antiphospholipid syndrome)	

can be made on this assessment. Factors occurring during pregnancy may also influence decisions about the need for short-term thromboprophylaxis, e.g., if ovarian hyperstimulation has been triggered, or the woman is hospitalised, immobile or unwell with a pyrexia.

Multiple Gestation

Women with twin pregnancies have at least double the incidence of gestational hypertension and pre-eclampsia as those with singleton pregnancies [18]. In a cohort study of multiple pregnancies conceived either spontaneously or after ART (either ovulation induction alone or IVF), those women who received ART were twice as likely to develop preeclampsia, after adjustment for age and parity [19].

Risk Assessment, Identification, and Management of Specific Pregnancy Complications

Hypertensive Complications of Pregnancy

Consideration should be given to the use of prophylactic aspirin 75 mg daily (Table 9.1) and enhanced blood pressure surveillance throughout pregnancy (Table 9.2). Serial ultrasound examinations are required to document fetal growth and umbilical artery Doppler velocimetry.

Table 9.3 Assessment of risk factors for venous thromboembolism at booking

Pre existing factors
Previous VTE
Family history of VTE
Thrombophilia
Inherited
Antithrombin deficiency
Protein C or S deficiency
Factor V Leiden
Prothrombin gene variant
Acquired (Antiphospholipid syndrome)
Persistent lupus anticoagulant
Persistent moderate/high titre anticardiolipin or beta-2 glycoprotein 1 antibodies
Age over 35 years
Obesity (BMI >30 kg/m^2 or weight >90 kg at booking)
Parity ≥ 3
Smoking
Medical morbidities, e.g.,
Heart or Lung disease
SLE
Cancer
Inflammatory bowel disease
Inflammatory polyarthropathy
Nephrotic syndrome
Sickle cell disease
Intravenous drug user
Gross varicose veins
Paraplegia

Pregnancy following ART is itself considered a risk factor for VTE, as is a multiple pregnancy (e.g., twins). Each of the above factors should also be considered in order to determine whether the woman's individual risks for VTE justify antenatal thromboprophylaxis with low molecular weight heparin. There are also temporary factors (e.g., surgery, dehydration, hyperemesis, ovarian hyperstimulation, systemic infection, immobility, long distance travel) which would heighten VTE risk and could be managed with short-term thromboprophylaxis (until the risk period is passed). It is advised that VTE risk is reassessed upon admission to hospital and after delivery [17]

Thromboembolism

Having conceived as a result of ART and having a multiple gestation are both risk factors for venous thromboembolism. These should be considered along with other factors to help decide if specific thromboprophylactic measures (including daily

administration of low molecular weight heparin) are indicated during or after pregnancy (Table 9.3).

Pre-existing Hypertension

Hypertensive disorders occur in about 10 % of pregnancies and are responsible for a third of severe maternal morbidity, as well as many maternal deaths [14]. Chronic hypertension is present in about 1–2 % of pregnant women with rates increasing as maternal age increases [10, 11]. Chronic hypertension may be primary (essential) in approximately 90 % of cases with the remaining 10 % secondary to one or more underlying diseases such as renal disease, collagen vascular disease, endocrine disorders, or coarctation of the aorta. Pre-existing hypertension is a well-recognised risk factor for pre-eclampsia and all its associated sequaelae [14]. There are no specific studies comparing the incidence of hypertensive complications in women with and without pre -existing hypertension who have conceived following ART.

Pregnancy Care for Women with Underlying Hypertension

Women with pre-existing hypertension on Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARB) or Chlorthiazide should be informed about the increased risk of congenital abnormalities and later pregnancy complications if these are taken during pregnancy. Antihypertensive medication should be changed to labetolol, methyl dopa, or other drugs that are known to be safe to use in pregnancy, ideally prior to commencement of ART schedules [14]. Low dose Aspirin (75 mg daily) should be prescribed in this group of women (Table 9.1). There is no evidence of benefit in starting low dose aspirin periconceptually [20].

Polycystic Ovarian Syndrome

Women with polycystic ovarian syndrome (PCOS) more often need ART to achieve pregnancy than women without this diagnosis; 13.7 % in a large Swedish study of 3787 births to women with PCOS, compared to a background rate of 1.5 % in more than one million women without PCOS [21]. The study also found these women were almost twice as likely to be obese. There were strong associations between PCOS and pre-eclampsia (adjusted odds ratio 1.45, with 95 % confidence interval 1.24–1.69) and between PCOS and gestational diabetes (adjusted odds ratio 2.32, with 95 % confidence interval 1.88–2.88) [21]. Adjustments in the odds ratios quoted here had been made for maternal age, parity, BMI, ART, smoking, year of delivery and years of education.

Another study looked at the adverse pregnancy outcomes in obese and non-obese women with PCOS who underwent ART, compared to obese and non-obese controls, who had ART for tubal factor infertility [22]. As this was an Asian population, obesity was defined as BMI more than 25 kg/m^2. No differences in the incidence of pregnancy-induced hypertension were found between the 4 groups; however, it was the obese women from PCOS and control groups who had the highest incidence of gestational diabetes (10.5 % and 8.6 %, respectively) [22].

Pregnancy Care for Women with PCOS

A risk assessment should be performed early in pregnancy to assess individualised risks for pre-eclampsia, gestational diabetes and venous thromboembolism (Tables 9.1 and 9.3). Most of these women will qualify for low dose aspirin and enhanced fetal and maternal surveillance (Table 9.2). Although in the United Kingdom, PCOS is not identified as a screening criterion for gestational diabetes (16), many women will qualify for screening on the basis of weight, racial origin or family history and thought should be given to offering women a glucose tolerance test (GTT) at 26–28 weeks. If the woman has a BMI more than 40 kg/m^2, then consideration should be given to performing an additional, earlier GTT at 16–18 weeks.

Thyroid Dysfunction

It is important to check thyroid function and correct clinical hypothyroidism or hyperthyroidism prior to ART. Derangement of thyroid function is likely to be a major contributor to subfertility. However, it is also apparent that subclinical hypothyroidism (i.e., elevated thyroid stimulating hormone levels in the presence of normal circulating free thyroxine and tri-iodothyronine levels) and the presence of thyroid antibodies are associated with adverse pregnancy outcomes. In a meta-analysis of women with subclinical hypothyroidism compared to those with normal thyroid function higher risks for pre-eclampsia (Odds Ratio 1.7, with 95 % confidence intervals 1.1–2.6) and perinatal mortality (Odds Ratio 2.7, with 95 % confidence intervals 1.6–4.7) were found [23]. Thyroid antibodies were associated with higher risks for miscarriage, recurrent miscarriage, preterm birth and maternal thyroiditis in the postpartum period [23].

Another systematic review looked at randomised controlled trials of levothyroxine versus placebo treatment for women with subclinical hypothyroidism or thyroid autoimmunity who were undergoing ART [24]. The conclusions (from 3 trials totalling 220 patients) were that levothyroxine treatment lowers miscarriage rate, increases live delivery rate, but no changes could be demonstrated in the incidence of pre-eclampsia [24].

Pregnancy Care for Women with Thyroid Dysfunction

Clinical or Subclinical Hypothyroidism, Thyroid Autoimmunity

Adequate maternal thyroid hormone production is especially important in the first trimester, when fetal brain developments start and the fetus does not produce its own thyroid hormones. Pre-conceptually and throughout pregnancy, the aim should be to keep thyroid stimulating hormone (TSH) in the range 2–2.5 iu/l. This usually necessitates an increase in daily dose of levothyroxine of the order of 25–50 mcg. The TSH levels should be checked each trimester.

Clinical Hyperthyroidism

During pregnancy, mild hyperthyroidism, in which TSH is low but free thyroxine (T4) and tri-iodothyronine (T3) are normal, does not require treatment. More severe hyperthyroidism is treated with medication to suppress thyroid hormone production. While both Propylthiouracil and Carbamizole can be used, propylthiouracil is the preferred antithyroid agent in pregnancy. Antithyroid medication crosses the placenta in small amounts and can decrease fetal thyroid hormone production, so the lowest possible dose should be used to avoid hypothyroidism in the baby. During pregnancy, TSH, free T3 and T4 should be monitored, with medication adjusted to maintain FT4 levels at the upper limit of the normal range.

Other Intercurrent Medical Conditions

Any woman with a chronic medical condition who is aiming to conceive with ART should be counselled about the likely effects of their condition on pregnancy outcome, the effects of pregnancy on their medical condition and they should have their drug medication reviewed for safety. A multidisciplinary approach may be required, as there can be a conflict of interest with respect to what may be best for the mother and what for the fetus. In these circumstances, skilled counselling about the safest and most sensible course is needed. For some conditions, multidisciplinary review may conclude that pregnancy is very hazardous; in which case, proceeding with ART would be unethical.

An example of inadequate pre-conceptual preparation was reported by the French Study Group for Oocyte Donation, who looked at the maternal and fetal outcomes of pregnancies achieved by oocyte donation in women with Turner's Syndrome [25]. There were 93 patients in this study, of whom only 35 had undergone echocardiography or cardiac magnetic resonance imaging in preparation for ART and only 6 had documented aortic root diameters. Of the 82 women whose pregnancies continued beyond 20 weeks, 31 had hypertensive complications,

including 4 cases of eclampsia. Two mothers died from aortic rupture, with evidence of aortic root dilatation. Almost a third of the babies were growth-restricted and there was one fetal death attributed to maternal eclampsia. Only 40 % of the reported pregnancies resulted in normal fetal and maternal outcomes.

Pregnancy Care for Women with Underlying Medical Conditions

For most *chronic inflammatory conditions* (e.g., autoimmune arthritis, inflammatory bowel disease), keeping the disease processes quiescent during pregnancy is critical for a favourable pregnancy outcome. Anti-inflammatory and disease-modifying drugs can be adjusted to those with the best safety record for use in pregnancy. It is not generally advisable to withdraw drugs that are keeping inflammation under control, since managing a serious disease flare during pregnancy could involve use of much larger doses of drugs, with greater fetal exposure to them overall with the additional risks to the pregnancy of inflammation which is associated with preterm labour.

Meticulous glycaemic control periconceptually and in early pregnancy is vital for good outcomes in women with *diabetes mellitus*. High dose folic acid supplements (5 mg daily) are recommended [16].

For women with *epilepsy*, periconceptual review of anticonvulsant drug treatment and use of high dose folic acid supplements are important [26].

Women with *renal disease* need careful assessment prior to ART as they may be on medication (e.g., ACE inhibitors) that should be changed prior to conception. Baseline blood pressure and proteinuria should be established. Meticulous blood pressure control during pregnancy is essential, as are serial tests of renal function, including quantitative proteinuria. Women with renal disease are at increased risk for pre-eclampsia during pregnancy, so should be given aspirin prophylaxis and have enhanced maternal surveillance (Tables 9.1 and 9.2).

Women with *bleeding or clotting problems* need careful planning for their initial ART procedures, as well as for the risks they may encounter during pregnancy; those with thrombophilia or a prior history of thromboembolism may require thromboprophylaxis to cover ovarian stimulation schedules.

Multidisciplinary care for these and other less common conditions needs to continue during pregnancy to ensure the best maternal and fetal outcomes.

Maternal Obesity

Obesity has become an increasing problem over the last 30 years, including in pregnant women. Maternal obesity has significant health implications during pregnancy, contributing to increased morbidity and mortality for both mother and baby

Table 9.4 Pregnancy risks associated with increased maternal BMI

	Overweight (BMI 25–30)	Obese class 1 (BMI 30–35)	Obese class 2 (BMI 35–40)	Obese class 3 (BMI > 40)
Hypertension	1.9	3.5	5.0	6.6
Gestational diabetes	1.7	3.7	6.0	8.5
Labour induction	1.2	1.3	1.4	1.6
Caesarean Section	1.4	1.8	2.5	2.8
Postpartum haemorrhage	1.4	1.8	2.4	2.7
Macrosomia >4 kg	1.5	1.9	2.1	3.2

Odds ratios for pregnancy outcomes in the BMI groups, compared with women of normal weight (BMI 20–25 kg/m^2) from a retrospective study of 30,298 women over 8 years [27]

[27–29]. As BMI increases, so do the risks for gestational diabetes, thromboembolism, gestational hypertension, including pre-eclampsia (Table 9.4) [27]. Obese women are less likely to go into labour spontaneously, more likely to have a prolonged pregnancy and have labour induced, less likely to achieve a normal delivery and more likely to deliver by caesarean section [27, 30]. Intrapartum and postpartum complications are more common in obese mothers, such as uterine rupture associated with a previous uterine scar, primary postpartum haemorrhage, and postpartum infection [27, 28, 31]. Obesity is also associated with a higher risk of adverse neonatal outcomes, including congenital anomalies, macrosomia, shoulder dystocia, neonatal intensive care admission, and perinatal death [27, 28, 30, 31].

Obesity also affects the responses to ART. The higher a woman's BMI, the more days of gonadotrophin stimulation she is likely to need and the greater the chance of cancellation of an IVF treatment cycle [32, 33]. An interesting observation from a report of 152,500 ART cycle starts in the years 2007–8, for women of known BMI, was that the failure to achieve a clinical intrauterine pregnancy, which became more common as BMI increased, was more marked in fresh cycles using autologous, as opposed to donor eggs [34]. The incidence of fetal death and stillbirth also increased as maternal BMI increased. It is evident that obesity creates an adverse environment for the oocyte, embryo and fetus through many endocrine and inflammatory mechanisms [34, 35]. A meta-analysis of studies of IVF outcomes after fresh donor oocytes in recipients of known BMI (totalling 4758 women) confirmed that there were no worse outcomes for miscarriage and live births in women with BMI ≥30 kg/m^2 [36]. These results were interpreted to show that oocyte quality is more important in terms of getting a good outcome from IVF in obese women than endometrial receptivity. These studies did not, however, look at maternal complications during pregnancy.

There has been much discussion about the ethics and economic aspects of offering IVF to those of high BMI. The risks of failure to achieve an intrauterine pregnancy and miscarriage rise with maternal BMI, but are significantly worse even in the "overweight" women whose BMI is 25–29.9 kg/m^2, as compared to those whose BMI is less than 25 kg/m^2 [37]. Recommendations for the BMI cut-off for being offered IVF varies between countries and Societies: less than 30 kg/m^2 in the United

Kingdom for National Health Service-funded cycles [38], and less than 32 kg/m^2 in New Zealand [39]. However, some have argued that restriction of access to ART on the basis of BMI is unjust and that it is worse to defer pregnancy until suitable weight loss has occurred, since advancing maternal age brings even more problems [39].

Pregnancy Care for Obese Women

It is recommended that increased folic acid doses of 5 mg daily are given periconceptually to obese women, as neural tube defects are twice as likely to occur in this group, compared to normal-weight women [40]. Individualised risk assessment for thromboembolism, gestational hypertension and gestational diabetes at the start of pregnancy will lead to decisions about the need for thromboprophylaxis, low dose aspirin and screening for gestational diabetes in the second trimester (Tables 9.1 and 9.3). Dietary and healthy lifestyle advice and support is also important, to try and reduce gestational weight gain to 5–10 kg [28]. Vitamin D supplements of 10 mcg daily are also recommended, due to a higher incidence of vitamin D deficiency in obese women.

Pregnancy Post-bariatric Surgery

Women with high BMI who have failed to lose weight with dietary modification and exercise alone, may consider the option of undergoing bariatric surgery which may lead to rapid weight loss, return of periods and ovulation [28, 41]. If these women do not spontaneously conceive, they are more likely to be at an optimal BMI for ART. Pregnancy will then be safer for them, than if they were still morbidly obese. Bariatric surgery involves either restrictive procedures such as gastric banding or sleeve gastrotomy alone or restrictive plus malabsorptive procedures, such as Roux-en Y bypass. Women are advised not to conceive during the period of rapid weight loss following surgery and should ideally wait 12–18 months before trying to conceive.

There is a potential for nutritional deficiencies of protein, iron, calcium, folate, vitamin B12 and vitamin D, particularly after malabsorptive bariatric surgical procedures. An assessment of serum levels of these factors should be done at the start of pregnancy and repeat assessments in each trimester. Adequate nutritional replacements should be provided, based on these results [28, 41].

For women who have had gastric banding procedures, surgical complications can happen during pregnancy, including band slippage and migration, which causes severe vomiting. There are also reports of intestinal herniation, obstruction and perforation following bariatric surgery. These complications may be difficult to diagnose during pregnancy, so symptoms of epigastric pain or vomiting should not be ignored [41].

Pregnancies Following Gamete Donation

Pregnancies that are created from oocyte, sperm or embryo donation have for a long time been suspected of having a high incidence of gestational hypertension and pre-eclampsia. A retrospective cohort of 72 women who had conceived with sperm, ooctye or embryo donation were compared with age and parity-matched women who conceived either spontaneously or with intrauterine insemination with their partner's sperm. [42] The incidence of gestational hypertension and pre-eclampsia in the gamete donation group overall was 12.5 % and 18.1 %, respectively; compared with 2.8 % and 1.4 % in the control group. Other, larger studies reporting pregnancy complications after intrauterine insemination (IUI) with either partner or donor sperm confirmed higher incidence of pre-eclampsia after donor insemination (3.7 % difference, with 95 % confidence interval −0.8 to +7.8 %) [43]. Logistic regression analysis found that the highest incidence of pre-eclampsia was in women who conceived with donor sperm after only a few cycles of IUI.

A single-centre study of 71 donor oocyte recipients and 108 women (aged over 38 years) who conceived with IVF using autologous oocytes addressed maternal and fetal pregnancy complications [44]. Multivariate analysis found that, after controlling for multiple gestation, the use of donor oocytes was not a major risk factor for adverse obstetric outcomes (adjusted odds ratio for pre-eclampsia 1.25, with 95 % confidence intervals 0.53–2.93). However, the two groups were not well matched for age and there were far more multiple pregnancies in the donor oocyte group; these factors may have confounded the findings. It was observed that in women over the age of 38 years, twin or higher-order multiple pregnancies were more likely following the use of donor oocytes, even if fewer embryos were transferred in the IVF process. The increased risk of pre-eclampsia that multiple pregnancy brings is well recognised [2].

The largest cohort study to address the impact of oocyte donation followed 205 women who conceived with donor oocytes and compared them with 205 women who had undergone IVF, specifically intracytoplasmic sperm injection (ICSI) with autologous oocytes; thus all the pregnancies had arisen from the same ART technique [45]. Cases were individually matched for age, ethnicity, parity and number of fetuses. All the cycles were with fresh oocytes. This study confirmed that oocyte donation was associated with a significantly increased risk for gestational hypertension (incidence 19.1 % in donor oocyte pregnancies versus 8.3 % in autologous oocyte pregnancies). When singleton and twin pregnancies were separated, the most marked difference in incidence of gestational hypertension was in the twin pregnancies (24.6 % in donor oocyte group versus 7 % in autologous oocyte group). There was a higher, but statistically non-significant, incidence of pre-eclampsia in donor oocyte pregnancies, but no differences in the incidence of gestational diabetes. There were no differences between the groups for overall perinatal outcomes.

Pregnancy Care for Women Following Gamete Donation

Use of prophylactic low-dose aspirin should be considered in this group, due to the higher risks of gestational hypertension, especially in multiple pregnancies (Table 9.1), with enhanced blood pressure surveillance (Table 9.2).

Conclusion

Pregnancies resulting from ART may have increased risks for maternal medical complications, especially gestational hypertension, pre-eclampsia, thromboembolism and gestational diabetes. These risks largely arise due to the characteristics of the women who undergo ART and are most marked in older women, those with high body mass index or polycystic ovary syndrome and in multiple pregnancies; but risks especially for pre-eclampsia are high when donor gametes have been used.

The important principle for good pregnancy care is that of thorough risk assessment for each of these complications in early pregnancy, in order to plan surveillance *including* additional blood pressure surveillance and glucose tolerance tests or to institute prophylactic treatment such as low dose aspirin, low molecular weight heparin, high dose folic acid and others as appropriate.

Women with significant underlying medical conditions need careful assessment prior to commencement of ART protocols to consider maternal and fetal risks in pregnancy, plan appropriate health surveillance during pregnancy and consider adjustment of medication.

Finally, the clear information about adverse pregnancy outcomes for those with high BMI and in those with twin or higher order multiple pregnancies should guide appropriate ART practices including single embryo transfers, mild stimulation protocols and weight reduction prior to ART.

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