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Review

Multiple pregnancies following assisted reproductive technologies — A happy consequence or double trouble?

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SUMMARY

The association between assisted reproduction technologies (ART) and multiple pregnancy is well-established, with a multiple birth rate of 24% in ART pregnancies. Multiple pregnancy is associated with significantly increased maternal and perinatal morbidity and mortality, as well as increased costs to the National Health Service. Evidence relating to the obstetric outcomes of ART twins versus naturally conceived twins is discussed in this review. Methods to reduce the risk of multiple births including elective single embryo transfer and multifetal pregnancy reduction are also discussed.

1. Introduction

The incidence of multiple births has risen steadily over the last 30 years, mainly due to the increasing use of assisted reproduction technologies (ART) and the increase in average maternal age at conception. ART is defined as any procedure that entails the handling of both eggs and sperm, or of embryos, for the purpose of establishing a pregnancy [gamete intrafallopian transfer (GIFT); in-vitro fertilisation (IVF); intracytoplasmatic sperm injection (ICSI)] [1]. In 2009, 16 women per 1000 had multiple births accounting for 3% of all live births [2]. The current rate of multiple births in ART is 24% [2]. Although multiple pregnancy is associated with adverse pregnancy outcomes, a significant proportion of infertility patients considers multiple pregnancy to be an ideal treatment outcome [3].

Multiple pregnancy is associated with significantly higher risk than singleton pregnancies for both the mother and the babies. Maternal antepartum, intrapartum and postpartum complications are more frequent, as are perinatal sequelae. Multiple pregnancies therefore require more monitoring and increased contact with healthcare professionals, resulting in an increased financial burden to the National Health Service (NHS). Indeed the maternal care for twin pregnancies appears to be twice as costly as the care for mothers with singleton pregnancy, because of the increased caesarean section rate and the need for specialist obstetric care [4]. Increased rates of prematurity will increase costs of caring for the neonate, as well as the costs of prematurity-induced lifelong disability. This paper aims to review the maternal and perinatal consequences of multiple pregnancy. The outcome of ART twins versus naturally conceived twins is also discussed. Current best practice advice on minimising the risk of multiple pregnancy in ART will also be outlined.

2. Maternal consequences of multiple pregnancy

Multiple pregnancy is associated with increased maternal morbidity compared with singleton pregnancy [2]. There is good evidence that the incidence of pregnancy-induced hypertension is increased with multiple pregnancy. A cohort study reporting on 34,374 pregnancies with one to four fetuses published in 2005 found the incidence of pregnancy-related hypertensive disease to be 6.5% for singletons versus 12.7–19.7% for multifetal pregnancies ($P < 0.001$) [5]. Sibai et al. undertook a prospective multicentre study of 684 twin gestations versus singletons and found higher rates of both gestational hypertension [relative risk (RR): 2.04; 95% confidence interval (CI): 1.60–2.59] and pre-eclampsia (RR: 2.62; 95% CI: 2.03–3.38) [6]. In addition, early severe pre-eclampsia and haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome was seen more frequently with multiple gestations. A systematic review by Duckitt et al. also demonstrated that multiple pregnancy is a clear risk factor for developing pre-eclampsia, with a tripling of the woman's risk (RR: 2.93; 95% CI: 2.04–4.21) [7] compared with a singleton pregnancy [7]. This systematic review found only one study on triplet pregnancies, showing that a triplet

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pregnancy similarly triples the risk of developing pre-eclampsia compared with a twin pregnancy (RR: 2.83; 95% CI: 1.25–6.40) [7].

The physiological adaptations to pregnancy are more marked in multiple pregnancy with the blood volume increasing by around 50–60% in twin pregnancies [8]. The size of the uterus is greatly increased in multifetal pregnancies, causing a greater pressure on venous return which can result in backache, varicose veins, separation of the rectus abdominis muscle and dyspnoea due to the displacement of the diaphragm [9].

The risk of complete miscarriage is higher in multiple pregnancies. Additionally the rate of spontaneous reduction of multiple pregnancies to a singleton is estimated at 14% [10]. The risks of antepartum haemorrhage (due to the greater surface area of the placental bed) and postpartum haemorrhage are also increased in multiple pregnancies [2].

An increased incidence of gestational diabetes in twin pregnancies has been reported in two large cohort studies. Schwartz et al. [11] recorded data on 29,644 deliveries with 429 twin deliveries and found an increased rate of gestational diabetes in the twin pregnancies (7.7% vs 4.4%, $P < 0.05$). This was confirmed in a study by Ruhn-Hain et al. [12] which found a higher rate of gestational diabetes in twin pregnancies when compared with singleton pregnancies (3.98% vs 2.32%, $P = 0.01$) in a population of 23 056 women with 553 twin pregnancies.

Multiple pregnancy is a known risk factor for venous thromboembolism. Simpson et al. [13] produced data from a cohort study of 395 335 pregnancies in 2001, finding multiple birth to be significantly associated with antenatal venous thromboembolism.

Multiple pregnancy carries a higher chance of caesarean section delivery compared with singleton pregnancies and this carries its own set of complications. The effect of a planned caesarean section in improving the outcome for the second twin is still uncertain and current practice is to offer an elective caesarean section if the first twin is not cephalic (in the absence of other indications for caesarean section) and a trial of vaginal delivery if both twins are cephalic [14].

There are limited data on maternal outcomes of higher-order multiples, such as quadruplets and quintuplets, as they occur less frequently. Prematurity is a major problem in this group, occurring in up to 98% of pregnancies [15]. A series was reported by Collins et al. for 71 sets of quadruplets and listed pregnancy-induced hypertension (32%), anaemia (25%), urinary tract infection (14%), gestational diabetes (10%) and postpartum haemorrhage (21%) as frequent maternal complications [15].

3. Perinatal consequences of multiple pregnancies

The most frequently reported perinatal consequence of multiple pregnancy is the risk of preterm labour. Approximately 94% of multiple gestations are twins [16]. Recent US national statistics published in 2011 found that in 137,217 twin pregnancies 58.8% delivered preterm (<37 weeks) and 11.4% were delivered very preterm (<32 weeks of gestation) [17]. In the same report of 5095 triplet pregnancies, 94.4% delivered preterm (<37 weeks of gestation) and 36.8% delivered very preterm (<32 weeks of gestation). Preterm delivery puts the babies at risk of all the conditions associated with prematurity including intraventricular haemorrhage, periventricular leukomalacia (PVL), necrotising enterocolitis, retinopathy of prematurity, and respiratory distress syndrome, all of which may result in long-term morbidity, for example cerebral palsy associated with PVL and mortality [18]. The neonatal mortality rate of twins is six to seven times that of singleton pregnancies, at 18 per 1000 live births, whereas the neonatal mortality of triplets and higher order multiples reaches 39.6 per 100 live births [19]. The main reason for the elevated perinatal mortality rate seen in multiple pregnancies is the effects of preterm birth [20].

With multiple pregnancy the babies are at increased risk of intrauterine growth restriction and in the UK the Human Fertilisation and Embryology Authority (HFEA) reported that half of all twins (naturally occurring and ART twins) are born prematurely [21]. Of the 137 217 twin deliveries in the USA in 2009, 56.6% had low birth weight (<2.5 kg) and 9.9% had very low birth weight (<1.5 kg). Of the 5095 triplet pregnancies in the USA in 2009, 95.1% had low birth weight (<2.5 kg) and 35% had very low birth weight (<1.5 kg) [17]. The higher risk of preterm delivery and low birth weight increases the need for specialist neonatal resources [21].

The risk of congenital anomalies is higher in multiple pregnancy and includes an increased risk of fetal trisomies, neural tube defects and structural malformations of the gastrointestinal tract [22]. A recent European multicentre epidemiological study of 5.3 million births from 1984 to 2007 found the risk of congenital anomalies to be 27% higher in multiple than in singleton births (RR: l.27; 95% CI: 1.24–1.3) [23].

The excess risk of cerebral palsy in multiples compared to singletons is now well established [21,24]. Petterson et al. [25] published an epidemiological study of 5132 twin pregnancies compared with singleton pregnancies in Western Australia in 1993 and found that twin babies had a 4.6-fold higher rate of cerebral palsy compared to singleton babies. These results were reproduced in a European multicentre study of 6613 children in 2004, which again found that multiples had a significantly higher rate of cerebral palsy than singletons (RR: 4.36; 95% CI: 3.76–4.97) [26]. The HFEA now quotes that twin babies are four times more likely and triplets 18 times more likely to have cerebral palsy compared with singleton babies [21].

Monochorionic twins carry an extra risk compared with dichorionic twins, in the form of twin–twin transfusion syndrome (TTTS), which occurs in 10–15% of monochorionic pregnancies and accounts for significant perinatal morbidity [27]. Monochorionic monoamniotic pregnancies (accounting for 1% of twin pregnancies) carry the additional risk of cord entanglement [27]. For these reasons monochorionic twin pregnancies require care in a specialist obstetric unit and usually a minimum of two-weekly ultrasound surveillance for growth assessment.

The overall stillbirth rate is increased with multiple pregnancies at 12.3 per 1000 twin births and 31.1 per 1000 triplet births compared with 5 per 1000 in singleton births [2]. First-trimester intrauterine death in a twin has not been shown to have adverse consequences for the survivor; however, if it occurs in the late second and third trimesters, it often precipitates preterm labour and is associated with an increased risk of cerebral palsy [25].

4. Outcomes of ART versus naturally conceived twins

The number of women having ART (IVF/ICSI) pregnancies is increasing worldwide, and the rate of multiple pregnancy is higher with ART. It has been suggested that obstetric outcomes in pregnancies after IVF/ICSI are poorer when compared with those after natural conception, and this affects the counselling of patients and the guidance of clinical practice [28]. Apart from the overall complications of a twin pregnancy per se, ART twin pregnancies usually have additional obstetric risk factors including advanced maternal age, nulliparity, differing aetiologies of infertility, fertility medications and interventions associated with infertility investigation/treatment which may represent potential risk factors for increased perinatal morbidity [29]. On the other hand, ART twins have a decreased rate of monochorionicity, and couples achieving pregnancy through ART tend to be of higher socioeconomic status with