CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

Commentary

Multiple pregnancy affects 0.9–3.1% of births worldwide. Prevalence rates vary significantly. For example, twinning rates are 6–9 per 1,000 births in East Asia, but 18 per 1,000 in central Africa. This variation is due to differences in dizygotic (DZ; non-identical) twinning rates (thought to be genetic). Monozygotic (MZ; identical) twinning occurs at a relatively constant rate of 3.5–4 per 1,000 around the globe. In high-income countries, there is further variation related to the use of assisted reproduction (AR). For example, in England and Wales, 14.4 out of every 1,000 women giving birth in 2020 had a multiple birth, whereas in the United States, the twin rate was 31.1 per 1,000 live births, and triplet and higher-order births comprised 79.6 per 100,000 births. Because of the higher morbidity and mortality of twin pregnancies, in recent years there has been a concerted effort to restrict AR to single embryo transfer (SET), which is associated with a significantly lower rate of multiple pregnancy compared to transferring more than one embryo. For example, in the UK in 2006, the Human Fertilisation and Embryology Authority (HFEA) published a report with a set of policies in order to reduce multiple births from AR, including SET. Single embryo transfers increased from 13% of in vitro fertilisation (IVF) cycles in 1991 to 75% in 2019, and a reduction in the multiple birth rate was seen from 27% in 2007 to 6% in 2019 in patients aged 35 and under.

Both maternal and fetal/neonatal complications are more common in multiple compared to singleton pregnancies. The main maternal problems during pregnancy include anemia, hypertensive disorders, gestational diabetes, haemorrhage and intrahepatic cholestasis of pregnancy (ICP). Preterm labour and caesarean section are commoner than in a singleton pregnancy. Fetal problems common to all multiple births include congenital abnormalities, miscarriage, single fetal death, growth disorders and cerebral palsy. Chorionicity (the number of chorions/placentas) and zygosity (the degree of genetic similarity/dissimilarity) affect these risks. Thus, some complications such as conjoined twins and monoamniotic (MA) twins only occur in monochorionic (MC) MZ pregnancies because they result from an abnormal connection between the two circulations in a shared placenta. In DZ twins, each twin has its own separate placenta and circulation, even though they may be adjacent.

Multiple pregnancies require specialised and individualised care. Usually, this is provided by a multidisciplinary team comprising an experienced midwife and obstetrician, allowing discussion and decision-making, and access to immediate diagnostic ultrasound (US) and multidisciplinary opinions such as anaesthetic, neonatal/paediatric and psychological services. Complicated multiple

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

pregnancies should be managed in a tertiary care centre where there is additional expertise, such as the laser ablation needed to treat MCMZ pregnancies with conjoined circulations.

Cornerstones of management in pregnancy are the need for accurate fetal measurement to optimise dating of gestational age, and documentation of chorionicity. High-level US expertise is needed because of the high incidence of fetal anomaly, the need for detailed evaluation of the fetal circulations and the difficulty of assessing fetal size (and growth) in a 'crowded' uterus. The mothers need frequent assessment to detect hypertension and anemia, and early identification and management of preterm labour.

Delivery should take place in an obstetric unit with level 3 neonatal care, both because of the high incidence of preterm birth (average gestational length is only 36 weeks in twins and 34 weeks in triplets) and the high incidence of hypoxic and mechanical complications of labour. An experienced obstetrician, midwife and anaesthetist must be available 24/7. A neonatal paediatrician and a neonatal team should be available for delivery, with one paediatrician present for each infant, especially if preterm or operative delivery or fetal abnormalities are anticipated. The timing of delivery is determined by chorionicity and the presence of complications. The mode of delivery is influenced by the fetal presentations, the difference in birthweights (BWs), gestational age, the presence of fetal complications and the woman's preferences. Active management of the third stage of labour is advocated. After delivery, the mother will need extra support both in hospital and at home.

1 Introduction

'Multiple pregnancy' is a pregnancy with two or more fetuses, including twins (the commonest multifetal pregnancy), triplets and higher-order multiples. The overall prevalence of multiple pregnancy varies worldwide from 0.9 to 3.1% [1,2,3,4]. The rate of MZ twin (identical twins) birth rate remains fairly constant at a rate of 3.5–4.0 per 1,000 around the globe [4]. Thus, the variation across different populations is due to variation in DZ births; this is thought to mainly be influenced by genetics and is reflected in racial and ethnic differences, with low rates of 1.3 per 1,000 births in Japan and rates as high as 50 per 1,000 births in Nigeria [5]. Substantial increases in twinning rates have been observed in Europe, North America and Asia. Africa is the continent with the highest rates at 17.1 per 1,000 deliveries, and Asia is the lowest at 9.2 per 1,000. Due to population growth, Asia and Africa are now home to more than 80% of the world's twin births [4,6]. A shift towards an older maternal age at conception has also contributed to the increasing rates [7]. In high-income countries, there

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

is further variation related to the use of AR. For example, in 2021, 13.7 per 1,000 women giving birth in England and Wales had a multiple birth, whereas in the United States, the twin birth rate was 31.2 per 1,000 live births [1,2].

Until recently, the incidence of multiple births within England and Wales was continually rising, reflecting the effects of increased maternal age, parity and use of AR. Following the introduction of ovulation induction and multiple-embryo-transfer fertility, the UK triplet rate more than quadrupled between 1970 and 1998. However, since 1998, triplet and higher-order multiple rates have fallen annually, most likely reflecting changes in AR practice and guidance. In 2006, the HFEA published a report entitled 'One Child at a Time' with a set of policies to reduce multiple births from AR, including SET [8]. Single embryo transfers were seen to increase from 13% of IVF cycles in 1991 to 75% in 2019, and a reduction in the multiple birth rate was seen from 27% in 2007 to 6% in 2019 in patients aged 35 and under [9]. Office for National Statistics (ONS) data from 2021 for England and Wales demonstrated that twin pregnancy rates have continued to decrease, with birth rates equivalent to reported rates in 1996 [1]. In England and Wales in 2021, only 102 women gave birth to triplets and there was one higher-order multiple pregnancy (live born or stillborn) [1]. Multiple birth rates have also been affected by the use of selective reduction (SR; often in the first trimester).

1.1 Developmental Aspects

Multiple pregnancies are either polyzygotic (PZ) or MZ. Dizygotic twins are far more common than MZ twins, accounting for approximately 70% of all twin pregnancies [5]. In PZ pregnancies, each embryo is derived from a different ovum and, thus, are 'non-identical'. This arises when polyovulation occurs in a cycle, with dual fertilisation from a single source. Each zygote will develop its own amnion, chorion and placental circulation and can be defined as 'polychorionic'.

In MZ pregnancies, a zygote is formed from the union of one ovum and one sperm, which subsequently divides to form two 'identical' individuals (Figure 1) [10], although this is not invariable as both genotypic and phenotypic differences can sometimes occur. The pattern of placentation is dependent primarily upon the timing of division. In general, when division occurs within three days of fertilisation, dichorionic (DC) placentation occurs, in which each fetus has its own placental circulation. Division at three to nine days results in MC twin placentation, in which there is sharing of one placenta. Similarly, amnionicity, which reflects the number of gestational sacs present, is largely dependent upon the timing of division. Splitting after nine days results in MA

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

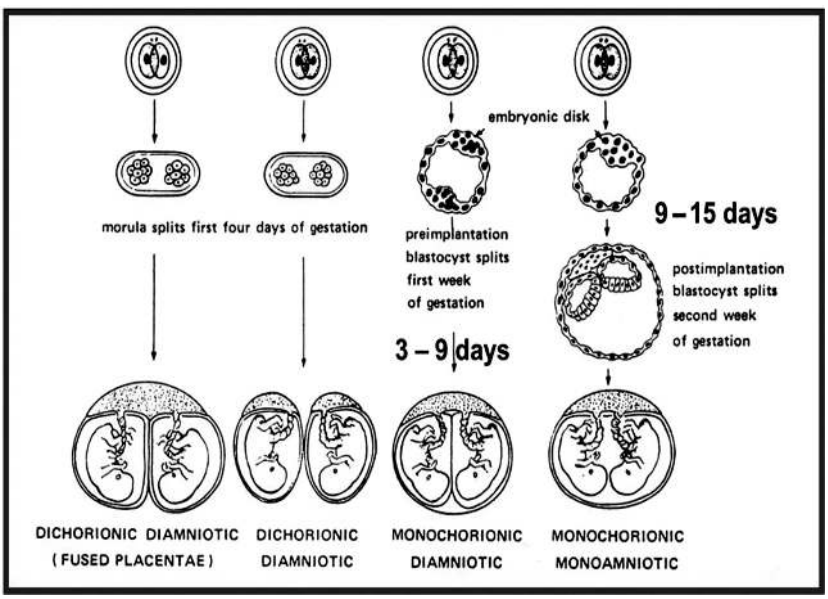

Figure 1 MZ twins: relationship between chorionicity and amnionicity. Reproduced with permission from Ward, RH, Whittle, MJ (eds). Multiple Pregnancy. London: RCOG Press, 1995

twins, in which one sac is shared by both [11]. Before this, each fetus forms and develops an individual sac. Monoamnionicity is rare, representing <1% of twin pregnancies [11]. Cleavage occurring after the 12th day will result in conjoined twins. For triplet and higher-order multiples the same principles apply, with different combinations of chorionicity and amnionicity possible (e.g., DC triamniotic (DCTA) triplets would comprise an MC diamniotic (MCDA) twin pair and a 'singleton'). From a clinical perspective, it is chronicity that influences pregnancy risk and management.

2 Risks Related to Multiple Pregnancies

2.1 Maternal Risks

Women with a multiple pregnancy are at an increased risk of obstetric complications, severe maternal morbidity and mortality. Table 1 shows that many maternal conditions are more likely in a multifetal pregnancy. Women with multiple pregnancies are also more prone to minor complications of pregnancy, including increased abdominal pain, malaise, acid reflux, poor sleep, constipation, varicose veins, dependent oedema and symphysiopubic dysfunction. These women therefore require more frequent monitoring than those with low-risk singleton pregnancies.

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

Table 1 Maternal risks associated with multiple pregnancy with associated singleton and multiple gestation prevalence

Maternal risks	Singleton pregnancy prevalence (%)	Multiple pregnancy prevalence (%)
Hyperemesis gravidarum (Section 2.1.1)	1.3	2.9 [15]
Anemia (Section 2.1.2)	38.7	67.3 [16]
Urinary tract infections (Section 2.1.3)	19.0	17.0 [17]
Hypertension and pre-eclampsia/eclampsia (Section 2.1.4)	6.5	12.7–20.0 [18,19,20]
Gestational diabetes (Section 2.1.5)	4.8	6.8 [21]
ICP and other liver disease (Section 2.1.6)	1.3	6.7 [22]
Haemorrhage (>1,000 ml) (Section 2.1.7)	8.7	17.0 [23,24]
Idiopathic polyhydramnios (Section 2.1.8)	0.4–3.3	0.4–3.3* [25]
Preterm labour/birth (Section 2.1.9)	8.2	60.3 [26]
Operative vaginal birth (Section 2.1.10)	5.3	14.0 [27,28]
Caesarean section (Section 2.1.11)	23.8	42.9 [29,30]
Postnatal illness (Section 2.1.12)	8.3	11.3 [31]
Maternal morbidity and mortality (Section 2.1.13)	1.3 0.1	6.2 [32] 0.4 [14]

*An increased incidence of polyhydramnios in multiple pregnancy can be seen due to complications of monochorionicity and/or the presence of fetal anomalies. There is no evidence that uncomplicated multiple pregnancy has an increased risk of idiopathic polyhydramnios.

Twin pregnancy is associated with greater severe maternal morbidity and mortality [12,13]. Maternal mortality is also higher than in singleton pregnancy [14].

For many of these risks the management will be the same as for singleton pregnancy. Those where management may vary in multiple pregnancy will be discussed further in Section 3.

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

2.1.1 Hyperemesis Gravidarum

Nausea and vomiting are common and seen in approximately 50–90% of pregnant women [33], and multiple pregnancy is a known risk factor for worsening symptoms. The most severe form, hyperemesis gravidarum, has been shown in systematic reviews to occur in 0.3–10.8% of pregnancies [34]. A UK population study demonstrated a prevalence of 1.48% and an increased risk in twins compared to singletons, adjusted odds ratio (AOR: 2.09, 95% confidence interval (CI): 2.02–2.16) [35]. This is similar to another large cohort that demonstrated a 61% increase in the development of hyperemesis gravidarum in twin pregnancies compared to singletons [36]. In any woman diagnosed with hyperemesis gravidarum, a first-trimester US should be performed to diagnose or exclude a multiple pregnancy.

2.1.2 Anemia

Secondary to increased oxygen demands and plasma volume expansion (one-third greater than singletons), the risk of anemia is heightened in multiple pregnancy. A study of 2,130 pregnancies (1,684 singletons and 446 twin pregnancies) revealed 67.3% of twin pregnancies were anemic (defined as Hb <105 g/l) compared with 38.7% of singleton pregnancies [16]. Fetal demands are also greater, particularly for folate.

2.1.3 Urinary Tract Infections

Urinary tract infections are more common in twin and triplet pregnancies than in singleton pregnancies [17]. The incidence of pyelonephritis does not appear to be increased [37].

2.1.4 Hypertensive Disorders

Gestational hypertension and/or pre-eclampsia complicate 10–20% of multiple pregnancies, which is an incidence of two- to five-times higher than in singleton pregnancies [20,38]. However, it is likely the true underlying tendency is underestimated, as many multiple gestations will deliver preterm compared to singleton pregnancies, so birth occurs before worsening hypertensive disease ensues. There are many different pathophysiological processes that may contribute to the increased risk, which appears to be dose-dependent (i.e., reliant on placental mass and number of fetuses), with reported rates in triplets of 20.0% compared to 12.7% in twins [39]. The incidence is also higher among nulliparous compared to parous women. Importantly, the onset, progression and severity of pre-eclampsia are often sooner, quicker and greater in multiple pregnancies [37,40].

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

As such, this results in higher rates of eclampsia, placental abruption and maternal mortality and neonatal adverse outcomes [41,42].

2.1.5 Gestational Diabetes

Women with multiple pregnancies may also be at increased risk of gestational diabetes [16]. A study of 759,718 singleton and twin deliveries published in 2021 highlighted a prevalence of gestational diabetes in twins at 6.82% compared to 4.8% in singletons [16]. A dose–response relationship exists with higher rates in higher-order multiples [41].

2.1.6 ICP and Other Liver Disease

The incidence of ICP in multiple pregnancy is higher, with some studies reporting rates of up to 22% [37,43]. Data published in 2018 reported that twin pregnancies conceived through AR are twice as likely to develop ICP compared with spontaneously conceived twin pregnancies [44]. A retrospective cohort study demonstrated rates of ICP of 6.7% in twins versus 1.3% in singletons [22]. An increased risk of adverse outcome has also been reported associated with total bile acid levels [22]. Twin pregnancy is also an independent risk factor for acute fatty liver, a rare complication of pregnancy associated with significant maternal mortality [37].

2.1.7 Haemorrhage

There is a high incidence of antepartum and postpartum haemorrhage (PPH), with the average blood loss 500 ml higher than in a singleton pregnancy [24,37]. Antepartum bleeding is particularly common. A major cause is placental abruption, which may arise secondary to uterine over distension and decompression following rupture of membranes or first twin delivery [37]. The larger placental surface area in multiple pregnancy is also considered a predisposing factor for placenta praevia [45], and the incidence of velamentous cord insertion and vasa previa is also increased [37,46]. Increased placental surface area, uterine over distension and higher caesarean section rates all contribute to the increased risk of postpartum blood loss. Other characteristics associated with PPH >1,000 ml in twins include episiotomy and neonatal weight [23].

2.1.8 Polyhydramnios

Multiple pregnancies account for about 10% of cases of polyhydramnios [47]. This may be idiopathic, related to gestational complications such as maternal diabetes, or relate to specific complications of monochorionicity such as twin-to-twin

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

transfusion syndrome (TTTS) [37]. In this setting, the risks of preterm labour and/or preterm rupture of membranes, cord prolapse, malpresentation and abdominal discomfort are increased [47].

2.1.9 PTB

Approximately 50% of all multiple pregnancies birth preterm (<37 complete weeks' gestation), and they account for about 20% of all preterm births (PTBs) [26,48,49]. Large variation in PTB rates has been reported. In Scotland (n = 1,432 live multiple births), 9.9% delivered before 32 weeks, 41.3% at 32–6 weeks and 51.2% before 37 weeks, whereas in Austria (n = 2,311), 12.7% delivered before 32 weeks, 55.7% at 32–6 weeks and 68.4% before 37 weeks [50]. The rate of PTB is significantly increased in MC compared to DC twins, likely to be related to the complications of monochorionicity [51]. Risks to the mother relate to the need for hospitalisation, use of tocolytics and possible intrauterine transfer.

2.1.10 Operative Vaginal Birth

Compared to singleton pregnancies, there is an increased rate of operative vaginal births [27,28]. The maternal risks associated with instrumental delivery are the same as for singleton birth.

2.1.11 Caesarean Section

Women with multiple pregnancy are more likely to have an elective or emergency caesarean section, with rates as high as 75% reported worldwide [52]. A 2019 Cochrane review reported that 42.9% of women with multiple pregnancy who aimed for a vaginal birth had a caesarean section for at least one fetus [29].

2.1.12 Postnatal Illness

A 2011 systematic review concluded that multiple birth might be associated with an increased risk of postpartum depressive symptoms [53]. Given the high fetal morbidity and mortality rates associated with multiple pregnancy, bereavement and grief support are often required. Furthermore, with the potential psychosocial and financial difficulties associated with multiple pregnancy, a high index of suspicion for postnatal depression is recommended [53].

2.1.13 Maternal Morbidity and Mortality

Severe maternal morbidity is increased in multiple pregnancy [12], with comparative studies demonstrating that the relative risk (RR) of severe maternal

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

morbidity compared to singletons was 4.3 (95% CI: 3.7–5.0). Risks were higher in triplets (RR: 6.2, 95% CI: 2.5–15.3) [13].

Maternal mortality is 2.5-times higher in multiple than in singleton births in the UK [54] and World Health Organisation (WHO) multi-country survey data demonstrated rates of maternal death of 0.4% in twins and 0.1% in singletons [14]. Specific factors contributing to maternal death in multiple births are the use of tocolytic agents, pre-eclampsia and eclampsia, placental abruption, caesarean delivery and PPH [37].

2.2 Fetal Risks

Women with multiple pregnancy are also at increased risk of fetal complications, as shown in Table 2.

Table 2 Fetal risks associated with multiple pregnancy with associated singleton and multiple gestation prevalence

Fetal risks	Singleton pregnancy prevalence (%)	Multiple pregnancy prevalence (%)
Congenital anomalies (Section 2.2.1)	2.70	3.49 [3]
Structural	2.35	3.23
Chromosomal	0.35	0.26
Early pregnancy loss (Section 2.2.2)	5.40*	15.00–35.00 [55,56]
Single fetal death (Section 2.2.3)	0.40	6.00 [57,58]
Discordant fetal growth and growth restriction (Section 2.2.4)	8.00	25.00 [59]
Preterm birth (Section 2.2.5)	8.20	60.30 [2]
Cord prolapse (Section 2.2.6)	0.10–0.60	Up to 1.80 [60,61]
Twin entrapment (Section 2.2.7)	N/A	0.10 [62]
Cerebral palsy (Section 2.2.8)	0.20	0.70–5.10 [63,64]
Perinatal mortality^ (Section 2.2.9)	0.14–0.32	0.62–0.73 [65]

* Overall figure for pregnancy loss <20 weeks after confirmation of fetal heart activity, but ranges from 0.8 to 33.7% based on gestational age and number of prior pregnancy losses [55]

^ Range given as perinatal mortality rate depends on chorionicity

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-1-009-52610-4 — Multiple Pregnancy
Jack Hamer, Jennifer Tamblyn, James Castleman, R. Katie Morris
Excerpt
More Information

2.2.1 Congenital Anomalies

There is an increased risk of congenital anomalies in multiple pregnancy compared to singletons, reported as 27% higher [66]. In Europe, the prevalence has increased from 5.9 per 10,000 multiple births in 1984–7 to 10.7 per 10,000 in 2004–7. Non-chromosomal anomalies increased from 5.03 per 10,000 births to 10.00 over the same period, it is suggested that this may relate to an increased risk in DC twins conceived by AR or to parental characteristics associated with AR. For chromosomal anomalies, the prevalence increased from 0.58 per 10,000 births to 0.90 [3].

The risk rate per fetus for DZ twins is most likely similar to that of singletons, but two- to three-times higher in MZ twins, which reflects primarily an increased risk of abnormal cleavage and midline structural defects, including syringomyelia, cloacal anomalies and holoprosencephaly [66,67,68].

Approximately 1 in 25 DC, 1 in 15 MCDA and 1 in 6 MA twin pregnancies are discordant for anomaly, with a major structural defect affecting only one fetus [68,69]. The European data recorded that for twin pairs with at least one non-chromosomal abnormality, there was concordance in 11.6% [3]. The most common structural defects in twin pregnancies include cardiac anomalies, neural tube defects, brain defects, facial clefts, and gastrointestinal and anterior abdominal wall defects [70]. A 2020 study of 488 twins reported the rates of different structural anomalies: genitourinary defects represented 24%, with cardiac and gastrointestinal anomalies representing 20 and 18.5%, respectively [71]. Importantly, if a discordant anomaly is noted, the likelihood is that it will originate within the smaller twin, however, the risk of adverse outcome for the normal twin is also increased [71,72].

Monozygotic twins are generally concordant for chromosomal or genetic defects (although discordance may occur secondary to postzygotic mutation, parental imprinting effects, asymmetrical X inactivation and differential deoxyribonucleic acid (DNA) methylation) [10]. European data report that for chromosomal anomalies, 5.53% of all twin pairs were concordant [3]. For DZ pregnancies, the risk of chromosomal abnormalities for each twin is no different to that for a singleton fetus, but since two fetuses are present, the chance of one being affected is doubled. For MZ pregnancies, the baseline risk is twice that of a singleton pregnancy, therefore four-times higher for at least one twin to be affected [73,74].

The implications of AR for DZ twin congenital anomaly rates are not fully understood, but recent data have demonstrated an increased risk of congenital heart defects in twin pregnancies conceived with AR compared to spontaneously conceived pregnancies [75].

© in this web service Cambridge University Press & Assessment www.cambridge.org