SECTION 1

Preliminaries
The risks associated with multiple pregnancies

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Introduction

The incidence of multiple pregnancies has increased dramatically during the past three decades primarily owing to the expanded use of infertility therapies and higher childbearing ages.

Women who become pregnant later have an increased risk of dizygotic twins, up to 37 years of age. Older maternal age accounts for 25–30% of the rise in multiple birth rates since 1970. Infertility treatment includes the use of ovulation-inducing drugs and assisted reproductive technology (ART). Births resulting from infertility treatment account for around 1–3% of all singleton live births, 30–50% of twin births and more than 75% of higher-order multiple births [1].

Multiple pregnancies are associated with considerable medical risks for the mother and offspring as well as excess obstetric and neonatal costs. It is increasingly thought that the high frequency of multiple births after ART is not acceptable, and strategies to reduce this frequency are being developed. However, patients and physicians all sometimes seem to underestimate the negative consequences of multiple pregnancy. This review therefore addresses the complications of multiple pregnancies, focusing on twin pregnancies, which constitute the vast majority (95–98%) of multiple pregnancies.

Trends in multiple births

In many countries, multiple birth rates began to decline in the 1950s, reaching a low point in the 1970s. Since then there has been a continuous increase in the frequency of twin pregnancy rates and twin birth rates in many countries in Western Europe and North America (Figure 1.1).

In most countries, rates of triplets and higher-order multiple births fluctuated around a relatively constant level until the mid 1970s. This was followed by a steep rise, after which there has been decline since 2000. In 11 European countries in 2000, multiple birth rates ranged from 11.7 to 19.0 per 1000 for twins and from 0.16 to 0.62 per 1000 for triplets and higher-order multiple births [2]. The latest report from the USA from 2004 showed that the twin birth rate was 32.2 per 1000, another record high. In contrast, the rate of triplet and higher-order multiple births showed a downward trend, the rate being 1.77 per 1000 [3].

Infertility treatment has played a major role in the increase in multiple pregnancies. The contribution of ART to multiple pregnancies is better known than that of ovulation stimulation without in vitro...
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Figure 1.1 Twin births in selected European countries. Adapted from [52], with permission.

Table 1.1 Approximate risk of multiple birth after infertility treatment

<table>
<thead>
<tr>
<th>Infertility treatment</th>
<th>Multiple of population frequency&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clomiphene citrate</td>
<td>12 Twins, 200 Triplets</td>
<td></td>
</tr>
<tr>
<td>Gonadotropins</td>
<td>20 Twins, 500 Triplets</td>
<td></td>
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<tr>
<td>IVF/ICSI cycles</td>
<td>30 Twins, 500 Triplets</td>
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<sup>a</sup> Population frequency is 1% for twins and 1 per 10,000 for triplets; ICSI, intracytoplasmic sperm injection. Adapted from Collins (49).

Zygosity and chorionicity

There are two major types of twin pregnancies: dizygotic and monozygotic twin pregnancies. Dizygotic twins result from the fertilization of two separate eggs. They have two functionally separate placentas (dichorionic) although these may fuse to resemble one single placenta macroscopically at birth. A thick membrane consisting of two layers of chorion and two layers of amnion separates the cavities. Monozygotic twin pregnancies arise from the fertilization of a single egg. If the split occurs within 3 days of conception the result will be a monozygotic dichorionic twin pregnancy with two placentas (which may also fuse as mentioned above). Later splitting, between days 4 and 8, will result in a
monozygotic monochorionic twin pregnancy with a single placenta and two amniotic cavities with a thin dividing membrane consisting of two layers of amnion. Splitting after day 8 will result in a monochorionic monoamniotic twin pregnancy with a single amniotic cavity and a single placenta. Conjoined twinning occurs rarely, in about 1: 50 000 pregnancies. It is caused by failure of complete separation of the embryo around the 15th to 17th day after conception.

The incidence of dizygotic twinning in the population is affected by many factors such as race, heredity, maternal age and ovulation induction with or without IVE. The rates vary from 3 to 40 per 1000 pregnancies. The rate of monozygotic twinning in the general population is thought to be fairly stable around the world and over time, 3 to 4 per 1000. In whites, about 30% of twin pregnancies are monozygotic and about 70% are dizygotic, about one third of the monozygotic twins are dichorionic and two thirds are monochorionic. Approximately 1 per 100 of monozygotic twins are monoamniotic.

The proportions of monozygotic and dizygotic twins are very different in spontaneously conceived twins as compared with iatrogenic twins; 95% of iatrogenic twins are dizygotic.

Zygosity and chorionicity are important variables for outcomes in multiple pregnancies. Perinatal mortality and morbidity are elevated in monozygotic and particularly in monochorionic twins. Monochorionic twins have a fivefold increase in fetal/perinatal loss, a tenfold increase in antenatally acquired cerebral lesion and almost twice the incidence of intrauterine growth restriction. The key to management of multiple pregnancies is accurate determination of chorionicity, which is best performed in the first trimester where accuracy rates approach 100% [7, 8].

Maternal morbidity and mortality

Multiple pregnancies are associated with a range of well-documented risks to the health of the mother. Multiple pregnancy increases the risk of maternal mortality as compared with singleton pregnancies, especially in developing countries. A mortality rate of 14.9 per 100 000 pregnancies was reported for multiple pregnancies in Europe in 1994, as compared with 5.2 per 100 000 for singleton pregnancies. In France, the corresponding figures were 10.2 per 100 000 and 4.4 per 100 000 [9]. In contrast, maternal mortality rates of 77 per 100 000 were associated with multiple pregnancies in Latin America between 1985 and 1997, as compared with 43 for singleton pregnancies [10]. Maternal deaths were caused by eclampsia, excessive blood loss and pulmonary edema following administration of par enteral beta-mimetics as tocolytics. Since maternal deaths are rare in the developed world, other measures of pregnancy outcome have been suggested such as “near misses” or severe obstetric morbidity (severe pre-eclampsia including eclampsia and HELLP [hemolysis elevated liver enzymes and low platelets] syndrome, severe hemorrhage, severe sepsis, uterine rupture). In a case-control study comprising 50 000 pregnant women, over 1 out of every 100 women suffered from severe obstetric morbidity [11]. Two thirds of these cases were related to obstetric hemorrhage and one third to severe pre-eclampsia. Multiple pregnancy was found to be an independent risk factor (adjusted odds ratio (OR) = 2.21, 95% confidence intervals (CI) = 1.24–3.96) for such a life-threatening event. In a retrospective Canadian cohort study the incidence of maternal complications in 165 188 singleton pregnancies and 44 674 multiple pregnancies were compared [12]. Multiple pregnancies were associated with significant increases in cardiac morbidity (myocardial infarction, pulmonary edema and heart failure), hemorrhage, pre-eclampsia, amniotic fluid embolism, gestational diabetes, and the need for obstetric interventions, hysterectomy and blood transfusion. A recent population-based report by Luke and Brown confirmed that higher plurality and higher maternal age were associated with increased risk of many pregnancy complications, e.g. diabetes, hypertension and excessive bleeding [13]. Multiple pregnancy is an independent risk factor and has a 2.3 OR for the woman (or mother) to be admitted to an intensive care unit [14].
Hypertensive disorders of pregnancy

Hypertension with or without proteinuria is one of the main maternal complications associated with multiple pregnancy. As compared with singleton pregnancies women with twin gestations have higher rates of hypertensive disorders; the OR in twins as compared with singleton pregnancies varies from 1.8 to 3.4 according to one review [15]. Pregnancy-induced hypertension and pre-eclampsia are both more common in women carrying twins. For example, in a secondary analysis of a large prospective multicenter trial of women with twin \( (n = 684) \) and singleton \( (n = 2946) \) pregnancies, designed to investigate the efficacy of low dose aspirin for the prevention of pre-eclampsia, rates of gestational hypertension and pre-eclampsia were twice as high in twin as compared with singleton pregnancies \( (13\% \text{ vs. } 5–6\% \text{ for both}) \) [16]. In addition, early severe pre-eclampsia and HELLP syndrome were seen more frequently with twin pregnancies. Moreover, women with twin pregnancies and hypertensive complications had higher rates of adverse neonatal outcomes than those with singleton pregnancies.

In triplet pregnancies the incidence of pre-eclampsia is between 24% and 60%, and it may be as high as 90% in quadruplet pregnancies [17]. A sixfold relative risk (RR) of eclampsia in multiple, when compared with singleton, pregnancies was found in a survey in the UK \( (28.1/10000 \text{ vs. } 4.7/10000 \text{ pregnancies, respectively}) \) [18].

No intervention (e.g., low dose aspirin) has shown to prevent or reduce the incidence of hypertensive complications in multiple pregnancies.

Obstetric hemorrhage

Severe obstetric hemorrhage contributes to severe maternal morbidity and is the third most common cause of direct maternal death in the UK. It was found that severe hemorrhage was 2.3-fold more common in multiple pregnancies [11]. The high incidence of uterine atony and dystocia, both contributing to postpartum hemorrhage and an increased rate of operative deliveries, are important reasons. Placental abruption and placenta previa are seen slightly more often in multiple pregnancies and may cause bleeding. Iron and folate deficiency are more often seen in multiple pregnancies and the incidence of anemia is doubled in twin pregnancies.

Obstetric intervention

Maternal morbidity is also related to mode of delivery, particularly emergency Cesarean section. Cesarean section is associated with more complications than vaginal deliveries, e.g. infections, hemorrhage and thrombo-embolic disease. A much higher frequency of Cesarean section is seen in multiple pregnancies as compared with singleton pregnancies, mainly attributable to malpresentations. Cesarean section in multiple pregnancies has been shown to be associated with an additional risk of endometritis and abdominal wound infections, as compared with Cesarean section in singleton pregnancies according to a Finnish study [19].

Prophylactic cervical cerclage has been used to prevent preterm birth in multiple pregnancies. A meta-analysis from two randomized controlled trials showed no benefit, and the routine use of cerclage cannot be recommended [20].

Emergent peripartum hysterectomy, defined as a hysterectomy performed at the time of delivery or in the immediate postpartum period, has been shown to be more common in multiple pregnancies than in singletons [21].

Maternal complications in triplet, quadruplet and higher-order multiple pregnancies

Maternal morbidity is related to the number of fetuses. A recent population-based study showed that the risks of maternal morbidity and obstetric complications (e.g., pregnancy-associated hypertension and eclampsia, anemia, diabetes mellitus, abruptio placentae, premature rupture of the membranes and Cesarean delivery were increased in triplet pregnancies \( (n = 5491) \), quadruplet pregnancies and higher-order multiple pregnancies.
(\(n = 423\)) as compared with twin pregnancies (\(n = 152,238\)), even after adjustment for the main confounding factors. A dose–response relationship was observed for pregnancy-associated hypertension, diabetes mellitus and abruptio placenta with higher ORs in women with quadruplet and higher-order multiple gestations than in women with triplet pregnancies [22].

Fetal and neonatal outcome

Mortality

Early fetal loss in the form of “vanishing twin” is a rather common occurrence following ART. In a review, the rates of “vanishing twin” were 33% and 56%, respectively when two or three gestational sacs were detected initially. When two or three embryos were initially detected, the rates were 28.5% and 51.5%, respectively [23].

All mortality rates (stillbirths, early neonatal, late neonatal and infant mortality) are higher in multiple pregnancies as compared with singletons and the rates increase with the number of fetuses. Differences in mortality rates from a population-based registry in England and Wales, are shown in Figure 1.2. The figure shows that multiple births contribute greatly to overall mortality rates, despite their relative rarity. In England and Wales, multiple births represented 2.5% of all births and 8% of stillbirths, 19% of all neonatal deaths and 7% of all post-neonatal deaths in 1991. Disparity related to multiplicity was greatest when it came to neonatal deaths, the rate for twins being 7 times higher and the rate for triplets and higher-order multiple births more than 20 times higher than the singleton rate.

Recent data from the USA show that the infant mortality rate in 2000 was 6.1 per 1000 live births for singleton pregnancies and 31.1 per 1000 for multiple pregnancies [24]. As in the UK, this rate increased...
with the number of fetuses, from 28.9 per 1000 live births for twins, to 63.2 per 1000 for triplets and 95.5 per 1000 for quadruplets. Although multiple births account for only 3% of births, they account for 14% of infant deaths in the USA.

A large population-based cohort study of more than 1,000,000 births in Australia and the USA, of which more than 20,000 were twins, found that twins had an approximately fivefold increase in the risk of fetal death and a sevenfold increase in the risk of neonatal death as compared with singletons. However, the risk varied between twin pregnancies, with second-born twins, twins from the same-sex or growth-discordant pairs and twins whose co-twin died in utero having an increased risk of death [25]. No significant difference was seen in gestational age-specific mortality rate between gestational week 23 and 35 when singletons, twins and triplets were compared [26].

**Gestational age and birth weight**

Preterm delivery (before 37 completed weeks) and low birth weight (< 2500 g) are the main factors accounting for the excess in neonatal morbidity seen in the infants from multiple births. On average, multiple birth infants are born much earlier and are smaller than singletons. A generally accepted clinical rule for multifetal pregnancies is that gestational age at delivery is about 3 weeks less for every additional fetus. As in singletons, the causes of preterm birth can be divided into three groups: spontaneous preterm labor; preterm premature rupture of the membranes (PPROM); and indicated preterm delivery on maternal or fetal indications. One study comprising 434 sets of twins found that spontaneous labor accounted for 54%, PPROM for 22% and indicated preterm delivery on maternal or fetal indications. One study comprising 434 sets of twins found that spontaneous labor accounted for 54%, PPROM for 22% and indicated delivery for 23% of the preterm deliveries. (The corresponding figures for preterm singleton deliveries were 44%, 31% and 23%, respectively) [27]. Chorionicity plays an important role: the risk of preterm birth before 32 weeks is almost doubled in monochorionic twins compared with dichorionic twins [28]. Table 1.2 shows the main differences between singletons, twins and triplets and higher-order multiples in gestational age and birth weight using the latest National Vital Statistics Report for the year 2004 in the USA [3]. In 2004, the average birth weight of twins was nearly 1000 grams lower than that of singletons and the average triplet weighed about 50% less than the average singleton.

There is controversy concerning which fetal growth curve should be used in multiple pregnancies. Fetal growth curves are similar for singletons, twins and triplets up to about 28 weeks of gestation. After this the curve of multiples begins to deviate from that of singletons and at approximately 35 weeks of gestation the curve of triplets begins to deviate from that of twins. Some investigators suggest that plurality-specific birth-weight-by-gestation standards should be used for assessment of fetal growth in multiple births, rather than singleton standards.

In general, twin pregnancies are at tenfold risk of resulting in growth-restricted babies as compared with singletons. The risk is higher in monochorionic pregnancies than in dichorionic pregnancies. One study demonstrated that the chance of having at least one growth-restricted twin was 34% in monochorionic and 23% in dichorionic twin pregnancies. The chance of both twins having growth restriction was fourfold higher in monochorionic pregnancies [3, 28].

Perinatal morbidity and mortality in twin pregnancies is related to intrapair birth weight discordance. The birth weight discordance for twins is calculated by dividing the difference between the weights of the two fetuses by the weight of the largest fetus. Compared with the less than 5% birth weight discordance category, the adjusted OR for stillborn fetuses associated with 20% to 29%, 30% to 39% and > 40% discordance was 1.7, 3.1 and 4.3, respectively, for the smaller twin and 1.8, 3.4 and 2.9, respectively, for the larger twin in same-sex twin pairs and 2.7, 6.2 and 12.8, respectively for the smaller twin in opposite-sex twin pairs [29]. The association of fetal death with birth weight discordance is also seen in triplet pregnancies. A birth weight discordance of 29% or more is associated with a significant risk of fetal death when compared
**Table 1.2** Gestational age and birth weight characteristics by plurality: USA 2004

<table>
<thead>
<tr>
<th></th>
<th>Singletons</th>
<th>Twins</th>
<th>Triplets</th>
<th>Quadruplets</th>
<th>Quintuplets and higher-order multiples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>3972558</td>
<td>132219</td>
<td>6759</td>
<td>439</td>
<td>86</td>
</tr>
<tr>
<td>Percent very preterm</td>
<td>1.6</td>
<td>11.8</td>
<td>35.9</td>
<td>64.9</td>
<td>81.4</td>
</tr>
<tr>
<td>Percent preterm</td>
<td>10.8</td>
<td>59.7</td>
<td>93.0</td>
<td>95.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Mean gestational age</td>
<td>38.7 (2.4)</td>
<td>35.2 (3.6)</td>
<td>32.1 (83.9)</td>
<td>29.7 (4.5)</td>
<td>28.4 (2.7)</td>
</tr>
<tr>
<td>(standard deviation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent very low birth weight</td>
<td>1.1</td>
<td>10.2</td>
<td>33.2</td>
<td>65.1</td>
<td>84.9</td>
</tr>
<tr>
<td>Percent low birth weight</td>
<td>6.3</td>
<td>56.6</td>
<td>94.1</td>
<td>98.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Mean birth weight</td>
<td>3316 (570)</td>
<td>2333 (634)</td>
<td>1700 (559)</td>
<td>1276 (552)</td>
<td>1103 (383)</td>
</tr>
<tr>
<td>(standard deviation)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Very preterm is less than 32 completed weeks of gestation. Preterm is less than 37 completed weeks of gestation. Very low birth weight is less than 1500 grams. Low birth weight is less than 2500 grams.

Source: From [3].

with less than 10% discordance. For the smallest, middle and largest triplets, the adjusted ORs are 10.9, 22.6 and 2.4, respectively.

**Neonatal morbidity**

The vast majority of excess morbidity in multiple births is attributable to preterm delivery and intrauterine growth restriction. Many multiples require treatment and extended care in neonatal intensive care units (NICUs) [30]. According to one study, 15% of singletons, 48% of twins and 78% of triplets and higher-order multiples were admitted to NICUs. In the study by Gardner and colleagues, twins, who constituted only 2.4% of all neonates, contributed disproportionately to neonatal morbidity, e.g. low Apgar score at 5 minutes (7.5%), intraventricular hemorrhage (IVH) grades 3 and 4 (11.4%), sepsis (7.6%), necrotizing enterocolitis (NEC) (9.9%) and respiratory distress syndrome (13.8%) [27]. In view of the large differences in gestational age at birth between singletons, twins and higher-order multiple births, several investigators have tried to correct for this and other confounding variables. One study with data from a large neonatal database showed that the gestational age-specific long-term adverse outcome (NEC, IVH grade 3 or 4 or severe degrees of retinopathy of prematurity) was similar for singletons \( (n = 36931) \), twins \( (n = 12302) \) and triplets \( (n = 2155) \) at all viable premature weeks of gestation (week 23–35) [26]. In an Israeli national population-based study, respiratory distress syndrome was found to be more common among multiples despite higher exposure to antenatal steroids [31].

**Fetal abnormalities**

An individual fetus in a multiple gestation may be affected by both chromosomal and structural abnormalities. Women pregnant with twins are at greater risk of fetal chromosomal abnormalities than those with singletons. The increased risk of chromosomal abnormalities may be partially attributable to the fact that many mothers of dizygotic twins are of advanced maternal age. In a dizygotic pregnancy, each fetus has its own independent risk of a chromosomal or structural abnormality, so the overall risk of an abnormality increases as the number of fetuses increases. In a dizygotic twin pregnancy the risk of one fetus being aneuploid is approximately twice that in a singleton.
pregnancy. The risk of a chromosomal abnormality in a monozygotic multiple gestation is similar to the risk in a singleton pregnancy. However, monozygotic gestations are also at increased risk of other complications unique to monochorionic gestations, such as twin-to-twin transfusion syndrome (TTTS), twin reversed arterial perfusion syndrome and conjoined twins.

There are few large population-based studies comparing the prevalence of congenital malformations in twins and higher-order multiple pregnancies with singletons. In a review, Little and Bryan concluded that there is “almost certainly” an excess of malformations in twins as compared with singletons, the RR varying between 0.9 and 1.5 [32]. Monozygotic twins seem to be more affected than dizygotic twins, and the highest figures are found in monoamniotic twins.

All anatomical sites are involved but some specific malformations have been found to occur excessively in twins (e.g., cardiac, neural tube and brain defects and gastrointestinal and anterior abdominal wall defects). A large international registry study ($n = 260,865$ twins) recently confirmed the higher risk of malformations in twins, as compared with singletons, the RR being 1.2 (95% CI 1.21–1.28). It was not possible to distinguish the RR between dizygotic and monozygotic twins [33].

Genetic counseling and testing is complex and challenging in multiple pregnancies. Options for screening tests are limited and less effective and amniocentesis or chorionic villus sampling may be associated with a higher risk of miscarriage. The ethical dilemmas facing the patient and doctors are complex when there is a diagnosis of a fetus with a non-fatal abnormality in a multiple gestation. Options include expectant management, termination of the entire pregnancy, or selective termination of the abnormal fetus. The procedural complications (e.g., miscarriage and preterm birth) after selective feticide seem to have decreased with greater experience. However, chorionicity should be determined before the procedure, since the technique is different in monochorionic and dichorionic pregnancies.

### Special considerations

#### Twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome usually presents in the mid-trimester with gross discordance in amniotic fluid volume, and it complicates one in five of all monochorionic pregnancies. This results from chronic circulatory imbalance between the vascular anastomoses that occur in practically all monochorionic placentae. It is associated with high rates of perinatal mortality from ruptured membranes, hydrops and growth restriction, and significant morbidity from cardiac and neurological sequelae. If untreated, early onset, severe TTTS is associated with perinatal mortality rates of more than 90% and more than 30% of survivors have abnormal neurodevelopment as a result of the combination of a severe antenatal insult and the complications of severe prematurity [34]. Ultrasound may be valuable in the prediction of TTTS. Increased nuchal translucency in weeks 10–14 has been found to be an early sign of TTTS, as has folding of the intertwin membrane in weeks 15–17. Since there is a wide clinical and sonographic variation in the manifestation of the syndrome, use of a specialized staging system of TTTS by Quintero et al. was proposed in 1999 [35]. Treatment strategies for this serious condition have remained controversial but two main approaches have been used. Serial aggressive amniodrainage is commonly used, being a relatively simple technique. It involves the repetitive percutaneous removal of 1–2 liters of amniotic fluid. The rationale for this technique involves the repetitive percutaneous removal of 1–2 liters of amniotic fluid. The rationale for this technique is mainly to prevent preterm labor related to hydramnios. However, despite reported survival rates of up to 83%, this therapy has been associated with high perinatal morbidity, especially long-term neurodevelopmental damage, of between 5% and 58%. Fetoscopic selective laser photocoagulation of the vascular anastomoses at the intertwin membrane has been advocated at specialist centers. This treatment has been associated with survival rates of between 55% and 69% and reduced neurologic morbidity of between 5% and 11% in survivors. In a