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Multiple pregnancy is a condition where more than one fetus occupy the same intrauterine cavity. By means of its rarity in spontaneous pregnancies, it indicates that by nature the human female uterus is programmed to carry one fetus at a time. The incidence of multiple pregnancy is on the increase because of fertility treatment especially assisted reproductive technology. Unfortunately, multiple pregnancy is associated with several complications from conception until the postpartum period. Maternal uterine anomalies also pose special challenges if associated with multiple pregnancy from diagnosis until management. Miscarriages are higher and some of them are not noticed if the pregnancy continues with one fetus. There are complications related to uterine space like preterm labour which is the commonest. Rupture of membranes with or without preterm labour is also common. Monochorionic multiple pregnancies poses specific challenges in respect to abnormalities during organogenesis from embryonal to vascular malformations. Fetus growth discordance and single twin demise are uncommon but challenging.

**Keywords:** multiple pregnancy, miscarriages, dichorionic, monochorionic, preterm labour, anomalies, complications

### 1. Introduction

Multiple pregnancy refers to simultaneous development of more than one fetus in a female. Simultaneous development of two foetuses is called twins and that of three is triplets and four is quadruplets and so on. The incidence of multiple pregnancy is about 1% indicating that by nature, human reproduction is programmed to carry and nurture one fetus at a time [1]. The incidence of spontaneous twin pregnancy is 1:90, the incidence of triplets is 1:8000 and the incidence of quadruplets is 1:700000. Among the quadruplets the most frequent is the tetrachorionic tetra-amniotic type. These rates have increased 300–400% due to the development of assisted reproductive techniques. The expected average gestational age at delivery for twins is 36–37 weeks, while for triplets is 33–34 weeks and 30–31 weeks for quadruplets [2]. Multiple pregnancy is associated with several maternal and neonatal complications which will be discussed in this chapter.
2. Early pregnancy complications

A pregnancy is defined by detection of a positive serum hCG. Biochemical pregnancy is when serum hCG is positive without a detectable gestational sac. The incidence of miscarriages is based on pregnancies where a gestational sac has been detected and report are based on pregnancies following assisted reproduction. Unlike ectopic pregnancies which present with symptoms and their incidence is more reliable. The incidence of miscarriages is estimated to between 12 and 15% of all pregnancies. The number of miscarriages may be two to four fold if early unrecognised miscarriages are included [3]. As many as 60% of all conceptions abort in the first trimester and at least 50% of all losses happened unnoticed [3]. In spontaneous conception, spontaneous miscarriage is more common in multiple pregnancy. It has been suggested that more twins are conceived than born. Three times more twin were observed among aborted pregnancies [4, 5]. The patients who achieve a positive pregnancy test with more than one gestational sac initially are more likely to deliver at least one baby [3]. Therefore, there are patients who were pregnant with more than one fetus who end experience a miscarriage of other fetus(es) being unnoticed. The presence of intrauterine haematoma in the first trimester is associated with the loss of one or both foetuses before 20 weeks of gestation, but the size of the haematoma is not an independent factor [6].

A larger proportion of monozygotic multiple pregnancy were thought to have more genetic aberrations compared to dizygotic embryos and singletons. Contrary to expectation the risk of Downs’ syndrome per fetus is lower in multiple pregnancy than in singleton pregnancies. The prevalence of twins with Downs syndrome was lower in with particularly low prevalence in same sex twins [7, 8]. Unlike chromosomal aberrations, structural anomalies have been found to occur more often in monozygotic twins compared with dizygotic twins and singletons. Congenital anomalies may be the results of the teratogenic insult that causes the twinning [9]. The risk of congenital anomalies in monochorionic twins is twice as high compared to dichorionic twins and singletons [10]. Monozygotic twinning itself can be regarded as an abnormality of morphogenesis [11]. The risk of congenital anomalies in twins is higher than in singleton supporting the notion of monozygotic twinning regarded as an morphogenic anomaly. The anomalies vary from nervous system, cardiovascular, genito-urinary and twin specific anomalies like twin reversed arterial perfusion [10].

In early pregnancy there are complications specific for unusual multiple pregnancies types. Heterotopic pregnancy (Figure 1) is a rare clinical condition in which intrauterine and extra-uterine pregnancies occur at the same time. The incidence is estimated to be about 1 in 30,000 spontaneous pregnancies while a higher prevalence may occur in assisted reproduction techniques that may reach up to 1 case per 100 in some literatures. It is a challenge to diagnose such a problem due to complex clinical and laboratory findings [12, 13]. Commonly the ectopic pregnancy is within the fallopian tube and uncommonly in the cervix or ovary. Though heterotopic pregnancy is more common following assisted reproduction, cases following spontaneous pregnancies have been reported [14].

The complications expected are a combination if what is expected from an intrauterine pregnancy like abortion and rupture of the fallopian tube from the ectopic pregnancy.

The other unusual type of multiple pregnancy is twin ectopic pregnancy which may be bilateral or unilateral. The incidence of twin ectopic pregnancies (Figure 2)
is quite rare and is estimated to be 1 in 125,000 pregnancies and 1 in 200 pregnancies following tubal ligation. Many factors increase the risk of ectopic pregnancy, important being pelvic inflammatory disease, pervious pelvic surgery leading to adhesions and assisted reproductive techniques [15]. If not managed timely this can lead to critical complications of severe haemorrhagic shock [16]. The unilateral twin ectopic pregnancy (Figures 3 and 4) would appear large due to the presence of two gestational sacs, but gestational age and the corresponding trophoblastic invasion would be less, as compared with a singleton ectopic pregnancy of the same gestational age [17]. Unfortunately, this may not be recognised leading to underestimating the prevalence.
3. Late pregnancy complications

3.1 Preterm labour

Preterm labour is a common complication of multiple pregnancy. This is thought to be secondary to accommodation challenges as the uterus is developed to accommodate one fetus. As this occurs in some patients and not others, the theory may not be completely correct. Elasticity of the uterine muscles should be playing a role on the duration of pregnancy. The prevalence of preterm delivery is higher in patients with uterine anomalies especially with unicornuate [18] or uterine didelphys and is expected to even higher if there is more than one fetus in these anomalies. The other obstetric complications with uterine anomalies are spontaneous miscarriages, preterm delivery, preterm rupture of membranes, intrauterine growth restriction, rudimentary horn rupture and increased need for operative delivery [19]. Congenital uterine
anomalies are seen in 1–10% of the general population and are as a result of abnormal formation, fusion or reabsorption of the Mullerian duct. A unicornuate uterus is present in 0.1% of the general population in which an underdeveloped or rudimentary horn may be present (Figure 5). Rudimentary horn rupture occurs in 50–90% of cases if the pregnancy is located in this horn [20]. The incidence of rudimentary horn pregnancy as singleton is estimated to be 1 in 76,000–150,000 pregnancies [21] and such pregnancies associated with twins is unknown.

Didelphys uterus correspond to the class III of Mullerian anomalies from the 1988 American Fertility Society classification. Prevalence of all types of female congenital reproductive tract anomalies is estimated at 4–7% and are mostly benign. Uterine didelphys is a rare type of anomaly with estimated prevalence of 0.3%, caused by failure of fusion of the inferior parts of the paramesonephric ducts resulting in separate uterine cavities with 2 cervices and a double or single vagina (Figures 6 and 7). Uterine didelphys with dicavitary (Figure 8) twin pregnancy is exceedingly rare; the reported incidence is 1 in 1,000,000 pregnancies [22, 23]. The complications in uterine didelphys is similar to ones in unicornuate uterus as they are related to accommodation restriction. Such twins are always binovular, the ova being from one or both ovaries. Preterm labour may occur at the same time but unilateral preterm labour has been reported [24].

3.2 Medical conditions associated with multiple pregnancy

1. Anaemia

2. Hypertensive disorders

3. Gestational Diabetes mellitus

Figure 5.
Unicornuate uterus (black arrow points rudimentary horn and the yellow arrow points to the unicornuate uterus).
Iron deficiency anaemia is a very prevalent condition in pregnancy, affecting nearly 18% of all pregnant women during all trimesters, with as many as 29% of women affected during the third trimester [25]. In twin pregnancies, the maternal iron demands are magnified, estimated at 1.8 times higher more than in singleton pregnancies [26], due to greater maternal red blood cell mass and plasma volume expansion as well as increased fetal and placental requirements. The maternal
haemoglobin in multiple pregnancies is lower in all trimesters compared to singleton pregnancies.

Hypertensive disorders are among the most common complications occurring during pregnancy and one of the indication for admission with associated maternal and neonatal morbidity and mortality. The prevalence of preeclampsia is estimated to be 4.6% globally and in multiple pregnancies the prevalence is fourfold more than in singleton pregnancies. Multiple pregnancy is identified as a risk factor for preeclampsia. The predisposing factors implicated are larger placental mass and associated markedly elevated circulating placental markers [27]. Preeclampsia phenotypes appear to be different when comparing preeclampsia in singleton and multiple pregnancies as the documented known risks like advanced maternal age, Diabetes mellitus co-morbidity are not associated with preeclampsia in multiple pregnancies. Multiple pregnancy is therefore an independent risk factor for preeclampsia [28]. Screening for preeclampsia in multiple pregnancy is not effective as the markers used do not have references in these patients [29]. Preeclampsia is commonly associated with monochorionic placentation compared to dichorionic placentation [30].

The risk of developing gestational Diabetes mellitus during pregnancy might be variable according to the race, age, nutrition, pre-pregnancy rate or body mass index, familial history, hormonal and genetic factors. There are conflicting data regarding whether women with multiple pregnancy have higher risk of gestational Diabetes mellitus compared to women with singleton pregnancies. The expectation looking at the pathophysiology of gestational Diabetes mellitus based on the hormones of pregnancy that have insulin antagonist effects, gestational Diabetes in multiple pregnancy should be more common as these hormones are higher compared to singleton pregnancies. The other factors may be playing a role rather than multiple pregnancy alone [31].

Figure 8. Dicavitary twin pregnancy.
3.3 Pregnancy specific complications

1. Preterm labour
2. Antepartum haemorrhage
3. Fetal weight
4. Fetal growth related
5. Polyhydramnios
6. Monochorionic specific

Antepartum haemorrhage occurs more frequently in twin pregnancy than in singleton pregnancies because of increased prevalence of preeclampsia in twin pregnancies with its associated placental abruption and the larger area of placental tissue with the likelihood of separation. There is no difference in the occurrence between monozygotic and dizygotic twins [31].

Twin-specific factors are zygosity, sex and birth order. Zygosity seems to play a role in intrauterine twin growth, with dizygotic twins being heavier than monozygotic twins [32]. Birth weight does not only depend on the sex of the twin but also on the sex of the co-twin. Gestation for females lasts longer than males, but despite their longer gestational age, birth weight of females is less than that for males [33].

Single intrauterine fetal demise in a twin pregnancy is a serious complication of pregnancy. It is a relatively rare complication of multiple pregnancy with a prevalence of 5–6% of all twin pregnancies [34, 35]. Single intrauterine demise during the first trimester is not an uncommon event and seems not to impair further development of the surviving one. This phenomenon is described as the “vanishing twin syndrome”. The rate of disappearance in the first trimester could be as high as 29%. In contrast, the death of a twin in the late second trimester of pregnancy is a rare complication associated with increased maternal and fetal morbidity and mortality. This condition is highly associated with preterm labour, preeclampsia, intrauterine growth restriction of the surviving twin, neurological complications and even death as well as maternal disseminated intravascular coagulopathy [36]. Preterm delivery is the commonest adverse outcome occurring in more than 50% of twin pregnancies with a single fetal demise [35]. The dead twin may be reabsorbed by the body of the mother or be flattened against the side of the uterus by the sibling creating “fetus papyraceous” (Figure 9) [37].

Unique to multiple pregnancy gestation, discordance is the difference in the weights of the foetuses. Discordance is defined with the larger twin as the standard of growth and is calculated as: (larger estimated or actual weight – smaller estimated or actual weight)/larger estimated or actual weight. ACOG considers a 15–25% difference in actual weight among twins to be discordant. Risk factors for discordant growth are monochorionic twins, opposite sex of foetuses, and infrequent isolated transplacental viral infection [38].

Polyhydramnios refers to an excessive accumulation of amniotic fluid and is diagnosed when amniotic fluid index is more than 24 cm in the late second trimester or third trimester. Risk factors are fetal congenital anomalies, Diabetes mellitus, Rhesus isoimmunization, intrauterine infections and multiple pregnancy [39].
Polyhydramnios may be chronic or acute. Acute polyhydramnios is defined as a condition where the amniotic fluid exceeds 200mls or a standard deviation above the amount corresponding to the gestational age and as a rapid development of this increase within few days. This is often associated with monozygotic twin pregnancies. In monozygotic twin pregnancy, polyhydramnios is usually caused by unidirectional shunt between the two fetal circulations leading to anaemia of the donor and to polycythaemia of the recipient twin. The increased urine excretion of the hypervolaemic recipient twin results in “acute polyhydramnios” [40].

4. Monochorionic twins

Monochorionic diamniotic twins (Figures 10–12) presents with unique complications as a result of vascular malformations with shunts formation between the two foetuses.

4.1 Twin-twin transfusion syndrome

Twin-twin transfusion syndrome (TTTS) occurs in 10–15% of all monochorionic diamniotic twins. TTTS is a severe haemodynamic disorder characterised by hypovolaemia, oliguria of the donor twin and hypervolaemia, polyuria and polyhydramnios in the recipient. This is as a result of unbalanced bidirectional inter-twin blood flow. The severity depends on number and/or diameter of arteriovenous anastomoses from the donor to the recipient fetus.

4.2 Diagnostic criteria of TTTS is based on

1. Confirmed monochorionic pregnancy
2. Polyhydramnios in the recipient with deepest vertical pool pocket ≥8 cm
3. Oligohydramnios in the donor with a deepest vertical pool pocket ≤2 cm

4. Discordant fetal bladders with markedly enlarged bladder in the recipient and very small or non-visible in the donor.
4.3 Grading of severity of TTTS

Stage 1: The bladder is still visible in the donor
Stage 2: The bladder no visible in the donor
Stage 3: Critically abnormal Doppler in either twin: absent/reversed umbilical artery diastolic flow of the donor or recipient and/or absent/reversed ductus venosus flow or pulsatile flow in the umbilical vein of the recipient
Stage 4: Hydrops in either fetus
Stage 5: Demise in one or both foetuses.

4.4 Twin anaemic polycythaemis sequence

Twin anaemia polycythaemia sequence (TAPS) (Figure 13) is a form of intertwine unbalanced transfusion occurring in a placenta where interfetal anastomoses are very small. It is a form of TTTS with reduced impact. Diagnostic criteria of TAPS is as in Table 1 [41].

4.5 Twin reversed arterial (TRAP) perfusion

TRAP is defined as a degree of development of the fetus. It is classified according to specific organ with anomaly. The diagnosis has been made even in the first trimester in some cases using colour flow Doppler to document that the umbilical vein blood flow in the acardia twin goes from the twin to the placenta instead of the normal circulation which is from placenta to the fetus [42].
4.6 Acute feto-fetal transfusion

This condition refers to sudden drop in pressure and/or heart rate at one fetal end. This leads to unidirectional transfusion and acute exsanguination of the co-twin which behaves like acute donation of blood. After a single fetal death, transfusion occurs from the surviving twin to the dead fetus. Acute feto-fetal transfusion by single intrauterine death is a rare condition in which blood transfusion from the surviving twin to the dying twin takes place. This may occur during pregnancy and delivery. If it occurs during pregnancy the surviving twin may suffer a massive exsanguination into the circulation of the dying twin. The surviving twin may suffer from brain injury and spontaneous death Table 2 [41].
4.7 Conjoined twins

This is as a result of incomplete separation of monochorionic monoamniotic twins which should occur before eighth day after fertilisation. The points of union differ from the cephalic, thoracic, abdominal and caudal region. The incidence of conjoined twins is 1.5 per 100,000 deliveries and 50% of them are liveborns [43, 44]. The delivery is usually complicated as it should take place simultaneously and vaginal delivery is not possible (Figure 14).

<table>
<thead>
<tr>
<th>Prenatal</th>
<th>Middle cerebral artery (MCA) –peak systolic (PSV) ≥ 1.50 MoM in the anaemic fetus And MCA-PSV ≤ 0.8 MoM in the polycythaemic fetus Or Delta MCA-PSV ≥ 1.0 MoM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal</td>
<td>Inter-twin haemoglobin difference ≥ 8.0 g/dl And Inter-twin reticulocyte count ratio (anaemic/polycythaemic fetus) ≥ 1.7</td>
</tr>
</tbody>
</table>

Table 2. Diagnostic criteria for TAPS.

Figure 14. Conjoined twins.
5. Higher order multiple pregnancy

This refers to a pregnancy with three or more foetuses. Though rare, higher order multiple pregnancy have more serious complications than twin pregnancy. Preterm labour occurs at an earlier gestational age and lead to serious morbidity and increased maternal and neonatal mortality. Spontaneous miscarriages, preterm labour, preterm rupture of membranes, hypertensive disease in pregnancy, caesarean delivery, antepartum and postpartum haemorrhage are the anticipated challenges (Figure 15) [45].

6. Malpresentation

Malpresentation in multiple pregnancy is common as cephalic/cephalic presentation is estimated to be about 38–40% and vertex/non-vertex presentation accounts for approximately 34.8%. The general consensus is that a trial of vaginal delivery of vertex/vertex twins is appropriate at any gestational age. There is significant number of multiple pregnancies with abnormal presentation [46]. With abnormal presentation and abnormal fetal lie the option for delivery is surgical. The safest delivery mode of twins has been controversial as there has reported that postpartum haemorrhage is more often after vaginal delivery than after elective caesarean section. Elective caesarean section delivery is relatively safe for twin pregnancy, because the second twin in vaginal delivery has a high probability of birth injuries and death [45].

7. Postpartum haemorrhage

Uterine over-distension as in multiple pregnancy and singleton with large foetuses more than 4000 g is associated with uterine atony. In addition, the large placental size
in multiple pregnancy increases the surface area for bleeding after delivery [47]. Multiple pregnancy and caesarean section are well known risks factors for postpartum haemorrhage. Comorbidity in multiple pregnancy like hypertensive disorders increase the risk of postpartum haemorrhage even higher.

Growth discordance, especially complicated by fetal growth restriction is associated with increased risk of postpartum haemorrhage in women with twin pregnancies undergoing caesarean section, and more so in patients with dichorionic twins [48].

Low platelet counts of less than 100,000/ᶙ was also identified as one of the risk factors for postpartum haemorrhage in twin pregnancy who had elective procedure even without hypertension. Preoperative measurement of platelet counts is clinically useful for predicting the occurrence of postpartum haemorrhage in caesarean section for twins. Optimization of platelet counts may reduce the risk [49].

8. Maternal and neonatal mortality

The occurrence of severe maternal morbidity and maternal death is significantly higher among twin compared to singleton pregnancies [50]. Twin delivery has a negative impact on perinatal health indicators, since the mortality is higher, especially due to higher preterm births. Early neonatal mortality may be as high as seven times higher among twins compared to singletons. Morbidity and mortality of the second twin and subsequent foetuses in higher multiple pregnancy is even higher than the first, particularly for non-cephalic presentation [51, 52].

9. Conclusion

Multiple pregnancy poses challenges from conception until delivery. The delay of women in reproduction leads to the need of assisted reproductive techniques to be implemented increasing the prevalence of multiple pregnancy including higher order. The impact of multiple pregnancy on maternal and neonatal morbidity and increased cost to manage is enormous. Complications of multiple pregnancy are noticed early in pregnancy and continue to be present throughout pregnancy and delivery until in the postpartum period. Multiple pregnancy is significantly associated with severe maternal morbidity associated with worse perinatal outcome. Neonatal morbidity and mortality are significant in multiple pregnancy presenting challenges for health services.

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