

Guidelines On Management of Multiple Pregnancies: Part I

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1 INTRODUCTION

The aim of this guideline is to provide up-to-date recommendations on the management of multiple pregnancies. The guideline is divided into two parts: Part I examines the ultrasound diagnosis, prenatal screening and antenatal management of multiple pregnancies in general. Part II will focus on the specific antenatal complications related to particular types of twin pregnancies, the timing and the mode of delivery, and the intrapartum management of vaginal deliveries of twins.

2 DIAGNOSIS OF MULTIPLE PREGNANCIES

Early ultrasound examination should aim to diagnose not only the multiple pregnancies, but also the chorionicity.

Twin pregnancy results from fertilization of 2 separate ova producing dizygotic (non-identical) twins or fertilization of one ovum, which subsequently divides, giving rise to monozygotic (identical) twins. With rare exception¹, the dizygotic twins are dichorionic diamniotic (DCDA). The monozygotic twins can be DCDA, monochorionic diamniotic (MCDA), or very rarely monochorionic monoamniotic (MCMA), depending on the timing of division. Thus, MC twins are monozygotic while DC twins can be dizygotic or monozygotic.

The diagnosis of multiple pregnancies and the chorionicity can be reliably established by ultrasonography in early pregnancy. The best timing to determine chorionicity is at 6-9 weeks of gestation, when two chorionic sacs separated by a thick septum can be seen in DC twins, and there is one single chorionic sac with two fetuses inside in MC twins². Between 10-14 weeks of gestation, the septum between the 2 sacs in DC twins becomes progressively thinner to form the chorionic component of the intertwin

membrane. However, at the base of the membrane, there is a characteristic triangular tissue projection, which is termed 'lambda' or 'twin peak' sign^{3,4}. In the case of MCDA twins, the intertwin membrane is thin and approaches the placenta at around a 90° angle, which is called 'T' sign⁵. For MCMA twins, the ultrasound features include: 2 fetal poles within one chorionic sac, only one yolk sac, single placenta, and no intertwin membrane. As the intertwin membrane can be very thin in MCDA and therefore difficult to be visualized in the early gestation, the diagnosis of MCMA should always be confirmed on a subsequent scan⁶.

With advancing gestation, the 'lambda' sign becomes progressively more difficult to identify. Disappearance of the 'lambda' sign has been shown in about 9% of DC pregnancies between 16 and 20 weeks of gestation⁷. Hence, in the second or third trimester, the absence of the 'lambda' sign does not exclude the possibility of dichorionicity. On the other hand, if the 'lambda' sign is seen, it has excluded monochorionicity. The determination of the number of placentas and the fetal gender are helpful. Two separate placentas and different fetal gender indicate DC twinning. Thickness of the intertwin membrane is a less reliable indicator of chorionicity compared with 'T' or 'lambda' sign and the number of placentas⁸.

Once the number of fetuses and the chorionicity are determined on ultrasonography, it is also important to document the location and position of the each sac or fetuses in the uterine cavity for future reference.

3 PRENATAL SCREENING AND DIAGNOSIS

Prenatal screening for chromosomal anomalies is a common practice for singleton pregnancies in modern obstetrics. Women with multiple pregnancies very often would also seek advice

on these tests. However, the counseling for women with multiple pregnancies is more complicated. The in-charge obstetrician should discuss carefully with the women the implications of the test(s) including the detection rate, possibility of subsequent diagnostic procedures and selective fetocide, and their complication rates before embarking on the tests. The updated information regarding these screening tools is summarized here:

a. Screening for chromosomal anomalies

Screening tests for Down's syndrome employed in singletons are applicable to twins but the performance might be inferior compared with that for singletons.

The maternal age-related risks for chromosomal anomalies depend on the zygosity. In dizygotic pregnancies, the background risk for each twin is the same as in singleton pregnancies. Therefore, the chance that at least one fetus is affected is twice as high as in singleton pregnancies. In monozygotic pregnancies, the risk for chromosomal abnormalities is the same as in singleton pregnancies.

Using a combination of maternal age and second-trimester maternal serum biochemistry, the detection rate for Down's syndrome is estimated to be about 45% (compared with 60-70% in singleton), at a false-positive rate of 5%⁹.

Using maternal age and the first-trimester nuchal translucency (NT), a risk specific to each fetus can be generated. The sensitivity and false-positive rate for Down's syndrome in DC twin pregnancies are similar to those in singleton pregnancies¹⁰. However, the false-positive rate is higher in MC twins than in singletons because increased NT is also an early sign of twin-to-twin transfusion syndrome¹⁰.

With the addition of first-trimester maternal serum biochemistry to age and NT, the detection rate for Down's syndrome was 75% (compared with 85-90% in singleton), at a false-positive rate of 6.9% per fetus¹¹. Large population data on integrated screening in twins using first-trimester NT and second-trimester biochemistry has not been reported. It is estimated that at a false-positive rate of 5%, the detection rate is 85%, compared with 90% in singletons¹².

b. Screening for structural anomalies

Monozygotic pregnancies are associated with increased risk of congenital malformations.

The frequency of structural anomalies in dizygotic twins is similar to that of singletons but the frequency is 2-3 times higher in monozygotic twins¹³. An 18-22 week morphology scan is advised.

c. Invasive prenatal diagnosis

The determination of chorionicity is crucial before invasive prenatal diagnosis procedures.

First-trimester chorionic villous sampling (CVS) and second-trimester amniocentesis can be used for prenatal diagnosis. The pregnancy loss rates associated with CVS and amniocentesis in twin pregnancy have been reported to be comparable (2.9-4.5%)^{14,15}. The choice depends on several factors including gestational age on referral, placental location, operator experience with the specific procedure, and the likelihood of selective fetocide¹⁶. Chorionic villous sampling has the advantage of early diagnosis, thus allowing early selective fetocide if abnormal results are obtained. However, CVS in twin or multi-fetal pregnancy can be technically demanding and it is estimated that re-sampling may be needed in 2-3% of cases because of uncertainty of results¹⁶.

The determination of chorionicity is important before the invasive prenatal diagnosis procedure. For DCDA pregnancies, there is a possibility of dizygosity and hence, karyotyping for each fetus is needed. Proper evaluation and labeling of the fetal positions is important prior to the invasive procedure. The location of the intertwined membrane, fetuses, placentas, cord insertions and fetal gender should be obtained on ultrasonography and recorded for later reference. For MC pregnancies, the fetuses should have identical sets of chromosomes but very rarely, discordant karyotypes have been reported^{1,17}. The existing opinion is that if monochorionicity is certain, neither fetus has anatomical abnormality and fetal growth is not severely discordant, sampling one placenta or one amniotic sac is sufficient. However, if one, or both, of the fetuses has

structural anomalies, sampling of both fetuses should be considered^{16,17}.

If karyotyping of each fetus is required, as in DCDA twins, the most commonly used method in amniocentesis is the use of two different needles, inserted separately and sequentially into each amniotic cavity, under ultrasound guidance. Inadvertent sampling of the same sac was reported in up to 3.5% of samples¹⁸. Injection of dye into the first sac after the first sampling for identification is not necessary in most circumstances, provided the operator is experienced and high-resolution ultrasound equipment is available¹⁶. It should be reserved for cases in which the demonstration of intertwin membrane is difficult and for higher-order pregnancies.

For CVS, a major concern is sampling error and cross contamination and therefore accurate ‘mapping’ of the fetuses and placentas is essential. It is mandatory to use different needles for different placentas. If the placentas are contiguous, aspiration of the villi close to cord insertion might help to reduce the rate of cross contamination¹⁶.

d. Selective fetocide

Women with multiple pregnancies discordant for fetal anomaly should be adequately counseled the available options.

Major anomaly affecting only one fetus occurs in approximately 1-2% of twin pregnancies¹⁹. The couple of these pregnancies would face the dilemma of expectant management versus selective fetocide.

Expectant management of DCDA twins discordant for lethal anomalies such as anencephaly and trisomy 18 appears to be a reasonable option. The procedure of selective termination may increase the risk of miscarriage or damage of the co-twin. On the other hand, expectant management may not be beneficial in MC twins if the anomalies are associated with a risk of intrauterine death. Fetal demise of the abnormal one may cause hypoxic-ischemic damage to the co-twin due to the vascular communication in the placentas of MC pregnancies²⁰.

If the option of selective fetocide is decided, the main variable that determines the technique is chorionicity. In DCDA twins,

injection of potassium chloride into the fetal heart or the umbilical cord of the affected twin is an effective and safe procedure. The risk of miscarriage was reported to be 7.1% and there was no significant correlation between loss rate and the timing of procedure²¹.

In MC twins, selective termination needs to be performed by ensuring complete and permanent occlusion of both the arterial and venous flows in the umbilical cord of the affected twin. The current literature does not allow conclusions regarding what is the best method in MC twins due to the wide range of techniques reported, mainly through small case series, for different indications and at different gestational age¹⁹. The techniques involved are much more invasive and hence are associated with much higher risks of antenatal complications, compared with selective fetocides in DC pregnancies.

Women with multiple pregnancies discordant for fetal anomaly should be adequately counseled the available options. If selective fetocide is considered, nature of the procedures involved and the potential complications should be carefully addressed.

4 ROLE OF MULTIFETAL PREGNANCY REDUCTION (MFPR) IN HIGHER-ORDER MULTIPLE PREGNANCIES

MFPR to twins in high-order multiple pregnancies reduces perinatal morbidity and mortality.

Multifetal pregnancy reduction refers to the termination of one or more, presumably normal, fetuses in a multiple pregnancy. Up to date, there is no randomized controlled trial which assessed MFPR. Data from prospective controlled studies suggest that, for triplet or higher-order multiple pregnancies, MFPR to twins significantly reduces rates of pregnancy loss, antenatal complications, preterm birth before 36 weeks, caesarean birth and neonatal death., compared with expectant management²². However, one may still argue that the perinatal outcomes of triplet pregnancies have improved in the recent years with the advent of neonatal care and it may not justify the sacrifice of one potentially healthy baby²³. Therefore, women with higher-order multiple pregnancies should be adequately counseled regarding the pregnancy outcomes and potential problems with the higher-order gestation, and the advantages and possible risks of MFPR, including the loss of the entire

pregnancy. The women's wish and view should be respected. They should be guided to arrive at a decision they most want.

Most MFPR are performed by intrathoracic potassium chloride injection via transabdominal route under ultrasound guidance between 11 weeks and 14 weeks of gestation, after the main risk of spontaneous miscarriage in early gestation is over and when fetal structural assessment is feasible²⁴. Fetuses further away from the cervix and/or with abnormal ultrasound features (increased nuchal translucency, malformation, and relative intrauterine growth restriction) are terminated. In triplets which consist of a pair of MC twins, the best outcomes are achieved by reduction of the MC twins, provided the 'singleton' looks normal on ultrasonography²⁵.

Under experienced hands, the pregnancy loss rate, preterm deliveries at 25-28 weeks and at 29-32 weeks of gestation following MFPR were reported to be 6.8%, 4.3% and 10.2% respectively²⁴. In Hong Kong, fetal reduction in a multiple pregnancy is allowed up to before 24 weeks of gestation²⁶.

5 ANTENATAL CARE FOR MULTIPLE PREGNANCIES IN GENERAL

a. Monitoring of fetal growth

Serial ultrasound examination should be arranged after the diagnosis of multiple pregnancies.

The growth of multiple pregnancies is not significantly different from that of singletons in the first and second trimesters²⁷. However, slower fetal growth rate has been reported after 30-32 weeks of gestation, compared with singletons²⁷. The growth of individual fetuses needs to be monitored by serial ultrasound examination at ~ 4-weeks' intervals. This frequency of scanning can be adjusted according to other clinical indications, such as evidence of fetal growth impairment or preeclampsia. Apart from fetal growth, ultrasonography also helps to assess the liquor volume (by measuring the deepest vertical pocket of each sac), to exclude placenta previa, and at term, to ascertain the presentations.

b. Nutrition and supplementation

Dietary advice is important in management of multiple pregnancies.

There is an increase in the requirements for calories, protein, minerals and vitamins for multiple pregnancies²⁸. Iron deficiency anaemia is more common²⁹. Women carrying multiple gestations should increase their daily dietary intake by approximately 150-300 kcal above that for a singleton pregnancy^{30,31}. Dietary or vitamin/mineral supplementation should include adequate iron (eg, 60 mg daily with adjustments based upon hemoglobin and ferritin concentrations) and folic acid (1 mg per day)³⁰.

c. Preterm birth

There is currently no effective preventive measure for preterm birth in multiple pregnancies.

Preterm birth is the one of the major complications of multiple pregnancies. The chorionicity appears to a predictive factor. For twins, the risk for preterm birth before 32 weeks has been shown to be greater for MC twins (9.2%), compared with DC ones (5.5%)³². For triplets, dichorionic triamniotic ones have more than a 4 fold higher risk of delivery before 30 weeks of gestation, compared with trichorionic triamniotic ones³³.

Predicting which woman will have preterm birth remains a clinical challenge. The predictive values of markers such as cervical length measurements by transvaginal ultrasound, cervical fibronectin or home uterine activity monitoring are too low to be recommended for routine practice³⁴⁻³⁶.

Cervical cerclage, performed either because of short cervixes in twin pregnancies or as prophylactic treatment in triplet gestation, has failed to demonstrate any benefit in preventing preterm birth^{37, 38}. Similarly, other preventive measures, such as routine hospitalization and bed rest or the use of oral betamimetics as prophylactic tocolytic agent have not been shown to be beneficial in this regard^{39, 40}.

The benefits of antenatal corticosteroids have been well proven in singleton pregnancy⁴¹. Whether the results can be extrapolated to multiple pregnancies is unknown. The meta-analysis showed a trend towards reduction in respiratory distress syndrome but this did not reach statistical significance, which could be due to the

small sample size (2 trials, 140 babies)⁴¹. Until further evidence is available, multiple pregnancies should be treated in the same way as in singleton pregnancies for the potential benefits of antenatal corticosteroids.

d. Other common antenatal complications

Multiple pregnancies are associated with increased risks of preeclampsia, antepartum haemorrhage and gestational diabetes.

Woman with a twin pregnancy has a three-fold increase in risk for preeclampsia⁴², and this risk is not affected by the chorionicity or zygosity of the pregnancy⁴³. A triplet pregnancy would further triple the risk of pre-eclampsia compared with a twin pregnancy⁴⁴. Regular monitoring of maternal blood pressure and urine for protein throughout the antenatal period is necessary for multiple pregnancies. Symptoms such as nausea, vomiting and epigastric pain in the third trimester should raise the suspicion of acute fatty liver disease or HELLP syndrome.

Women with multiple pregnancies are at increased risk of antepartum haemorrhage from both placenta praevia⁴⁵ and placenta abruption⁴⁶. The management is similar to that in singleton pregnancy.

Gestational diabetes appears to be slightly more common in twin and triplet pregnancies^{47,48}, although this has not been confirmed in all studies⁴⁹. Strategies used to achieve blood glucose control in singletons appears to be adequate in multiple pregnancies⁵⁰.

- Monozygotic pregnancies are associated with increased risk of congenital malformations. An 18-22 week morphology scan is advised.
- Invasive prenatal diagnosis is technically more demanding in multiple pregnancies compared with singleton pregnancies. The number of sampling depends on the chorionicity.
- Women with multiple pregnancies discordant for fetal anomaly should be adequately counseled about the available options and their associated risks.
- MFPR to twins in high-order multiple pregnancies reduces perinatal morbidity and mortality. Women with these pregnancies should be appropriately counseled regarding the pros and cons of this option.
- Multiple pregnancies are associated with increased risks of antenatal complications such as miscarriage, preterm birth, intrauterine growth restriction, anaemia, preeclampsia, antepartum haemorrhage and gestational diabetes.
- Fetal growth in multiple pregnancies should be monitored by serial ultrasound examination.
- Preterm birth in multiple pregnancies cannot be reliably predicted. Routine cervical length measurement is not currently recommended. Cerclage, routine hospitalization or prophylactic tocolytics has no proven value in prevention of preterm birth.
- Dietary or vitamin/mineral supplementation should include adequate iron and folate.

6 SUMMARY OF KEY POINTS FOR PART I OF THE GUIDELINES

- Early ultrasound examination should aim to diagnose not only the multiple pregnancies, but also the chorionicity. The best timing is in the first trimester. The diagnosis of chorionicity becomes more difficult and less reliable in the late second or third trimester.
- Screening tests for Downs syndrome employed in singletons are applicable to twins but the performance might be inferior compared with that for singletons.

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This guideline was produced by the Hong Kong College of Obstetricians and Gynaecologists as an educational aid and reference for obstetricians and gynaecologists practicing in Hong Kong. The guideline does not define a standard of care, nor is it intended to dictate an exclusive course of management. It presents recognized clinical methods and techniques for consideration by practitioners for incorporation into their practice. It is acknowledged that clinical management may vary and must always be responsive to the need of individual patients, resources, and limitations unique to the institution or type of practice. Particular attention is drawn to areas of clinical uncertainty where further research may be indicated.