Review

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The Controversies and Challenges in the Management of Twin Pregnancy: From the Perspective of International Federation of Gynecology and Obstetrics Guidelines

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Abstract

The rate of multiple pregnancy is increasing, mainly because of the widespread use of assisted reproduction techniques and families' desire for twins. Twin pregnancy accounts for a higher risk of chromosomal abnormalities, structural malformations, and neonatal adverse events than singleton pregnancy. The presence of artery-vein anastomoses, unbalanced placenta sharing, and abnormal cord insertion in monochorionic twins is associated with twin complications such as twin-to-twin transfusion syndrome, selective intrauterine growth restriction, and twin anemia polycythemia sequence. Although many guidelines and studies have established and improved the processes about the antenatal surveillance and management of twin pregnancy, they also raise more controversies and challenges. This review aims to highlight the international consensus on the antenatal care of twin pregnancies and analyze the controversies and predicaments based on the published International Federation of Gynecology and Obstetrics guidelines and research.

Keywords: Ultrasonography; Pregnancy, twin; Selective intrauterine growth restriction; Intertwin discordance; Twin-to-twin transfusion syndrome; Twin anemia polycythemia sequence; Controversies

Introduction

Twin pregnancies account for 2% to 4% of all total births[1] and are associated with higher maternal and fetal risks such as preterm birth, fetal growth restriction (FGR), or congenital anomalies. Owing to the rise in use of assisted reproduction techniques, the incidence of monochorionic (MC) twin pregnancy has also increased. Approximately 20% of twin pregnancies result in MC.[2] Because it is commonly acknowledged that the fetal outcomes of MC twins are inferior to those of dichorionic (DC) twins, it is important to determine chorionicity in early pregnancy and plan for subsequent perinatal monitoring and interventions.

Many international expert teams such as the International Federation of Gynecology and Obstetrics (FIGO), the Royal College of Obstetricians and Gynecologists (RCOG), the National Institute for Health and Care Excellence (NICE), the American College of Obstetricians and Gynecologists, and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) have made efforts to standardize the management of twin pregnancy. However, differences in the guidelines hinder consistent results in clinical trials. The aims of this review are to highlight the international consensus of the antenatal care of twin pregnancies, for example, determination of chorionicity, ultrasound surveillance protocol, prenatal diagnosis procedure, and management of twin complications, and analyze the controversies and discrepancies based on the published FIGO guidelines and research.

Determination of chorionicity of twin pregnancy

Chorionicity is one of the most significant parameters for prognosis in twin pregnancy. The risk of intrauterine fetal demise is 11.6% in MC twins compared with DC twins.[3] Neurological morbidity is 4 to 5 times higher than in DC twins and consequently 25 to 30 times higher than in singletons.[4] Moreover, chorionicity determines the ultrasound surveillance patterns during gestation and also the techniques for selective fetal reduction. Therefore, accurate determination of chorionicity is essential to improve the pregnancy outcome of twins.

The accuracy of chorionicity determination before 14 weeks is 99% as the amnion and chorion are not fused at this stage, but it decreases to only 77% for MC after 14 weeks.[5,6] Herein, FIGO guidelines[7] suggest that chorionicity should be determined and documented clearly in the first trimester using the membrane thickness at the site of insertion of the amniotic membrane into the placenta, identifying the T sign or lambda (λ) sign. For women presenting for the first time after 14 weeks, chorionicity can still be determined by using the same signs as well as the discordant fetal sex. However, clinicians should be aware that there are still some limitations to ultrasound-guided assessment of chorionicity.[8] First, various reasons such as advancing gestation and regressing yolk sac can result in both false-negative and false-positive λ signs. In very rare situations, both T and

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λ signs can coexist. Second, sometimes intrauterine synechia can be considered as a thick intrauterine septum, leading to the misdiagnosis of DC twins. The thickness of intertwin membrane is not always a reliable marker for chorionicity. When using 2-dimensional ultrasound, an intertwin membrane thickness of 1.5 to 2.0 mm may be inconclusive for MC twins. Bracero *et al.*[9] reported that a cutoff value of 1.9 mm of the dividing membrane thickness is found to be the best predictor of chorionicity with the ultrasound beam parallel. However, there is still no consensus about the optimal cutoff value. Besides, approximately 3% of placentas in MC twins may be bilobar and appear as two placental masses.[10] Although the positive predictive value of sex discordance is almost 100%, the existence of MC dizygosity twins, sex chromosomal abnormality, and monogenetic disorders can lead to sex discordance in MC twins. Genital malformation such as hypospadias or cloacal malformation can result in confusion. Moreover, the ascertaining of amnionicity by the number of yolk sacs is not always true. Sometimes it is difficult to visualize the intertwin amniotic membrane if it is too thin or has collapsed because of severe oligohydramnios in the donor twin in twin-to-twin transfusion syndrome (TTTS).

Therefore, we should use a combination of the number of placental masses, λ and T signs, and intertwin membrane thickness to improve the accuracy of ultrasound assessment in clinical practice.[11,12] Furthermore, if sonographers cannot obtain a satisfied transabdominal ultrasound image, transvaginal sonography is recommended for a retroverted uterus or in patients with high body mass index in the ISUOG guidelines.[12] Patients should preferably be referred to the tertiary center. If it is still difficult to determine the chorionicity, it is safer to be treated as MC twins, which require additional fetal surveillance for specific complications.

The dilemma of ultrasound surveillance in twin pregnancy

The FIGO guidelines suggest[7] that in general ultrasound examination of twins, the following parameters should be assessed in cotwins in serial ultrasound scans: fetal biometry, estimated fetal weight (EFW), and amniotic fluid volume (AFV). In addition, peak systolic velocity of middle cerebral artery (MCA-PSV) should be assessed intensively from the second trimester screening for twin anemia polycythemia sequence (TAPS). In MC twins, ultrasound scan should be performed at least every two weeks since 16 weeks' gestation for assessment of the aforementioned parameters. In uncomplicated DC twins, it should be performed at approximately 20 weeks' gestation for detailed anomalies and thereafter every month. If there are any abnormal ultrasound findings, the scan should be more intensive. Besides, in all twin pregnancies, the 20-week scan should include measurement of cervical length to identify women at increased risk of extreme premature delivery.

A high degree of growth discordance is known to be associated with adverse perinatal outcomes regardless of chorionicity. Regular monitoring for intertwin-size discordance is therefore essential for antenatal care. A systematic review reported that twin pregnancy with discordant EFW is associated with the increased risk of intrauterine demise, whereas the risk of IUD is higher when at least one twin is small for gestational age.[13] However, another study showed that for DC twins, the discordance of fetal growth increased across gestation, and there was no consensus regarding the appropriate cutoff point to predict adverse perinatal outcome.[14] More research about variation of fetal growth discordance during gestation is necessary to define an appropriate cutoff point for prediction of adverse outcomes.

It is widely acknowledged that the growth patterns of twin and singleton pregnancies are different during the third trimester, and therefore, the growth charts should be distinct for more accurate assessment. Several studies have proven that use of twin-specific growth charts can reduce the diagnosis of FGR and unnecessary interventions in twins.[15,16] Therefore, twin-specific growth charts have been developed in different regions and populations, but its clinical application needs further improvement.[15–19] Moreover, per the FIGO guidelines, umbilical artery (UA) Doppler should only be carried out in high-risk pregnancies, but according to the ISUOG and RCOG guidelines and the consensus in China,[10,12,20] the UA Doppler is recommended at each scan to detect the complications in a timely manner and improve perinatal outcomes. Another study shows that abnormal UA Doppler in the midtrimester indicates poor outcome, and therefore, close surveillance is warranted in all MC twins.[21] However, another prospective study shows that abnormal UA is presented in a small part of uncomplicated twins in the second trimester, and most of them can achieve normalization, which seems that the routine monitoring for UA is not necessary.[22] Hence, the assessment of UA Doppler is still unclear. However, it is known that complications such as TTTS result from long-lasting transfusion and hemodynamic imbalance; hence, it is possible that the UA Doppler waveforms deteriorate before TTTS can be diagnosed, and routine monitoring thus seems reasonable in this situation.

The cervical-length screening in the second trimester is also a controversial issue. Given that the risk of preterm birth in twin pregnancies is 10 times higher than in singletons,[23] most experts in China recommend routine measurement of cervical length during the 18 to 24 weeks' ultrasound scan, which is consistent with the ISUOG and FIGO guidelines.[7,12,24] These guidelines suggest that a short cervix in asymptomatic women is a risk factor for preterm delivery, but its predictive value is poor in symptomatic women.[7] However, routine cervical length screening is not recommended in asymptomatic women per the NICE and American College of Obstetricians and Gynecologists guidelines,[24,25] because the sensitivity of cervical-length screening in twins is lower than that in singletons, and there are no effective interventions to prevent spontaneous preterm delivery.[26] Rehal *et al.*[23] conducted a randomized clinical trial among 1194 unselected twin pregnancies to explore the effect of early use of high-dose vaginal progesterone and found that it did not reduce the incidence of preterm birth before 34 weeks. Some cohort studies have also found that pessary and cerclage had no contribution in decreasing the risk of preterm birth before 32 weeks in twin pregnancies with short cervix.[27,28] Although data showed that pessary can reduce the rate of morbidity in neonate and the economic costs when compared with progesterone, more data are needed to reach a consensus for prevention of preterm birth in twins.[29] Therefore, the use of cervical-length screening is still contentious.[5,16]

There is still relatively little evidence-based guidance about the frequency of ultrasound examination in DC twins.[24] A recent large-scale prospective study reported excellent fetal outcomes in DC twins, in their fortnightly ultrasound scan research.[30] The study shows that this strategy may increase the detection rate (DR) for FGR cases. Although a longer scan

interval is likely to miss abnormal cases and may cause higher risk of poor outcomes, shortening the screening interval will lead to cost issues and unnecessary iatrogenic preterm delivery. More evidence is needed for appropriate ultrasound surveillance frequency in DC twins.

Therefore, the optimal cutoff points of EFW discordance, the use of twin-specific growth charts, and a consensus about ultrasound surveillance parameters are needed for better management in twin pregnancy.

Screening for chromosome abnormalities and invasive prenatal procedures in twin pregnancy

The FIGO guidelines state that the combined test (serum biochemistry screening and nuchal translucency) or the combination of maternal age, nuchal translucency, and cell-free DNA (cfDNA) test should be offered to screen chromosomal abnormalities in twins in the first trimester.[7,12,15,31] However, the patient should be informed that serum tests in twin pregnancies are less accurate than in singleton pregnancies. If necessary, combined screening for sonographic markers of chromosomal aneuploidy such as the nasal bone, tricuspid regurgitation, and ductus venosus is recommended.[31]

Cell-free DNA is the most sensitive and specific screening test for common fetal aneuploidies in twin pregnancies.[15,32] In singleton pregnancies, cfDNA analysis of maternal blood provides effective screening for trisomy 21, 18, and 13. A recent meta-analysis reported that the DR of cfDNA was >99%, and the false-positive rate was 0.04% in singleton pregnancies.[15,33] By contrast, noninvasive prenatal testing has a higher failure rate in twin pregnancies owing to many factors such as maternal body mass index, placenta-confined mosaicism, conception by in vitro fertilization, dichorionicity, and single-twin demise, and data on cfDNA tests in twin pregnancies are still limited.[15] Gil *et al.*[33] conducted a meta-analysis to describe the performance of cfDNA analysis in twin pregnancy. The results showed that the performance of cfDNA analysis for trisomy 21 may be similar to that in singleton pregnancy, with a DR of 99.7% and a false-positive rate of 0.04%.[33] However, the sample size of trisomy 18 and 13 was very limited to accurately assess the predictive performance of the cfDNA test. Currently, the application of cfDNA screening is advised in twin pregnancies. If the cfDNA results are positive and indicate a high risk for trisomy 21, chorionic villus sampling (CVS) should be carried out for a more accurate confirmation. Regarding the high risk of trisomy 13 and 18, if fetal defects are detected in the follow-up ultrasound scan, amniocentesis can be considered.

According to the FIGO guidelines, CVS is preferred in DC twins, because it can be performed earlier than amniocentesis, and genetic disorders can be identified earlier to reduce the risk of fetal loss.[7] The rate of fetal loss after invasive procedure is approximately 2% to 3.8% for CVS and 1.5% to 3.1% for amniocentesis in twins, which is higher than in singletons.[5,12,31,34–36] A recent meta-analysis showed that there is no significant difference between twin pregnancies undergoing and those not undergoing invasive procedure regarding the risk of fetal loss within four weeks after the procedure.[36] Another retrospective study showed that the risk of fetal loss was twofold higher in twin pregnancies undergoing CVS than those not undergoing CVS, but such an increased risk was reportedly associated with the maternal characteristic rather than the procedure itself.[37] Agarwal and Alfirevic[35] proposed that chorionicity should also be considered with respect to fetal loss rate because it presents with different perinatal outcomes, and few studies describe the outcome according to chorionicity. Other complications such as amniotic fluid leakage, chorioamnionitis, and severe fetal injury are very rare; thus, invasive prenatal diagnosis is still a safe procedure. These findings are helpful when counseling parents about the safety of the procedure, but there is a need for further large-scale studies to verify the actual rate of fetal loss.

There are some distinct differences between MC and DC twins.[38] Because DC twins have different genetic information, analysis of the estimated risks of chromosomal abnormalities, for example, Down syndrome, is different according to chorionicity. The assessment of estimated risk is equivalent with singletons in MC twins, whereas it should be calculated independently in each of the DC twins. It is also recognized that both amniotic sacs should be sampled regardless of chorionicity, unless the MC twins are concordant for growth and AFV and have no fetal abnormality.

Diagnosis of selective FGR (sFGR) in twins

sFGR occurs in 10% to 15% of twin pregnancies.[39] The diagnostic standard of sFGR is still heterogeneous in different countries for both MC and DC twins. According to the FIGO and ISUOG guidelines,[7,12] the diagnostic standards of sFGR are that one fetus has an EFW below the 10th percentile in DC twins and an intertwin EFW discordance of ≥25% in MC twins.[7] In the NICE guidelines, it is suggested that a fetal weight discordance >25% is a clinical indicator of sFGR. Khalil *et al.* established a consensus definition of sFGR through the Delphi procedure in 2019.[31,40]

Nikolaos thought that the Delphi diagnostic criteria may lead to less diagnosis of sFGR, less iatrogenic preterm birth, and no significant influence in perinatal outcomes in DC twins.[41] It is believed that sFGR in DC twins can be managed similar to FGR in singletons, but recent studies have found that the abnormal flow of umbilical and cerebral arteries seem to have different prognostic value between DC twins and singletons.[42] Therefore, the management strategy of sFGR in DC twins still needs further studies. Given that sFGR in MC twins is more common and considered to have a worse perinatal mortality and morbidity rate, most published studies have focused on the clinical characteristics and prognosis of selective intrauterine growth restriction (sIUGR) in MC twin pregnancies. However, a wide heterogeneity in the definition of sIUGR applied in different studies hinders the comparison and summarization of these new findings. The consensus definition of sFGR through the Delphi procedure takes vascular indices into account. This criteria were also adopted by the Chinese guidelines.[43] Interestingly, a recent study[44] that compared different diagnostic criteria of sIUGR claimed that when intertwin EFW discordance of ≥25% was used as the diagnostic standard, the incidence of sIUGR is similar regardless of whether abdominal circumference or EFW <10th percentile is included. A combination with UA PI of the small fetus >95th percentile may indicate a more severe case. Donepudi *et al.*[45] reported that the use of this new definition could help to detect more sFGR cases and that it was a sensitive predictor of donor demise after fetoscopic laser surgery when complicated with TTTS. More trials are needed to validate Khalil and colleagues'[40] consensus before they can be widely used

in clinical practice to make advances in fetal surveillance, counseling, and management.

Management of the co-twin in single intrauterine demise (sIUD)

sIUD can be caused by TTTS, maternal disorders, abnormal umbilical cord and placenta, or congenital abnormalities. It affects 6% of twin pregnancy[46] and leads to adverse outcomes such as cotwin demise, preterm delivery, and neurological impairment. The impact on the cotwin following sIUD is usually worse in MC twins because of the independent fetoplacental circulation, especially when the sIUD occurs within 28 weeks of gestation or is complicated by sFGR.[12,46–48] The data show that the risk of cotwin demise is 5 times higher (15% and 3%), and the neurodevelopmental impairment is 13 times higher (26% and 2%) in MC twins than in DC twins.[46,47] However, the aforementioned complications can still occur in DC twins, in which case the patient should be referred to a tertiary center. According to the international guidelines,[7,12,31] when sIUD occurs before the surviving cotwin is viable, immediate delivery of the surviving fetus is not advised because the brain damage has probably occurred. A serial fetal Doppler examination should be performed to assess for fetal anemia, in particular MCA-PSV in the surviving fetus. If necessary, magnetic resonance imaging (MRI) should be performed 4 to 6 weeks later after fetal demise.[12,31] However, Shinar *et al.*[49] found that although increased MCA-PSV may be a poor predictor of cerebral injury, early MRI within 2 weeks of sIUD is valuable to identify any cerebral injury with additional diffusion-weighted imaging. Thus, conservative surveillance is suggested when sIUD occurs prematurely, but the utility of MRI with diffusion-weighted imaging to detect brain injury needs more clinical trials.

Staging and management of TTTS

TTTS occurs in 10% to 15% of all MC diamniotic (MCDA) twins.[4] It is a severe complication leading to hypovolemia, oliguria, and oligohydramnios in the donor and hypervolemia, polyuria, and polyhydramnios in the recipient. The general consensus about the diagnostic criteria is based on the discordance of AFV: the donor twin has the deepest vertical pocket (DVP) of <2 cm (oligohydramnios) at any gestational age, and the recipient twin has a DVP of ≥8 cm (polyhydramnios) at ≤20 weeks and ≥10 cm after 20 weeks of gestation.[12] A recent study investigated DVP in MCDA twins throughout the gestation and established a reference range for AFV. The authors sought out that the DVP in MCDA twins varies with gestational age and increases between 16 and 26 gestational weeks.[50] The data show that the 97.5th centile of the DVP is 7 cm before 16 weeks' gestation, which increases to 8 cm after 18 weeks. Therefore, Khalil[51] recommends a lower DVP cutoff value (≥6 cm) to identify polyhydramnios before 18 weeks.

As is well known, the Quintero staging system is the most commonly used classification system of TTTS in the last two decades. However, this system is not a representation of the chronological evolution of the disease, and its prognostic value is contentious. A recent retrospective analysis showed a stage-related perinatal outcome. The rates of double survival and at least one survivor are significantly higher in cases of stage I and II when compared with those in cases of stage III and IV. But the overall survival rates between stages I *vs.* II and those in stages III *vs.* IV is not significant different. The study concluded that the staging system may have no necessity to differentiate between stages I and II *vs.* stages III and IV.[52]

Because unbalanced blood flows through placenta vascular anastomoses, cardiovascular dysfunction may occur in TTTS because of severe fetal hemodynamic instability, especially in the recipient. The Children's Hospital of Philadelphia (CHOP) has developed a score to evaluate fetal cardiac function. Gapp-Born *et al.*[53] found that higher CHOP scores (≥3) and myocardial performance index *z* score (>1.645) may be the predictors of recipient fetal loss. However, the studies investigating the CHOP cardiovascular score are still limited.[53,54] More observational and prospective studies are needed to validate the prediction value of cardiovascular parameters and improve Quintero's classification.

TTTS is a severe condition, and patients with TTTS should be referred promptly to a fetal medicine center. The treatment methods include laser coagulation, amniodrainage, selective fetal reduction, and conservative management. A randomized controlled trial has proven that the Solomon technique can significantly reduce postlaser TAPS and recurrence of TTTS, but the survival rate after the procedure is similar to standard laser coagulation.[55] Recently, an international randomized trial suggested that expectant management with heightened weekly surveillance is a reasonable option compared with immediate surgery for asymptomatic women with a long cervix in stage I TTTS before 26 weeks' gestation.[56]

More large-scale clinical trials are needed to validate a lower DVP to diagnose polyhydramnios in early pregnancy and the cardiovascular function in TTTS to modify the diagnostic standards and classification of TTTS. Laser therapy is the best available option for TTTS at Quintero staging II and greater; however, unexpected progression of TTTS stage I leads to challenges in fetal therapy and laser therapy in TTTS stage I is hence still controversial.[15]

Diagnosis and management of TAPS

TAPS is caused by the slow and chronic unbalanced fetofetal transfusion through minuscule placenta anastomoses, leading to anemia in the donor and polycythemia in the recipient, without differences between AFVs.[57] Because prenatal ultrasound has a good predictive value, the antenatal diagnosis of TAPS is based on the discordant fetal Doppler measurements.[58] According to the ISUOG guidelines,[10] the criteria are recommended as MCA-PSV >1.5 multiples of the median (MoM) in the donor and MCA-PSV <1.0 MoM in the recipient. In a recent study, a group of maternal-fetal medicine specialists proposed a consensus-based diagnostic criteria through the Delphi procedure. They agreed on the combination of MCA-PSV ≥1.5 MoM in the donor and MCA-PSV ≤0.8 MoM in the recipient or MCA-PSV discordance ≥1.0 MoM to diagnose TAPS.[59] Because ΔMCA-PSV is related to the intertwin hemoglobin difference, it seems a better antenatal indicator of TAPS. Several cohort studies show that an intertwin MCA-PSV discordance >0.5 MoM may be more sensitive to identify TAPS and proposed a new classification system of TAPS according to ΔMCA-PSV.[57,60] However, the evidence of modified prenatal diagnostic criteria is still insufficient, given the relatively low incidence of TAPS.

Treatment options for TAPS include expectant management, preterm delivery, intrauterine blood transfusion, selective feticide, and fetoscopic laser surgery. Intrauterine blood transfusion can be considered for severe anemia, but the possible adverse effect is deterioration of the polycythemia-hyperviscosity syndrome in the recipient twin.[57] Selective feticide can be the option in severe early-onset TAPS.[57] Laser surgery is the only causal treatment, but the recurrence rate after the procedure is 15%, which is higher than that for TTTS (1%).[57] There is still no consensus about the outcome and optimal management of TAPS.[57] Therefore, treatment choices should be individualized and discussed with the parents.

Strengths and limitations

This review aimed to refine the problems based on the latest FIGO guidelines and compared and summarized the international guidelines and clinical studies, for example, the pitfalls of chorionicity determination, essential parameters for monitoring and management of twin pregnancy, and the inconsistent diagnosis or intervention protocol for specific complications. At present, these issues remain unsolved in China. This prompts clinicians and researchers to propose stronger evidence and convincing opinions to improve specific clinical guidelines. It can benefit clinicians not only in China but also across the world.

The main weakness is that this review should be viewed using a dialectical perspective, as it is mainly based on the studies and guidelines around the word, especially in Western developed countries.

Conclusion

The FIGO practice guidelines highlight the importance of the accurate and early determination of gestational age and chorionicity, demonstrate the prenatal screening for chromosomal abnormalities, and provide routine ultrasound assessment and optimal management for pregnancy complications in twin pregnancy. The referral to a tertiary center is necessary.[61] However, there are still many challenges and controversies that remain unaddressed. For example, the cutoff value of cervical length to define increased risk of preterm delivery still requires validation, and the effective preventive strategy for preterm birth warrants further confirmation. Furthermore, increased efforts are needed to find a better way of ultrasound surveillance in twin pregnancy to identify the abnormalities in a timely and effective manner. The standard diagnostic criteria and superior management of specific complications remain controversial. The studies about the predictive indices for specific complications in an early gestational age are also important. More randomized controlled trials, cohort studies, or consensuses are needed to resolve these issues and establish consistent international protocol to improve the outcome of twin pregnancies.

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Author Contributions

Jingyu Liu: Conceptualization, Methodology, Evidence collection, Data/Evidence Analysis, Writing-Original Draft; Quanrui Liu: Data/Evidence collection, Writing - Original Draft; Jingya Zhao: Validation, Writing – Review & Editing; Danlun Li: Data/evidence collection; Yi Zhou: Idea & Conceptualization, Funding Acquisition, Supervision, Project Administration, Writing - Review & Editing.

Conflicts of Interest

None.

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