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Highlights from the International Twins Congress 2021

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To editor:

The Twins Congress (TC) 2021 took place in Beijing (China) from June 4–6, 2021. The TC was organized jointly with the International Society for Twin Studies and held in conjunction with the Fifth Joint World Congress on Twin Pregnancy. This was the first time the TC had been held in Asia.

The TC was chaired by professors Gian Carlo Di Renzo (Italy), Jeffrey Craig (Australia), Asma Khalil (United Kingdom), and Ruben Quintero (United States). The local host was Professor Huixia Yang. Other members of the International Advisory Committee included professors Liona Poon (Hong Kong SAR, China), Jose Luis Bartha (Spain), Roberto Romero (United States), Gerard H.A. Visser (the Netherlands), and Tak Yeung Leung (Hong Kong SAR, China).

The TC was held in collaboration with *Maternal-Fetal Medicine*. Sixty-eight experts from more than 20 countries were invited to give lectures addressing various aspects of twins and twin studies. The TC included four pre-TC workshops, three keynote talks, and 15 parallel sessions on diverse twin-related topics concerning: the growth and therapy of fetuses, perinatal mortality and morbidity, genomic studies and psychological research on twins, large collaborative studies in twin birth cohorts, and careers in twin research. This article summarizes selected highlights from selected sessions of the TC.

Fetal growth in a twin pregnancy

A pre-TC session was devoted to topics in the study of fetal growth in a twin pregnancy (TP). Katia Bilardo (the Netherlands) delivered a lecture on the standard of assessment of fetal growth in a multiple pregnancy based on Practice Guidelines set by the International Society of Ultrasound in Obstetrics and Gynecology.[1] Gerard H.A. Visser cited works about fetal growth and fetal birthweight in twins and the risk of perinatal and long-term adverse outcomes. He indicated that the best growth rate and size at birth in dichorionic diamniotic twins should be approximately 90th centile, similar to that in singleton pregnancy (SP). However, data on monochorionic (MC) diamniotic twins are more difficult to interpret. Nir Melamed (Canada) recommended using a growth chart for twins to assess fetal growth. His reasoning was that using a growth chart for twins during pregnancy to evaluate fetal growth was more clinically relevant for the diagnosis of small for gestational age infants and unlikely to miss cases at risk of stillbirth. Asma Khalil described selective fetal growth in MC twins. She indicated that survival from selective fetal growth restriction (sFGR) differs according to type and that type II (absent or reversed end-diastolic flow) has the highest risk and worst outcome. In addition, the risk factors for intrauterine fetal death from sFGR are early gestational age at onset and absent or reversed end-diastolic flow. Furthermore, the delivery of sFGR babies should balance the risk of intrauterine fetal death and prematurity.[2] Ramen H. Chmait (United States) cited his work on fetal growth after laser therapy for twin-twin transfusion syndrome (TTTS). He showed that laser therapy can elicit improvement for weight discordance in twins and reduce the risk of donor fetus intrauterine growth restriction (IUGR).[3]

Perinatal mortality and morbidity in a multiple pregnancy

Gerard H.A. Visser delivered a lecture on perinatal mortality in twins. He noted that perinatal mortality is higher in a TP than in a SP because twins carry a higher risk of preterm birth, FGR, and TTTS-related problems. However, the prevalence of perinatal mortality is substantially lower for twins born before 37 gestational weeks than for singletons after correction for gestational age at delivery. Thus, the overall increased perinatal mortality in twins is due mostly to the high prevalence of preterm birth. Paradoxically, if they stayed longer in utero, then more fetuses may die.[4] Jose Luis Bartha delivered a lecture illustrating that placental size, cord insertion, anastomoses, or placental sharing rather than vascular malperfusion (maternal or fetal) are the most important factors related to a complicated TP. Using examples, he also illustrated that studies of placental function might shed light on the pathogenesis and new biomarkers for the prediction and better management of complications in twins. For example, studies on DNA methylation have demonstrated that IUGR in MC twins is associated with impairments in lipid metabolism and transcriptional regulation of the placenta.[5] Li *et al*.[6] showed that expression of lectin and the mannose

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6-phosphate receptor (which are important for angiogenesis and fetal growth) in the endoplasmic reticulum was increased significantly in the placenta of a selectively growth-restricted twin of a MC twin pair. Asma Khalil summarized the guidelines on management of a TP set by the International Federation of Gynecology and Obstetrics (FIGO).[7]

Prenatal screening and diagnosis

Maria del Mar Gil Mira (Spain) discussed cell-free DNA testing in a TP. She indicated that for screening of aneuploidies in a TP, the risk of aneuploidies is identical for each fetus for monozygotic twins, so screening methods should be as those done in a SP. However, the risk of aneuploidies is different for each fetus for dizygotic twins, and three management options are available: (1) measure the total fetal fraction and set a cutoff for failure at a higher level than that for a SP; (2) measure the fetal fraction separately for each fetus and set a cutoff level with the lowest fraction; and (3) conduct the test as a SP. She indicated that in a TP, the best screening method for trisomy 21 is the cell-free DNA test in maternal blood combined with ultrasound in the first trimester. Katia Bilardo noted that a woman with a TP is at an increased risk of fetal demise, chromosomal anomalies, structural anomalies, and pregnancy complications, so early determination of chorionicity is very important. Furthermore, detection of structural abnormalities in a TP in the first trimester using ultrasound is similar to that done in a SP. MC twins with increasing discordance in crown-rump length and nuchal translucency are associated with a fetal structural abnormality, so MC twins should be offered a detailed early scan in a specialized center. Liona Poon discussed research about the prediction and prevention of major obstetrical syndromes in a TP in the first trimester, including screening for trisomy 21 by nuchal translucency, progesterone for reducing the prevalence of preterm birth, and aspirin for prevention of preeclampsia.

Periconceptional aspects of a multiple pregnancy

Roland Devlieger (Belgium) indicated that compared with a SP, the resting energy expenditure of the mother is approximately 10% higher in a TP, which results in a 40% increase in caloric requirement. In health, a TP requires increased energy intake in the first trimester of 200 kcal/d compared with that in the nonpregnant state and an increased energy intake of 500 kcal/d in the second trimester and third trimester, respectively. Twenty percent of the energy should come from protein and 40% each from carbohydrates and lipids. In addition, according to the gestational weight gain (GWG) for women with twin gestations recommended by the US Institute of Medicine, normal-weight women (body mass index (BMI) = 18.5–24.9 kg/m^2) should have 16.8 to 24.5 kg of GWG, overweight women (BMI = 25.0 to 29.9 kg/m^2) should have 14.1 to 22.7 kg of GWG, and obese women (BMI >30 kg/m^2) should have 11.4 to 19.1 kg of GWG.[8] Gian Carlo Di Renzo (Italy) noted that nutritional status and the maternal diet are key elements for the short- and long-term health outcomes of mother and offspring. However, at present, studies and recommendations focused on micronutrient status in a multiple pregnancy are lacking, and national and international guidelines for maternal nutrition in a TP are needed. He also emphasized the strong causal link between maternal iron-deficiency anemia and adverse birth outcomes.

The FIGO[9] recommends that all pregnant women should take continuous or intermittent iron supplementation (30 mg/d; 1–3 times per week) by the first prenatal visit to prevent anemia at term, and women with iron-deficiency anemia (defined as hemoglobin level <11 g/dL) at any stage should receive additional iron supplementation of 30 to 120 mg/d until anemia is corrected. Huixia Yang (China) discussed the metabolic characteristics of glucose in a TP. She indicated that a TP is associated with an increased risk of gestational diabetes mellitus[10,11] and that gestational diabetes mellitus during a TP might be associated with long-term simple cardiovascular events in the mother.[12] In addition, although accelerated fetal growth in a TP with gestational diabetes mellitus is unlikely to have short-term implications, it might be associated with fetal programming and long-term metabolic complications, including obesity, diabetes mellitus, and cardiovascular disease.[13] Furthermore, data regarding the diagnostic thresholds for gestational diabetes mellitus, the benefits of glycemic control, and optimal glycemic targets in a TP are lacking.

Preterm birth and prematurity

Eduardo Fonseca (Brazil) reported studies on progesterone for the prevention of preterm birth in twins. He concluded that progesterone may reduce the risk of preterm birth before 32 gestational weeks in a TP for a woman with a cervical length less than 30 mm. Hence, clinicians should continue to carry out universal transvaginal screening for cervical length at midtrimester in women with a TP to ascertain whether intervention is needed.[14–16] Vincenzo Berghella (United States) continued the discussion on preterm birth prevention in a TP. He focused mainly on use of a cervical cerclage or pessary. His literature review suggested that a cervical cerclage or pessary had no influence in preventing preterm births in twins if the mother had a normal cervical length. Most data show that use of a cervical cerclage in a woman with a cervical length less than 25 mm carrying twins is not advantageous and might increase the risk of preterm birth. However, there are limited data indicating that use of a cervical cerclage before 24 gestational weeks in a woman with a cervical length less than 15 mm carrying twins may have a positive effect.[17–20] Gerard H.A. Visser indicated that corticosteroids and magnesium sulfate are recommended for women carrying twins to prevent fetal respiratory distress syndrome, provide fetal neuroprotection, and should be used as in an SP. He emphasized that MC twins are at increased risk of perinatal complications, so chorionicity should be determined in early pregnancy and MC twins should be referred to a tertiary center. Simon Lam (Hong Kong SAR, China) explained the acute and long-term complications of preterm twin newborns. He indicated that obstetric management (close monitoring of fetal growth, maternal blood-pressure control, maternal blood-glucose regulation, timing of delivery) was important to ascertain the possibility of complications and risks of prematurity. Moreover, postnatal nutritional management could mitigate long-term cardiovascular and metabolic risks for preterm twin newborns. In addition, long-term management of twins with severe IUGR needed to account for the altered growth trajectories and tempo of puberty.

Care in labor and delivery of twins

Diogo Ayres do Campos (Portugal) talked about intrapartum monitoring and care in twins. He emphasized that

cesarean section should focus on monoamniotic, first-twin breech, and much larger second-twin cases. Usually, a vertex first twin can be delivered safely through the vagina. Moreover, during intrapartum, continuous cardiotocography (CTG) with dual-channel monitoring should be used. In addition, after delivery of the first twin, the fetal position of the second twin should be evaluated immediately by ultrasound and should be maintained in a longitudinal lie, and CTG should be restarted immediately. If there is abnormal CTG or excessive interval of twin-twin delivery (30–60 minutes), high vacuum, internal podalic version, breech extraction, or cesarean section should be undertaken. Therefore, simulation-based training is important for clinicians to gain expertise and confidence.

Tak Yeung Leung (Hong Kong SAR, China) indicated that based on retrospective studies, the optimal week of delivery is 37^{+0} to 37^{+6} weeks for a low-risk dichorionic diamniotic TP, 36^{+0} to 36^{+6} weeks for a low-risk MC diamniotic TP, and 33^{+0} to 33^{+6} weeks for an MC monoamniotic TP. Jon Barrett (Canada) delivered a lecture on induction of labor in twins. He pointed out that the most common indication for induction of labor in twins was gestational age, and the potential advantage was reduction in perinatal morbidity and mortality. He also noted that clinicians should consider delivery at 36^{+0} to 36^{+6} weeks in MC twins and at 37^{+0} to 37^{+6} weeks in dichorionic twins. He cited works showing that women with a TP undergoing induction of labor carry a similar risk of cesarean section and a similar duration of labor with women with a SP undergoing induction of labor.[21] Anton Mikhailov (Russia) discussed management of postpartum hemorrhage in a TP. He emphasized that teamwork between obstetricians, anesthesiologists, and nurses is crucial for postpartum hemorrhage management. Bleeding control is the main task, so dynamic control of blood loss at each stage and immediate transition to the next stage is very important. Huixia Yang discussed placenta accreta spectrum (PAS) disorders and their management in China, including the stage classification of PAS and consensus guidelines on PAS disorders in China. She also shared her experience on the surgical methods for PAS.

Twin-related complications and special issues

Seshadri Suresh (India) delivered a lecture on the outcomes of a complicated TP and emphasized how to counsel parents. He noted that clinicians should provide detailed counseling, give information on therapy choice to couples, and need to be supportive in the decision made by the couple. Aris Antsaklis (Greece) continued the topic and discussed the Committee Opinion of the American College of Obstetricians and Gynecologists on multifetal pregnancy reduction.[22] Luming Sun (China) discussed FGR features in a TP. She indicated that confirmation of gestational age and chorionicity must be clarified first when evaluating FGR in twins. Then, detailed anatomic ultrasound should be undertaken to detect structural anomalies. Next, evaluation for genetic anomalies or other risk factors (eg, infection, maternal complications, MC complications) should be carried out. She also summarized that ultrasound has a key role in looking for the etiology, diagnosis, and management of FGR in twins. Ruben Quintero (United States) delivered a lecture on care of MC monoamniotic twins. He indicated that monoamniotic twins have an associated increased risk of perinatal mortality. Cord entanglement is responsible for a large proportion of the attendant perinatal loss. Marked constriction of the cord may be detected by Doppler ultrasound of umbilical arteries. Medical amnioreduction may help prolong these pregnancies and improve outcomes, and surgery should be offered as a last resort.

Seshadri Suresh discussed TTTS in triplets. He noted that for dichorionic triplets, early fetal reduction of the MC pair should be considered, whereas for MC triplets, fetoscopic laser ablation is feasible. However, technical challenges exist and expertise is needed. Haruhiko Sago (Japan) talked about the risks of the Solomon method for TTTS by citing his own work.[23] He showed that the Solomon method led to superior survival outcomes and was the first-line surgical choice for TTTS. However, the Solomon method increased the prevalence of placental abruption, preterm premature rupture of the membranes, and fetal growth impairment, and the total laser energy was associated with preterm premature rupture of the membranes. Thus, close attention to adverse events is required for perinatal management after fetoscopic laser surgery to treat TTTS using the Solomon method. Valentina Tsibizova (Russia) recommended fetal echocardiography in all MC twins and that laser coagulation should be done before deterioration of cardiac function in TTTS. In addition, follow-up imaging in the event of TTTS and postnatal cardiac evaluation in all TTTS survivors were very important.[24,25]

Keynote lecture

Roberto Romero delivered a keynote lecture on the first day of the TC entitled "Great obstetrical syndromes and their consequences on the mother and perinate." He noted that the goal for the 21st century is to develop a new taxonomy of disease informed by its mechanism because then the causes of the disease can be understood and appropriate therapies developed. Obstetrical complications are syndromes with more than one cause, which is they are termed "great obstetrical syndromes." The unique features of great obstetrical syndromes are (1) multiple causes, (2) long preclinical phase, (3) fetal involvement, (4) adaptive in nature, and (5) the result of complex interactions between the maternal and fetal genome and the environment.[26,27] Development of a new taxonomy of obstetrical disorders based on understanding of the causes of each syndrome is a challenge. Discovering biomarkers is encouraged because it contributes to development of screening programs and making early interventions. Roberto Romero emphasized that obstetrics will become the most exciting discipline in medicine because it is the most complex subject with patients who are "invisible and inaccessible." Imagination and intelligence are needed to identify the biomarkers and early interventions to predict adverse pregnancy outcomes.

Gerry H.A. Visser and Juliet Butler presented their keynote lecture on the second day of the TC entitled "Rh disease still a burden: FIGO guidelines and call for action" and "Phenotypic difference in a scientifically studied pair of conjoined twins," respectively. Gerald H.A. Visser noted that rhesus disease results in more than 160,000 perinatal deaths and 100,000 cases of disability annually, which represents a reduction of only 50% relative to the era before immunoglobulin administration. He discussed measures to prevent sensitization to rhesus disease based on new guidelines for preventing rhesus disease proposed recently by FIGO/International Confederation of Midwives.[28] Juliet Butler noted that phenotypic discordance in MC twin pairs

is rare. There is limited knowledge regarding pathogenesis. The precise mechanisms causing discordance are not known, but genetic (chromosomal, single-gene defects, epigenetics (including differential methylation and imprinting)), and environmental (cell number at division, vascularity, placental attachment, embryonic signaling, postnatal experiences) factors might contribute to the distinct features of MC twins. Future studies should continue reporting and investigating such cases to aid deeper understanding of the mechanisms of twinning and implications for human diseases.

Other sessions held during the TC shared information on studies on genomics, psychology, and imaging, as well as large collaborative studies in twin birth cohorts. The TC was a successful gathering of scientific researchers, medical personnel, and representatives of multiple-birth organizations worldwide. We look forward to the next TC.

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Conflicts of Interest

None.

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