The Role of Ultrasound in Multiple Pregnancy

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The advances in reproductive technologies have changed the demographics of multifetal pregnancies. In the first trimester, ultrasound allows to diagnose the number of multiples, chorionicity and amnionicity, the presence or absence of nuchal translucency, early growth discordance, severe malformations and the origin of activities and contacts between multiples. In the second and third trimester, the opportunity to examine the cervix by transvaginal ultrasound should not be missed to detect the risk of premature delivery. Ultrasound is essential for the early grading and treatment of twin-to-twin transfusion syndrome (TTTS), the diagnosis of malformations and growth disturbances. Doppler velocimetry has proven to be able to reduce perinatal mortality in twin pregnancies. Finally, ultrasound is used for the detection of the position of multiples and the decision of the optimal route of delivery. This is of main importance in delayed interval delivery and expectant management of multifetal pregnancies and early cervical dilatation.

The clinical need for ultrasound is much greater in multiple than in singleton pregnancies. At present, the diagnosis of a multiple pregnancy is easily made with ultrasound. Once established, this diagnosis presents concern to parents and physicians alike: Patients typically want to know the likelihood of having healthy children. Physicians want to understand the mechanisms of twinning, the risks of poor growth, discordant and concordant aberrations and specific risks associated with monochorionic (MC) pregnancies or the optimal route of delivery, among other things. Because the most common cause of poor outcome among multiplets is preterm delivery, the examination of the cervix by transvaginal sonography (TVS) has become an issue of prenatal care. At the same time, the concern is directed not only towards intact survival but also towards long-term neurological and mental health. Ultrasound techniques ideally represent functional examinations of fetal hemodynamics (Doppler) and behavior that can be stored by video tapes or computer hardware. This capability offers new possibilities for studying development and the continuity from prenatal to postnatal life. Ultrasound examinations are a link between pre- and postnatal life especially as viewed as a continuum, the last examination depending on the previous one and imaging being combined with functional tests at the end. The division described below in the different sections is merely pragmatic.

First Trimester Ultrasound Examination

Number

A mere 25 years ago, more than 50% of multiple pregnancies were undiagnosed until labor. With the introduction of ultrasound, such occurrences are rare indeed. Advantages of universal early ultrasound screening, compared with a selective use, include the more accurate calculation of gestational age, diagnosis of non-viable pregnancies, detection of unsuspected malformations and the earlier identification of multiple pregnancies (twins undiagnosed at 26 weeks, odds ratio 0.08, 95% confidence interval 0.04 to 0.16; Neilson, 2001). Although an earlier detection of multiples has not been translated into significant improvements in outcome, the continuing high perinatal mortality rate associated with all orders of multiple pregnancy is a legitimate reason to perform additional studies in subgroups with multiple gestation and varying chorionicity!

For determining the number of multiples, the number of gestational sacs or yolk sacs can be misleading. Counting the number of fetuses relies on the detection of heart activity beating at 80–100 bpm at 6 weeks, up to 180 bpm at 9 weeks and then declining somewhat (Arabin, Mohnhaupt, et al., 1998).

The phenomenon of a disappearing fetus in first trimester multiple pregnancy was originally referred to as the *"vanishing twin syndrome"*. Currently, the preferred terminology is natural fetal reduction; both terms describe the spontaneous cessation of cardiac activity of a multiple pregnancy. Ultrasound studies support that the rate of multiple gestation is higher after conception than at delivery. The "take-home baby rate" was evaluated after artificial reproductive techniques (ART). The chance of delivering twins after two chorionic sacs were seen was 57%, with two viable embryos it was 87%. Similarly, with three gestational sacs, the chance of a triplet birth was 20%, and with three viable embryos it was 68% (Dickey et al., 1990). Early ultrasound "mapping" of the fetuses is of particular importance when invasive prenatal diagnosis is performed and when reduction is considered as an option.

Chorionicity and Amnionicity

Early diagnosis of membrane status is invaluable for antepartum surveillance and labor management. The diagnosis may be tedious thereafter. Multiple gestation can result from the fertilization of separate ova by different sperms resulting in dizygotic (DZ) or "higher zygotic" mul-

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https://doi.org/10.1375/twin.4.3.141 Published online by Cambridge University Press

tiples. The splitting of an already fertilized ovum results in monozygotic (MZ) twins. The rate of DZ twinning is influenced by maternal age, parity, heredity, ethnicity and ART. The rate of MZ twinning is thought to be constant throughout the world, but also seems to be influenced by ART (Blickstein et al., 1999). All DZ pregnancies are dichorionic diamniotic (DCDA). If an embryo splits at less than 4 days postfertilization, the result is DCDA, if it splits between day 4 to 7, it is a monochorionic diamniotic (MCDA) and between 8 and 13 days gestation, the result is a MCMA gestation. Splitting thereafter results in conjoined twins. The development of the *chorion* precedes that of the amnion; chorionic sacs can be imaged as early as 4–5 postmenstrual weeks appearing as a thick hyperechoic rim. With advancing gestation, the chorion laeve of the two sacs forms a triangular insertion ("lamda sign"). The DCDA inter-twin membrane consists of four compared to two layers formed in MCDA gestation (Figure 1). Two placentas are only seen in about one third of DCDA twin pregnancies but more often appear to be fused. The *amnion* is visualized between 7 and 8 weeks. In a MCDA multiple gestation, the junction of the amniotic sacs with the outer wall creates a "T-sign" at an approximately 90° angle (Figure 1). In MCMA pregnancies two or more embryos are seen in a single sac which can be reliably diagnosed at 8 weeks. *Yolk sacs* are located in the extraembryonic space attached to the embryo by the yolk stalk that contains blood vessels until around 8–9 weeks of gestation. Once the pregnancy reaches 10 weeks however, the extraembryonic space is progressively obliterated due to growth of the amniotic cavity. In MA twin pregnancies, only one (large or irregular) yolk sac may be diagnosed thus signifying a late division (Bromley & Benacerraf, 1995).

Umbilical Cord

Cord anomalies are seen with an increased frequency in multiple gestations. A *single umbilical artery* carries the same rate of associated anomalies as that of a singleton pregnancy (Benson & Doubilet, 1991). Visualization of cord insertion should be performed as early as possible. *Velamentous cord insertion* is observed in approximately 7% of twin pregnancies and regarded as "a rule" in triplet pregnancies. It is seen in more than 60% of pregnancies with TTTS versus 18.5% of those without the syndrome. In most cases of MA multiplets, *cord entanglement* is present from the first trimester of pregnancy (Arabin et al., 1999). It can be suspected by use of color Doppler. The diagnosis is established when arterial Doppler spectra with different heart rates are demonstrated within a small Doppler window (Arabin et al., 1999). Recently, it was concluded that the cause of unpredictable death in MA twins is more likely to be acute TTTS than cord entanglement because the close insertions of the cords into the placenta often are associated with large-caliber anastomoses and an imbalance in the two circulations leading to sudden fetal death (Sebire et al., 2000).

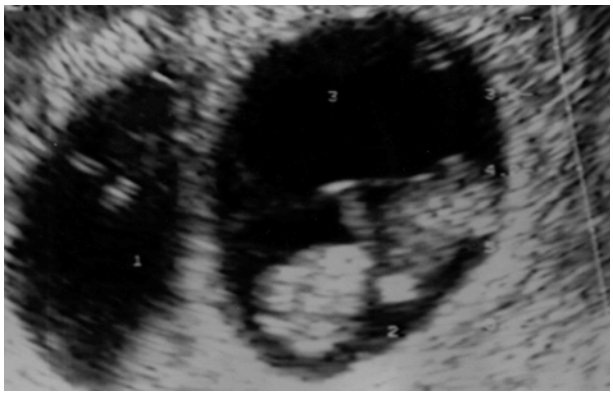

Figure 1

DCTA triplet pregnancy at 11 weeks. The separating membranes are thick and echogenic between triplet 1 and 2/3 with a triangular insertion ("lamda sign") and thin and hair-like with an insertion at around 90° between triplet 2 and 3 ("T-sign"). Two separate amnions are in the process to fuse.

Nuchal Translucency

A combination of maternal age and fetal nuchal translucency (NT) thickness is indicative for chromosomal aberrations and severe abnormalities. In DC twins, the sensitivity of NT determination is comparable to singleton pregnancies. However, the prevalence of increased NT is higher in MC multiple pregnancies where it is associated with adverse outcome mainly due to the development of severe TTTS (Sebire et al., 1996). Reverse end-diastolic flow in the ductus venosus (DV) may also predict TTTS mainly in combination with increased fetal nuchal translucency (Matias et al., 2000). Sebire et al. (1997) reported on the poor prognosis in cases with diaphragmatic hernia when NT had been observed in the first trimester. Accordingly, we observed increased NT in two MZ triplets of a DCTA triplet set. In both MZ triplets, we found normal DV blood flow but abnormal breathing patterns at 12 weeks; severe diaphragmatic hernia was diagnosed later. Both triplets died postnatally due to lung hypoplasia, the DZ triplet survived. This example stresses the complexity of NT determination in multiple gestation.

Early-Onset Discordant Fetal Growth and Early Anomalies

Discordance between multiples or gestational sacs in the first trimester of > 3 mm has been associated with an embryo loss rate of > 50% (Dickey et al., 1992). Discordant growth, as a difference in crown rump length (CRL) of > 5 days were reported associated with major anomalies and therefore represent an indication for further detailed survey (Weissman et al., 1994). In our center, we encountered 5 multiple pregnancies in which a discordance of > 5 days was observed in the first trimester. Of these, one triplet set underwent spontaneous reduction from 11 weeks onwards, in one twin pair a triploidy xxx was diagnosed by CVS at 11 weeks. In the other 3 multiple pregnancies, discordance continued throughout pregnancy, — but no significant anomaly could be detected. All these 3 out of 5 pregnancies originated from ART.

The type of malformations can be divided into those unique to mainly MC multiplets and those not unique to multiple gestation but affecting multiples and mainly MC multiples at an increased rate. *Conjoined twins* occur with an incidence of 1/33 000 to 1/165 000 (Benirschke & Kim, 1973). Ultrasound in the first trimester is essential since

https://doi.org/10.1375/twin.4.3.141 Published online by Cambridge University Press

survival depends on the type of union, shared organs and associated anomalies.

Twin reversed arterial perfusion syndrome (TRAP) or acardiac twin is reported to have an incidence of 1/30000 deliveries or 1/100 of MZ twins (Benirschke & Kim, 1973). The perfused twin may demonstrate absence of the head, heart and upper extremities. The perinatal mortality of the pump twin was originally thought to be > 50%, and now depends on the success of antenatal therapy (e.g., laser occlusion of the cord of the perfused twin). Chromosomal abnormalities are common. We observed a case with TRAP as early as at 10 weeks by TVS and followed the pregnancy by weekly ultrasound and color Doppler to demonstrate the reverse perfusion. At 11 weeks, fetal heart rate and movements of the pump twin decreased. At 12 weeks, intrauterine death was diagnosed and pregnancy was terminated.

Heterotopic pregnancies with unilateral or bilateral ectopic, cornual, ovarian, abdominal or cervical and intrauterine singleton, twin or triplet pregnancy may occur with increased frequency in patients with ART. TVS is essential for the differential diagnosis and the choice of treatment.

Among malformations not unique to multiples combinations are seen which can be categorized as discordant or concordant in terms of presence, type and severity in both DZ or MZ multiples. In the first trimester, anencephaly is the predominant concern.

Second and Third Trimester Ultrasound Examination

According to the Cochrane database, there is no evidence that routine ultrasound in the second or third trimester improves outcome in a total group of pregnancies. As a result of this review, it is unclear in to what extent ultrasound may be valuable in multiple gestation (Bricker & Neilson, 2001). Having said this however, clinicians may find many uses for ultrasound in individual cases. Gender detection can help to detect DZ (DC) multiplets if the opportunity for early diagnosis of chorionicity status had been missed. Surveillance should be performed at closer intervals (we recommend 2 weeks) in MC compared to DC pregnancies where the interval depends on the results of previous examinations.

Growth

A "physiologic" slowing of growth is reported in multiple compared to singleton gestations during the third trimester. It is more pronounced in triplets compared to twin gestations. In addition, the incidence of pathologic growth restriction is increased in multiple gestation compared to singletons. This phenomenon is quite distinct from aberrations and might be due to placental crowding and poor placentation site. Ultrasound plays a key role in detecting growth differences. It is questionable whether discordance can be regarded as an outcome variable by itself. Doppler velocimetry throughout gestation may reflect underlying causes of poor growth and can help to differentiate whether growth discordance is of clinical importance. When Doppler results of the umbilical artery were made available to clinicians, perinatal mortality of twin gestations decreased (Giles et al., 1988). Meanwhile, Doppler is applied in various fetal arteries and veins. Growth disturbances in MC gestation can be indicative for TTTS when associated with oligohydramnios/polyhydramnios and Doppler is essential for staging the severity.

Twin-To-Twin Transfusion Syndrome (TTTS)

Each year around 1000 MZ twins are born in the Netherlands, out of these, about 70% are MC and 15–25% of those develop chronic TTTS. The placental vascular anastomoses connecting different feto-placental circulations are responsible for a gradual net transfusion from the donor to the recipient leading to oligohydramnios, hypovolemia and oliguria in the donor ("stuck" multiple) and to polyhydramnios, hypervolemia and polyuria in the recipient (Benirschke & Kim, 1973). Recent ultrasound studies report on the visualisation of various anastomoses by color Doppler (Machin et al., 2000; Taylor et al., 2000). Ultrasound diagnosis of the fetal condition including Doppler velocimetry and echocardiography is essential, since when one twin dies, the other is threatened by death or severe neurological handicap. Optimal individual therapy presently requires the application of ultrasound criteria for assessment of the severity (staging) of TTTS (Quintero, 1998): *Stage I* includes the oligo-polyhydramnios sequence when the bladder in the donor is still full, *stage II* lacks bladder filling, *stage III* includes pathologic Doppler findings in umbilical arteries, in *stage IV* hydrops of the recipient is present and in *stage V* fetal death has occured. The best individual therapy relates to the severity of TTTS. We have reported on the successful treatment of stage IV TTTS by complete Laser occlusion at 18 gestational weeks (Arabin, Laurini, et al., 1998). Laser ablation of all anastomoses seems to be the only therapy that can cure severe TTTS. Serial amnioreduction may treat mild TTTS, as it can prolong pregnancy until viability and has less procedure related complications. The European Eurofoetus trial, which included three study arms, 1) laser, 2) amnioreduction and 3) randomisation between both methods does not yet include sufficient patients to reach any conclusions (Deprest, personal communication).

Malformations Not Unique for Multiplets

MC multiple gestations contribute disproportionately in the incidence of abnormalities. Discordances in DZ twins are usually due to different genetic predisposition. In MZ multiples, discordances may be a consequence of the underlying stimulus to splitting, variations in gene expression, lateral defects or vascular accidents. We have observed 4 cases with discrepant malformations in MZ multiplets within the past, including a malignant tumor, cardiac anomalies, microcephaly and Beckwith Wiedeman syndrome. In clinical practice, it means that it is not reassuring only to scan one of a set of MZ twins but to follow MC twins both with high accuracy throughout gestation.

TVS of the Cervix

Routine pelvic examination was not shown to be predictive of preterm labor in one large European study that compared two different policies, i.e. to do or not to do cervical examinations at each prenatal visit (Buekens et al., 1994).

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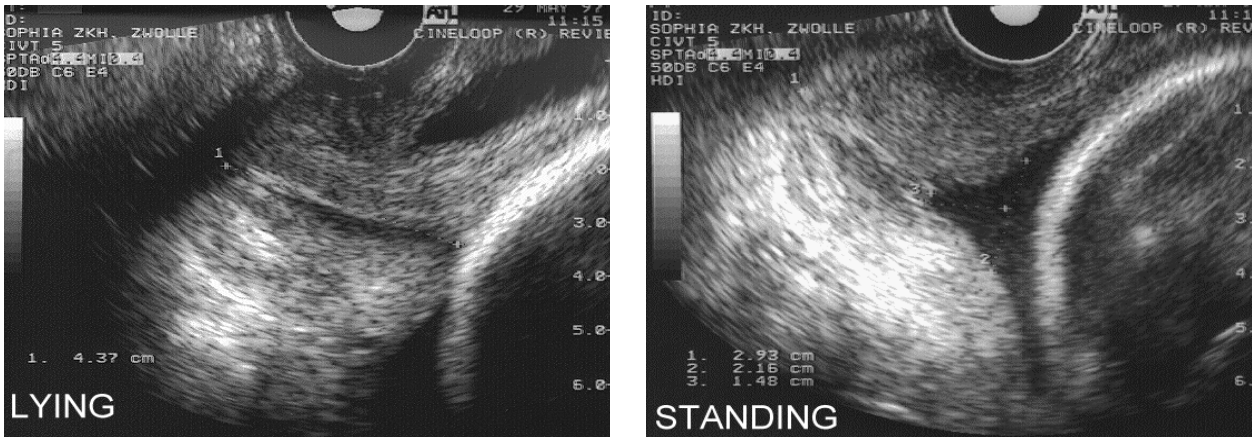

Figure 2

Transvaginal sonogram of the cervix of a twin pregnancy at 26 weeks in a lying (left) and standing (right) position. Note the shortening of the length and the opening of the internal os (right).

Subsequently, TVS of the cervix has been shown to be superior to the digital examination in estimating the risk of premature labor, as it is more objective for both inter-observer and intra-observer comparison. The cervical length, width of the external or internal os (funneling) and to some extent even the position of the cervix in relation to a horizontal line can be determined from ultrasound pictures. In multiple pregnancies, changes of the cervical consistency, length and opening of the internal os occur much earlier than in the average singleton pregnancy. These changes seem to be more significant in a standing position which we use for diagnostic purposes (Figure 2; Arabin et al., 1997). Many studies do not differentiate between gestational age, singleton or multiple pregnancy, maternal position nor the kind of interventions which had been applied to prevent prematurity, but just use one cut-off value for dividing risk and non-risk groups. This was our stimulus to investigate longitudinal sonographic criteria in twin and singleton pregnancies in a vertical and horizontal position. Up to now, *we have found that the funneling in a standing position was the most significant parameter to predict prematurity*.

Intrapartum Management

Having an ultrasound machine in the delivery room is obligatory to prevent unexpected complications during the delivery of multiples. In cases of bleeding the placenta more often reaches or even covers the internal os. In addition, vasa previa is seen 7 times more frequently in multiple gestations thus posing a risk of vessel rupture in labor with potential compromise to the fetus. In delayed interval delivery, TVS should be used to evaluate the cervix (if still present) and the position and condition of the remaining multiples and their cords.

Behavior of Multiplets

Ultrasound scans of multiple gestation are popular because of the enjoyment that parents receive from seeing their babies prenatally and the ability to obtain more comprehensive understanding of their development. Multiple pregnancies are natural models to study the phenomenon of prenatal inter-human contacts contributing to the neurological and psychological development. It is a challenge to detect inter-twin differences or differences between groups of twins which might be provoked by genetic, hormonal or nutritional conditions. We have described behavior of multiplets, the development of their activity, hemodynamics, reactions towards touch, external stimuli and possible influences of intrinsic versus extrinsic variables (Arabin, Mohnhaupt, et al., 1998). In the future, we hope that this tool may be illustrative of the individual neurological development.

Conclusions

Ultrasound can been used as an educational tool for parents emphasising the symptoms of prematurity, poor growth or the onset of TTTS. Parents thereby can better understand the development of their offspring and may change their life style accordingly. Most of our data are based on experiences from 700 twin, 40 triplet pregnancies and one quadruplet pregnancy followed at our unit from 1993–2000. We are grateful to our patients for allowing us to study the variety of problems associated with multiple pregnancy. Their sorrows have been and will continue to be our challenges.

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