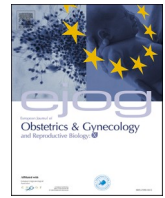




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Clinical guidance VVOG: Antenatal care for twin pregnancies

Subject

This clinical guidance paper focuses on antenatal care for women with twin pregnancies.

Acronyms, explanations and abbreviations

BMI	Body mass index
DA	Diamniotic
DC	Dichorionic
DNA	Deoxyribonucleic acid
DVP	Deepest vertical pocket
EFW	Estimated fetal weight
GCP	Good Clinical Practice
MA	Monoamniotic
MC	Monochorionic
MoM	Multiple of the median
NICE	National Institute of Health
NIPT	Non-invasive prenatal test
MCA PSV	Middle Cerebral Artery Peak Systolic Velocity
sFGR	Selective fetal growth restriction
TAPS	Twin anemia polycythemia sequence
TTTS	Twin-to-twin transfusion syndrome
VVOG	Flemish Society for Obstetrics and Gynecology
VWV	Flemish Working Group on Obstetrics

Background

Introduction

Since the 1990s, the number of twin pregnancies has increased dramatically, mainly due to the increasing use of fertility treatment [1]. In recent years, however, the numbers seem to have stabilized. In Flanders, twins now account for about 1.6 % of all births, one-fourth of which occur after fertility treatment [2].

Twins have higher perinatal morbidity and mortality, mainly due to preterm birth. For example, more than 10 % are born severely preterm (before 32 weeks) compared with only 1 % of singletons [2]. In addition, there are the typical complications of a monochorionic (MC) twin pregnancy where the common blood circulation can cause unique complications such as twin-to-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS).

Twin pregnancies are also associated with higher maternal morbidity, such as pre-eclampsia and gestational hypertension, postpartum hemorrhage and anemia [3]. This guideline summarizes the

most recent evidence surrounding antenatal care in twin pregnancies.

Purpose and target audience

This clinical guidance paper was developed for as a VVOG Clinical Guidance paper for the obstetrician-gynecologist who follows twin pregnancies.

Evidence

Development of the guidance paper

All English-language guidelines from Europe and North America published as of 2017 were searched in Pubmed Guidelines, Guidelines International Network and Guideline Central under the "Mesh Term" "Twin Pregnancy." Three guidelines were found "NICE guideline UK Twin and Triplet Pregnancy", "ACOG Practice Bulletin Twin, Triplet, and Higher-Order Multifetal pregnancies" and the "SOGC Management of Dichorionic Twin Pregnancies" [4–6]. Based on the AGREE-II method [7], each individual guideline was rated as good to very good by the panelists. To adjust existing guidelines, the ADAPTE tool was used [8]. S. van der Heijden and L. Lewi reviewed the recent literature. L. Lewi co-authored "SOGC Guideline No. 441: Management of Monochorionic Twin Pregnancies" (in press) and the update of the "ISUOG Practice Guidelines: role of ultrasound in pregnancy" [9] during the development of this guideline. The recommendations are summarized in Table 1. The grade of recommendation and quality of evidence is represented in Table 2.

Degree of recommendation and quality of evidence

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
1. Determination of gestational age, chorio- and amnionicity should be done before 13 ⁺ ₆ weeks. The gestational age after <i>in vitro</i> fertilization is determined by the embryonic age and the day of transfer. In spontaneous twins, the crown-rump length of the largest twin determines gestational age. Chorio- and amnionicity determination is done by evaluating the entire intertwin septum. Amnionicity determination in monochorionic twins can only be done	xxxx	+++

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(continued)

from 8 weeks onwards when the amnion becomes visible. In case of doubt or diagnosis after 13⁺⁶ weeks and same sex, it is best to refer to an expertise center. The fetuses are also labeled in the 1st trimester for longitudinal follow-up.

Evidence +++

Accurate determination of gestational age, as with singletons, is important for growth monitoring and decisions in spontaneous or indicated preterm birth and is best done before 13⁺⁶ weeks. Usually, the gestational age of spontaneous twins is determined by the crown-rump length of the largest twin to avoid calculating the due date based on an already growth-restricted fetus [10].

Accurate knowledge of chorio-amnionicity is also essential because MC twins (20 % of all twins) have a higher risk of mortality than dichorionic (DC) twins due to transfusion imbalances such as TTTS and TAPS [11]. MC twins are connected by blood vessel connections on the common placenta (Fig. 1) [12]. Knowledge of chorionicity is also important in risk assessment for chromosomal abnormalities because MC twins are monozygotic. With fetal death of one member of MC twins, there is also a 50 % chance of death of the co-twin and a 35 % chance of antenatal brain damage due to acute exsanguination of the surviving twin into the body of the deceased co-twin [13–15].

Chorionicity can be determined very accurately between 11⁺⁰ and 13⁺⁶ weeks by evaluating the intertwin septum because amnion and chorion are still visible separately [16]. After 13⁺⁶ weeks, it is often not possible to determine with certainty in same-sex twins whether they are DC or MC twins. In DC twins, the septum consists of a thick chorionic layer with a thin amniotic membrane (amnion-chorion-amnion) on either side. The chorion layer inserts at the level of the placenta as a "full lambda" sign (Fig. 2). The septum in MC diamniotic (DA) twins consists only of two thin amniotic membranes (amnion -amnion) which inserts at the level of the placenta as an "empty lambda" sign. (Fig. 3).

Before 11⁺⁰ weeks, in DC twins, there are two separate gestational sacs and each fetus and yolk sac is in its own exocoelomic cavity (Fig. 4). In MC twins, there is one gestational sac with the two fetal poles and yolk sacs in a common exocoelomic cavity (Fig. 5).

DC twins, by definition, are always DA. Amnionicity in MC twins cannot be determined until eight weeks' gestational age because, before then, the amniotic membrane is not yet visible. MA twins share one amniotic sac. Thus, MA twins lack an intertwin septum (Fig. 6) [17]. If in doubt, a transvaginal ultrasound can confirm its absence. Often, there is only one yolk sac, and the umbilical cords are already intertwined from the 1st trimester, but this is not essential for the diagnosis [18,19]. Chorio- and amnionicity is thus determined by the intertwin septum before 13⁺⁶ weeks. The number of placental masses is unreliable because the MC placenta may be bilobar [20].

Rare are intermediate forms in which the septum is partly amnion-amnion and partly amnion-chorion-amnion. These are partial MC-DC twins and they should be followed as MC twins. In some MCDA twins, the septum is incomplete-partial DA-MA twins and they should be followed as MA twins [21]. Thus, it is important to always look at the entire septum.

During the 1st trimester scan, the fetuses are also labeled according to their position in the uterus for further individual follow-up. In 80–90 % of pregnancies, they lie side by side: one fetus on the right (baby 1 or A) and the other on the left (baby 2 or B) [22]. If they lie above and below each other, the lower fetus can be called baby 1 or A and the upper baby 2 or B. Other factors that help distinguish the babies are also best noted such as the location of their placenta, umbilical cord insertion, growth or other anatomical features.

Recommendation ++++

There is consensus that in every twin pregnancy, term and chorio-amnionicity should be determined in the 1st trimester and that the fetuses should be labeled for further longitudinal follow-up. In Flanders, patients have low-threshold access to a 1st trimester ultrasound at the gynecologist's office. It is useful to keep a photograph or video clip showing the intertwinseptum or its absence, illustrating chorionicity and amnionicity. If in doubt about chorionicity or amnionicity or if twins are diagnosed after 13⁺⁶ weeks and of the same sex, it is best to refer the pregnancy to a center of expertise.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
2. NIPT is the most accurate screening method for trisomy 21 in twin pregnancies and is offered preferentially after a normal 1st trimester ultrasound.	xxxx	+++

Evidence +++

A recent meta-analysis on NIPT in twin pregnancies showed a detection for trisomy 21 (N=137) of 99 % for a false positive rate of 0.02 % [23]. For trisomy 18 and 13, the detection was over 90 % with a false positive rate less than 1 %, but because trisomy 13 and 18 are more rare, only a limited number were included. In contrast, the combined test based on maternal age, nuchal thickness and serum PAPP-A/free beta-HCG detects only 85 % of pregnancies with trisomy 21 with a false positive rate of 5 % [24]. Thus, as for singletons, NIPT in twins has a higher detection rate for trisomy 21 with a lower false positive rate compared to the combined test. Compared with singletons, NIPT in twins has a slightly lower detection rate for trisomy 21 (99 % vs. >99 %) and is more likely to have an inconclusive result [25]. For trisomy 13 and 18, experience with NIPT is still relatively limited. In a "vanishing twin," NIPT can be false positive because DNA from the deceased and usually abnormal member is still circulating for a long time [26]. Here, a combined test based on neck fold measurement and maternal age (with or without free beta-HCG) [27] or a diagnostic test (miscarriage risk 1 %) [28] may offer an alternative.

About 90 % of DC twins are dizygotic. Thus, usually only one member will have a chromosomal abnormality while the other is normal. NIPT can then indicate that at least one twin has a chromosomal abnormality, which should always be confirmed by a diagnostic test. If the chromosomal abnormality is confirmed in one twin, a selective reduction can be done by intracardiac injection, preferably during the 1st trimester (procedure -related miscarriage risk of 1 %) [29]. If the 1st trimester ultrasound shows a structural abnormality in DC twins, it is best to schedule a chorionic villus sampling instead of NIPT. Thus, as with singletons, NIPT is offered only after a normal 1st trimester ultrasound scan.

All MC twins are monozygotic, and usually, both will have the chromosomal abnormality. Rarely it happens that only one fetus has an abnormality, which is then called heterokaryotypic monozygotic twins [30]. Selective reduction in MC twins can be achieved by occluding the umbilical cord of the affected twin around 16–18 weeks with a 10 % risk of miscarriage [31]. In case of an abnormality in only one twin, an amniocentesis of both amniotic sacs is always suggested instead of NIPT to diagnose possible heterokaryotypic monozygotic twins [30]. Diagnostic tests in twins are best performed in a center of expertise because they are technically challenging and because the diagnostic test and possible reduction are best performed by the same person [32].

Recommendation xxxx

Since the diagnostic accuracy of NIPT is better than the combined test and NIPT has been reimbursed in Belgium since July 2017, NIPT is the first choice if expectant twin parents wish aneuploidy screening. NIPT is best done after a normal 1st trimester ultrasound scan. An abnormal NIPT result should always be confirmed by a diagnostic test

Table 1

Summary of recommendations.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
1. Determination of gestational age, chorio- and amnionity should be done before 13 ⁺⁶ weeks. The gestational age after <i>in vitro</i> fertilization is determined by the embryonic age and the day of transfer. In spontaneous twins, the crown-rump length of the largest twin determines gestational age. Chorio- and amnionity determination is done by evaluating the entire intertwin septum. Amnionity determination in monochorionic twins can only be done from 8 weeks onwards when the amnion becomes visible. In case of doubt or diagnosis after 13 ⁺⁶ weeks and same sex, it is best to refer to an expertise center. The fetuses are also labeled in the 1st trimester for longitudinal follow-up.	xxxx	+++
2. NIPT is the most accurate screening for trisomy 21 in twin pregnancies and is offered preferentially after a normal 1st trimester ultrasound.	xxxx	+++
3. Low-dose aspirin (160 mg) starting in the 1st trimester can be considered if: nulliparity, BMI above 35 kg/m ² , maternal age above 40 years, pregnancy interval of more than 10 years, a positive family history for pre-eclampsia, chronic hypertension, history of gestational hypertension, autoimmune disorders, diabetes, or chronic renal insufficiency. Alternatively, one can do a risk calculation based on maternal risk factors, mean blood pressure, pulsatility index of the arteria uterina (with or without placental growth factor). Given the 10-fold higher risk of preterm pre-eclampsia, it is best monitor blood pressure and proteinuria every consultation.	xxx	++
4. Lifestyle advice is the same as for a singleton pregnancy. Multivitamins are recommended from 12 weeks onwards. Iron status is best checked at 20 and 28 weeks. An additional iron supplement may be associated from 20 weeks. With a normal starting weight, a weight gain between 17 and 25 kg is optimal.	GCP	-
5. Every uncomplicated dichorionic twin pregnancy should be offered ultrasound monitoring at 12, 16, 20, 24, 28, 32, 34 and 36 weeks. A detailed anatomic review in the 1st trimester is recommended because any selective reduction is safer in the 1st trimester.	GCP	-
6. Every uncomplicated monochorionic twin pregnancy should be offered ultrasound monitoring every two weeks starting at 16 weeks to provide timely twin-to-twin transfusion syndrome, twin anemia polycythemia sequence and growth restriction, preferably performed by a gynecologist with special competence in prenatal ultrasound.	GCP	-

Table 1 (continued)

7. Twins with structural abnormalities are best referred to a center of expertise. Monochorionic twins with more than 20 % growth difference before 28 weeks or with an abnormal Doppler pattern in the umbilical artery of the smallest member, twin-to-twin syndrome, twin anemia polycythemia sequence, death of one member and monoamniotic twins are also best referred to a center of expertise.	GCP	-
8. In dichorionic twins with growth restriction, follow-up is as in a singleton pregnancy.	GCP	-
9. Transvaginal cervical length measurement between 18 and 24 weeks is most accurate in predicting preterm birth in twins (cut-off 25 mm). In contrast, fetal fibronectin has no proven utility in asymptomatic twin pregnancies.	xxx	+++
10. Routine progesterone for all twin pregnancies is not recommended	x	++++
11. In an asymptomatic cervical shortening of ≤ 25 mm before 24 weeks, vaginal progesterone (200 mg, once daily) may be considered; with an asymptomatic cervical length ≤ 15 mm or open cervix before 24 weeks, a cerclage may be considered.	xxx	++
12. Mandatory bed rest or a vaginal pessary has no place in the prevention of preterm birth in twins.	x	+++
13. In cases of threatened preterm birth, the administration of antenatal corticosteroids is advised through 33 ⁺⁶ weeks. Up to 31 ⁺⁶ weeks, intravenous magnesium is useful for neuroprotection. Tocolysis may be considered to administer lung maturation or for transfer to a center with neonatal intensive care unit.	xxxx	+++
14. In an uncomplicated dichorionic twin pregnancy, elective delivery is best offered between 37 ⁺⁰ and 37 ⁺⁶ weeks and in an uncomplicated monochorionic twin, between 36 ⁺⁰ and 36 ⁺⁶ weeks.	xxxx	++
15. The delivery method should be discussed in the third trimester. There is no advantage to delivering mono- or dichorionic twins via cesarean section if the lower twin is head down, the gestational age exceeds 32 weeks and there is sufficient experience with vaginal twin deliveries.	xxxx	++++

Table 2

Grade recommendation and quality of evidence.

Grade recommendation	Quality of evidence = level of strength of evidence
xxxx: strong for	++++: high
xxx: weak for	+++ : moderate
xx: weak against	++ : low
x: strongly against	+ : very low
GCP: good clinical practice	- : no obvious

that is best performed in a center of expertise.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
3. Low-dose aspirin (160 mg) from the 1st trimester can be considered in nulliparity, BMI above 35 kg/m ² , maternal age above 40 years, pregnancy interval of more than 10 years, a positive family history for pre-eclampsia, chronic hypertension, history of gestational hypertension, autoimmune disorders, diabetes, or chronic renal insufficiency. Alternatively, one can do a risk calculation based on based on maternal risk factors, mean blood pressure, pulsatility index of the arteria uterina (with or without placental growth factor). Given the 10-fold higher risk of preterm pre-eclampsia, it is best to check blood pressure and proteinuria every consultation.	xxx	++

Evidence ++

Preterm pre-eclampsia occurs in 6 % of all twin pregnancies compared to 0.6 % of all singleton pregnancies [33] with a greater risk of preterm birth, placental abruption and poor neonatal outcome [34]. The ASPRE study showed that low-dose aspirin (150 mg) more than halves the risk of preterm pre-eclampsia in high-risk singleton pregnancies [35]. In twins, the evidence is less strong. A recent meta-analysis showed that ≥100 mg aspirin started before 16 weeks lowers the risk of pre-eclampsia also in twins but the included studies had low quality [36].

Twins at increased risk of pre-eclampsia can be selected based on maternal risk factors as suggested by the NICE guideline [37]. A more accurate screening test is based on maternal risk factors, mean blood pressure, pulsatility index of the uterine artery (with or without placental growth factor) as in singleton pregnancies. For a false positive rate of 10 %, this combined test detects 86 % of twin pregnancies with early pre-eclampsia before 32 weeks [38]. Recently, the ASPRE-T study started to investigate the utility of low-dose aspirin in the prevention of pre-eclampsia in twin pregnancies.

Recommendation xxx

Although the evidence in twins is still limited, it seems appropriate to suggest low-dose aspirin to all twin patients at increased risk of preterm pre-eclampsia according to the NICE guideline or to the combined screening test proposed by the Fetal Medicine Foundation (<https://fetalmedicine.org/research/assess/preeclampsia/First>). Since 150 mg is not available in Belgium, 160 mg can be prescribed for practical reasons. Given the 10-fold higher risk of preterm pre-eclampsia, it is best to check blood pressure and proteinuria every consultation.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
4. Lifestyle advice is the same as for a singleton pregnancy. Multivitamins are recommended from 12 weeks onwards. Iron status is best checked at 20 and 28 weeks. An additional iron supplement may be associated from 20 weeks. With a normal starting weight, a weight gain between 17 and 25 kg is optimal.	GCP	-

Evidence

There are few specific studies on exercise, nutrition, energy needs, optimal weight gain and nutritional supplements in twin pregnancies [39]. According to the US National Academy of Medicine, optimal weight gain in twin pregnancy is 17–25 kg at normal starting weight, 14–23 kg if overweight and 11–19 kg if obese. Compared with a singleton pregnancy, twin pregnancies are more likely to have postpartum hemorrhage, of which one in 20 women needs a transfusion of four units or more, embolization, tamponade or hysterectomy [40]. Iron requirements during pregnancy are also twice as high due to the increased blood volume and blood production of two fetuses [41].

Recommendation GCP

Advice on a healthy lifestyle is the same as for a singleton pregnancy. Multivitamins can be started from 12 weeks. Given the higher iron requirement, an additional iron supplement can be associated at 20 weeks. At 20 and 28 weeks, it is advisable to check the iron status. If correction is not possible with oral medication, intravenous iron is reimbursed in Belgium during pregnancy from a hemoglobin of 9 g/dl with low serum ferritin, serum iron, and transferrin saturation. Intravenous iron is also reimbursed when, within the six weeks before the planned delivery, the hemoglobin is lower than 13 g/dl, and the serum ferritin is less than 100 mcg/L, and the transferrin saturation is less than 20 %, or the CRP is more than 5 mg/dl.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
5. Every uncomplicated dichorionic twin pregnancy should be offered ultrasound monitoring at 12, 16, 20, 24, 28, 32, 34 and 36 weeks. A detailed anatomic review in the 1st trimester is recommended because any selective reduction is safer in the 1st trimester.	GCP	-

Evidence

A detailed anatomical review in the 1st trimester already detects 25 % of abnormalities in DC twins [42]. If parents opt for selective reduction, it is best done in the 1st trimester because the risk of miscarriage (1 % versus 8 %) and the risk of severe preterm birth (3 % versus 20 %) is lower than if the reduction is performed later [29].

Twins are more likely to have fetal growth restriction [43], in which one twin grows typically normally while the other lags in growth. This is called selective growth restriction (sFGR) and can only be diagnosed on ultrasound scan. Fetal growth is monitored by the estimated fetal weight (EFW) based on parietal diameter, head and abdominal circumference and femoral length. sFGR is best defined in clinical practice as a difference in EFW of 20 % or more [44,45], calculated as (largest EFW - smallest EFW) / largest EFW. sFGR is a major cause of stillbirth, iatrogenic preterm birth and neonatal mortality [46–48].

There is currently no consensus on whether the growth of twins should be plotted on a singleton or a twin curve. Since the growth rate of twins declines from 28 weeks onwards, a singleton curve will over-diagnose growth restriction. On the other hand, there is concern that using a twin curve will normalize the decline in growth rate and thus miss fetal distress [49].

Recommendation GCP

Since a significant proportion of abnormalities can already be detected in the 1st trimester and early selective reduction is safer, each DC twin should undergo minimal anatomic review in the 1st trimester according to the VVOG guideline "Ultrasound examination in low-risk

pregnancy." At 20 and 30 weeks, the 2nd and 3rd trimester screening is done according to the same guideline. Since sFGR is a major cause of perinatal morbidity and mortality, additional ultrasound is indicated at 16, 24, 28, 32, 34 and 36 weeks for fetal growth monitoring (Fig. 7). Pending controlled studies, singleton curves can be used for growth monitoring.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
6. Every uncomplicated monochorionic twin pregnancy should be offered ultrasound monitoring every two weeks starting at 16 weeks to timely detect twin-to-twin transfusion syndrome, twin anemia polycythemia sequence and growth restriction, preferably performed by a gynecologist with special competence in prenatal ultrasound.	GCP	-

Evidence

MC twins have a higher risk of fetal and perinatal mortality than DC twins due to transfusion imbalances such as TTTS and TAPS [11]. TTTS is characterized by a severe difference in amniotic fluid with deepest vertical pocket (DVP) of less than 2 cm in the donor with small or empty bladder and > 8 cm (before 20 weeks) or > 10 cm (after 20 weeks) in the receptor with overfilled bladder [50] (Fig. 8). TTTS occurs in one in 10 MC twins and usually occurs between 16^{de} and 26^{ste} gestational weeks [15]. Untreated, it almost always leads to fetal death, miscarriage or extreme preterm birth [51]. Fetoscopic laser coagulation of the blood vessel connections is the best treatment for TTTS [50], with survival of both fetuses in 65 % and at least one fetus in 85 % [52].

TAPS is characterized by a severe difference in hemoglobin between the twins. Criteria for a TAPS diagnosis are a discordance in middle cerebral artery peak systolic velocity (MCA-PSV) of ≥ 0.5 MoM [53] with increased velocities in the anemic donor and a low-normal MCA-PSV in the polycythemic recipient as well as a difference in echogenicity in the placental parts (placental dichotomy) an/or a dark congested liver in the recipient twin. TAPS occurs in about one in 20 MC twins and usually after the 26st gestational week [15]. In TAPS placentas, there are only tiny blood vessel connections through which a slow net transfusion of red blood cells occurs [54]. Because of the slow transfer a difference echogenicity develops in the placenta with an thick white donor piece and a thin dark piece of the receptor (Fig. 9) which often also has a dark liver with the illumination of the small venules what is called the "starry sky" or starry aspect of the receptor's liver [55] (Fig. 9). Untreated, TAPS can result in fetal demise of the donor twin [15,56]. Treatment of TAPS depends on the severity and gestational age at diagnosis and may include fetoscopic laser coagulation of the blood vessel connections as in TTTS, intrauterine transfusion with or without exchange transfusion, selective reduction or elective delivery [56].

sFGR in MC twins is associated with more serious complications than in DC twins, especially when the growth-restricted twin dies spontaneously *in utero* [57].

One in 10 MC twins has a structural abnormality, usually only in one twin [45]. Mainly cardiac abnormalities occur more frequently [58] and acquired abnormalities such as pulmonary valve stenosis, coarctation, or brain abnormalities sometimes become apparent late in pregnancy [59, 60].

Comparative studies on the best follow-up schedule for MC twins are lacking. A recent study showed that ultrasound follow-up every two weeks detects 90 % of all TTTS pregnancies in time before fetal death or cervical dilation occurs [61].

Recommendation GCP

MC twins are best monitored by ultrasound every two weeks to detect timely problems such as TTTS, TAPS, sFGR and structural

abnormality (Fig. 7). This involves monitoring each fetus' growth, amniotic fluid, umbilical artery Dopplers and MCA PSV. At 20 weeks, an expert ultrasound should be done to detect structural abnormalities. After 20 weeks, heart and brain development continues to be monitored. Given the complexity of ultrasound and the high risk of complications, ultrasound monitoring of MC twins is best done by a gynecologist with special competence in prenatal ultrasound.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
7. Twins with structural abnormalities are best referred to a center of expertise. Monochorionic twins with more than 20 % growth difference before 28 weeks or with an abnormal Doppler pattern in the umbilical artery of the smallest member, twin-to-twin syndrome, twin anemia polycythemia sequence, death of one member and monoamniotic twins are also best referred to a center of expertise.	GCP	-

Evidence

Selective reduction is an option when there is severe structural abnormality in one twin [29]. The option of fetal therapy should be discussed in MC twins with early severe sFGR, TTTS, TAPS and death of one member [62]. MA twins constitute 5 % of all MC pregnancies [42] and have an increased risk of fetal death more so than MCDA twins [63]. In MA twins, the umbilical cords insert close together on the placenta with large blood vessel connections. Pressure on the entangled umbilical cords can give rise to acute transfusion imbalances with sudden death of usually both fetuses [64]. Structural abnormalities are found in one in 5 MA pregnancies [65].

Recommendation GCP

When there is an indication for selective reduction or invasive fetal therapy, it is best to refer to a center of expertise. Given the rarity and complexity of MA twins, they are also best followed up in a center of expertise.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
8. In dichorionic twins with growth restriction, follow-up is as in a singleton pregnancy.	GCP	-

Evidence

There are very few studies that specifically describe the follow-up of sFGR in DC twins. In DC twins, sFGR may be due to a discordant chromosomal or genetic abnormality or a congenital infection of one twin. As for a singleton pregnancy, early FGR of one or both members before 24 weeks is best referred to a center of expertise for structural follow-up and possible invasive diagnostics.

Since each has its own placenta, one assumes that the well-being of the growth-restricted twin can be followed as in a singleton pregnancy with longitudinal monitoring of growth, computerized analysis of heart rate variability, the Doppler pattern in the umbilical artery, MCA and the ductus venosus [66]. In contrast to a singleton pregnancy, any premature delivery should take into account the disadvantages for the normally growing twin. After an elective preterm birth, the normally growing twin is most at risk for respiratory complications [67]. An abnormal Doppler pattern of the umbilical artery may be tolerated longer in a twin setting [68] and more studies are needed to examine its prognostic value in twins.

Recommendation GCP

The follow-up of growth restriction in DC twins is as in singletons, but in the event of fetal distress of the smaller twin remote from term,

one must consider the complications of iatrogenic preterm birth for the normally growing twin.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
9. Transvaginal cervical length measurement between 18 and 24 weeks is most accurate to predict severe preterm birth in twins with asymptomatic cervical length shortening (≤ 25 mm). In contrast, fetal fibronectin has no proven benefit in asymptomatic twin pregnancies.	xxx	+++

Evidence +++

Severe preterm birth occurs in 14 % of MC and 7 % of DC twins [11]. An asymptotically shortened cervix (≤ 25 mm) between 18 and 24 weeks increases the risk of severe preterm birth [69]. Serial measurements, for example, at 20 and 24 weeks, are probably more useful than a single measurement where especially rapid and early shortening has the highest risk [70]. About one in 10 twins has a cervical length ≤ 25 mm and in one in 25, the cervix is shorter than 15 mm at the time of the 20-week scan [71]. Fetal fibronectin has no place in screening for preterm birth in asymptomatic twins [69].

Recommendation xxx

Because twin pregnancies have a 10-fold higher risk of severe preterm birth and the possibility of preventive measures (see below), it seems useful to offer all twin pregnancies a cervical length measurement at the time of the 20-week ultrasound. Fetal fibronectin has not been proven useful in screening for preterm birth in asymptomatic twin pregnancies.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
10. Routine progesterone for all twin pregnancies is not recommended	x	++++

Evidence +++++

Two large randomized studies [72,73] could not demonstrate a benefit from the routine use of vaginal progesterone for uncomplicated twin pregnancies, even at a high dose (600 mg) starting in the 1st trimester. With a long cervix (≥ 30 mm) in the 1st trimester, progesterone might even increase the risk of preterm birth [73].

Recommendation x

Since no benefit could be demonstrated and there may be an adverse effect, routine prescription of progesterone to all twin pregnancies is not recommended.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
11. In the case of an asymptomatic cervical shortening of ≤ 25 mm before 24 weeks, vaginal progesterone (200 mg, once daily) may be considered; in the case of an asymptomatic cervical shortening ≤ 15 mm or open cervix before 24 weeks, a cerclage may be considered.	xxx	++

Evidence ++

A recent meta-analysis of randomized studies suggests that progesterone reduces the likelihood of delivery before 34 weeks in twin pregnancies with a cervical length of ≤ 25 mm. Doses administered ranged from 90 mg to 600 mg [74]. Based on limited data, it was long believed that cerclage had no benefit and was even harmful in twin pregnancies with a shortened cervix [75,76]. However, a recent

meta-analysis of observational studies suggests a possible indication for cerclage in cases of a very short (≤ 15 mm) or open cervix before 24 weeks [77]. Also, a recent small randomized study (N = 30) showed that cerclage for an open cervix (1–5 cm) before 24 weeks reduces the risk of preterm birth and extends pregnancy by an average of six weeks (29 versus 23 weeks) [78].

Recommendation xxx

Based on current evidence, there is a possible benefit of vaginal progesterone to prevent preterm birth in asymptomatic cervical length shortening (≤ 25 mm) established before 24 weeks. The optimal dose is not known and pending better data, the same dose as in a singleton pregnancy (200 mg) is suggested.

In the case of a very short (≤ 15 mm) or open cervix before 24 weeks, there is a potential benefit of cerclage. Given the rarity and complex counseling, referral to a center of expertise may be useful.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
12. Mandatory bed rest or a vaginal pessary has no place in the prevention of preterm birth in twins.	x	+++

Evidence +++

There is no evidence that mandatory sick leave, bed rest or restriction in normal physical activity reduces the risk of preterm birth for uncomplicated twin pregnancies [79]. These limitations can have a negative physical, emotional and financial impact [80]. Even for women at increased risk of preterm birth due to a short cervix or other risk factors, there is no benefit from bed rest or exercise restriction, which may even be harmful [79,81].

Although promising, several large randomized studies could not demonstrate a benefit of the vaginal pessary either for twin pregnancies in general [82,83], or for pregnancies with a shortened cervix [84,85].

Recommendation x

Given no proven benefit and possible adverse effects, bed rest and restriction in normal physical activity are not recommended - even for twin pregnancies at increased risk of preterm birth. The pessary currently has no proven benefit for twins in general or in cases of shortened cervical length and thus is not recommended for the prevention of preterm birth in twins.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
13. In cases of threatened preterm birth, the administration of antenatal corticosteroids is advised through 33 ⁺⁶ weeks. Up to 31 ⁺⁶ weeks, intravenous magnesium is useful for neuroprotection. Tocolysis may be considered to administer lung maturation or for transfer to a center with neonatal intensive care unit.	xxxx	+++

Evidence +++

Recent studies showed that antenatal corticosteroids reduce the risk of neonatal mortality and developmental problems in twins at risk of being born within one week between 24⁺⁰ to 34⁺⁰ weeks [86–88]. Although data on magnesium sulfate in twins are limited [89,90], magnesium is also believed to reduce the risk of spastic paresis in severely preterm-born twins [91]. Tocolysis may be considered to administer lung maturation or for transfer to a center with a neonatal intensive care unit [92,93].

Recommendation xxxx

Before 34 weeks, as in a singleton pregnancy, antenatal corticosteroids are highly recommended in the event of an impending birth within seven days. Before 32 weeks, intravenous magnesium sulfate reduces the risk of spastic paresis. Tocolysis may be administered to complete a course of lung maturation or allow transfer to a center with a neonatal intensive care unit (if needed).

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
14. In uncomplicated dichorionic twin pregnancy, it is best to offer elective delivery between 37 ⁺⁰ and 37 ⁺⁶ weeks and in uncomplicated monochorionic twins, between 36 ⁺⁰ and 36 ⁺⁶ weeks.	Xxxx	++

Evidence ++

More than half of twins are already born at 37 weeks [2]. For uncomplicated DC twins, birth between 37 and 38 weeks is associated with the lowest risk of perinatal mortality and morbidity. An elective delivery between 37 and 38 weeks does not lead to more complications or an increase in sections compared with a wait-and-see policy. In MC twins, the best time to birth seems to be between 36 and 37 weeks because after 37 weeks, the risk of fetal and neonatal mortality increases [94].

Recommendation xxxx

Since 38 weeks is "post-dates" for DC twins and 37 weeks for MC twins with an increase in perinatal complications, elective birth is best advised between 37 and 38 weeks for DC twins and 36–37 weeks for MC twins.

RECOMMENDATION	DEGREE OF RECOMMENDATION	QUALITY OF EVIDENCE
15. The delivery method should be discussed in the third trimester. There is no advantage to delivering mono- or dichorionic twins via cesarean section if the lower twin is head down, the gestational age exceeds 32 weeks and there is sufficient experience with vaginal twin deliveries.	xxx	++++

Evidence +++++

In uncomplicated twin pregnancies with the first member in the head position (80 % of cases), vaginal delivery is safe for both DC and MC twins [95,96]. Before 37 weeks, a planned cesarean section is even associated with more neonatal complications than a planned vaginal delivery [95]. A recent randomized study could show no difference in maternal and perinatal complications between a planned c-section or vaginal delivery between 32 and 38 weeks with the presenting twin head down [97]. If the presenting twin is cephalic at 32 weeks it usually remains cephalic [98]. When the second twin is not head down, a breech extraction with or without an internal podalic version leads to a lower risk of cesarean section and better outcomes for the second twin compared to an external version [99,100]. Effective loco-regional anesthesia and the availability of acute tocolysis are important here [101,102]. One in 10 non-preterm twins will turn from cephalic to breech or transverse position after the birth of the first twin [103]. In experienced hands, the probability of a cesarean section for the second twin is about 5 % [97], so the ability to perform a c-section quickly is important. Some centers, therefore, perform all vaginal twin births in the operating room [104]. There are insufficient data to make strong recommendations for delivery before 32 weeks, twins with sFGR or EFW below 1500 g and with a history of cesarean section [105–109].

Recommendation xxx

The method of delivery should be discussed in the 3rd trimester. There is no benefit of a planned cesarean section if the gestational age is more than 32 weeks, the lower twin is head down and there is sufficient experience with vaginal twin delivery with possible need to perform an internal podalic version and breech extraction.

Quality control

This guideline-update was made public to all VVOG members for comments and modifications for 2 weeks via the website (www.VVOG.be). Thereafter, this guideline was approved for publication and implementation by the VWV.

Implementation

This guideline will be published in EJOG+ and in Gunaikeia (official journal of the VVOG) and on the VVOG website, which is accessible to all VVOG members.

Restrictions

- This guideline does not contain specific recommendations for triplet pregnancies.
- This guideline highlights only the 15 main topics of twin pregnancies, and rare complications such as Twin Reversed Arterial Perfusion Sequence and conjoined twins are not covered.

Panelists

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Time frame for review

This guidance-update will be reviewed against the latest literature after a three-year period by the VWV.

A first review was done in April 2025 with the adaptation of the TAPS criteria. Instead of the cut-off of > 1.5 MoM and < 0.8 MoM and a difference of > 1 MoM, a difference of 0.5 MoM seems to be a safer cut-off as also recently recommended by the SMFM [53], because clinically relevant intertwin differences in hemoglobin can occur with lesser discordances. To reduce the false positive rate – there should also be signs of a chronic red blood cell transfusion as evidenced by the presence of either a clear difference in echogenicity between the placental part of donor and recipient or a dark, congested liver in the recipient twin.

Disclaimer

We have taken the utmost care to prepare and maintain this Clinical Guidance paper. Nevertheless, the VVOG accepts no liability for any inaccuracies, nor for damage, adverse effects or inconvenience of any kind (actions, omissions and decisions based on this information).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendices

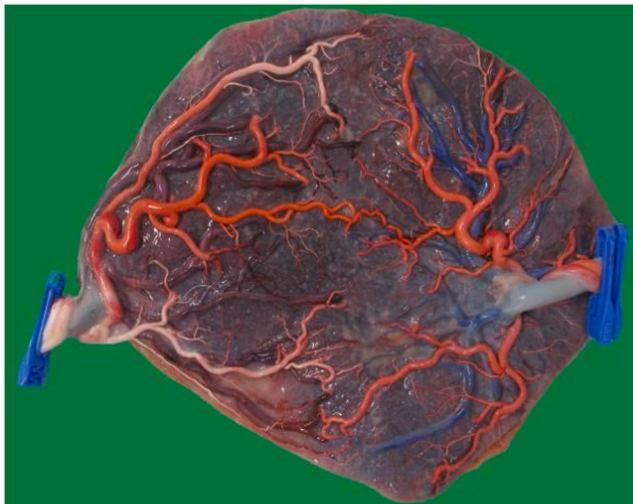


Fig. 1. Placenta of uncomplicated monochorionic diamniotic twins born at 36 weeks after dye injection demonstrating the different blood vessel connections. The amnion and intertwinseptum were removed



Fig. 2. Ultrasound image of dichorionic twins at 12 weeks. The intertwinseptum consists of a thick chorionic layer with two thin amniotic membranes (amnion-chorion-amnion) along both sides. The chorionic layer inserts at the level of the placenta as a "full lambda" sign

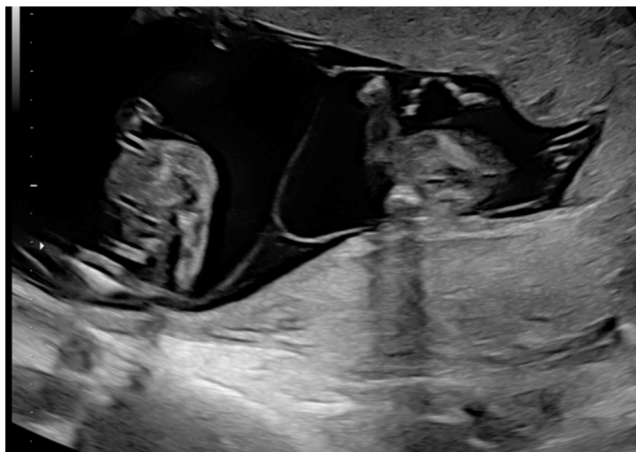


Fig. 3. Image of monochorionic diamniotic twins at 13 weeks. The intertwinseptum consists only of two thin amniotic membranes (amnion-amnion) that inserts as an "empty lambda" sign



Fig. 4. Image of dichorionic twins at 9 weeks. There are two separate gestational sacs and each fetus and yolk sac is in a separate exocoelomic cavity



Fig. 5. Ultrasound image of monochorionic twins at 10 weeks. There is one gestational sac and a common exocoelomic cavity containing both fetuses and yolk sacs



Fig. 6. Ultrasound image of monoamniotic twins at 13 weeks. Both fetuses are in a common amniotic sac with umbilical cords already visibly entangled

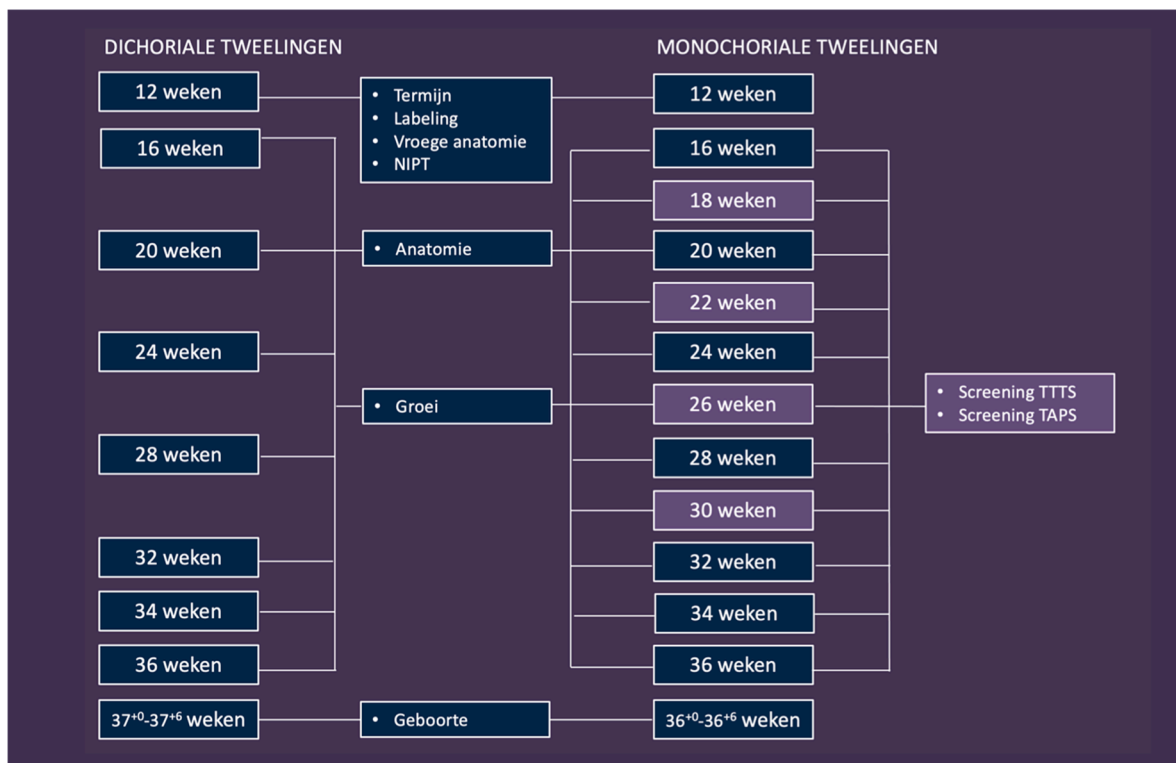


Fig. 7. Schematic for the ultrasound follow-up of di- and monochorionic twins

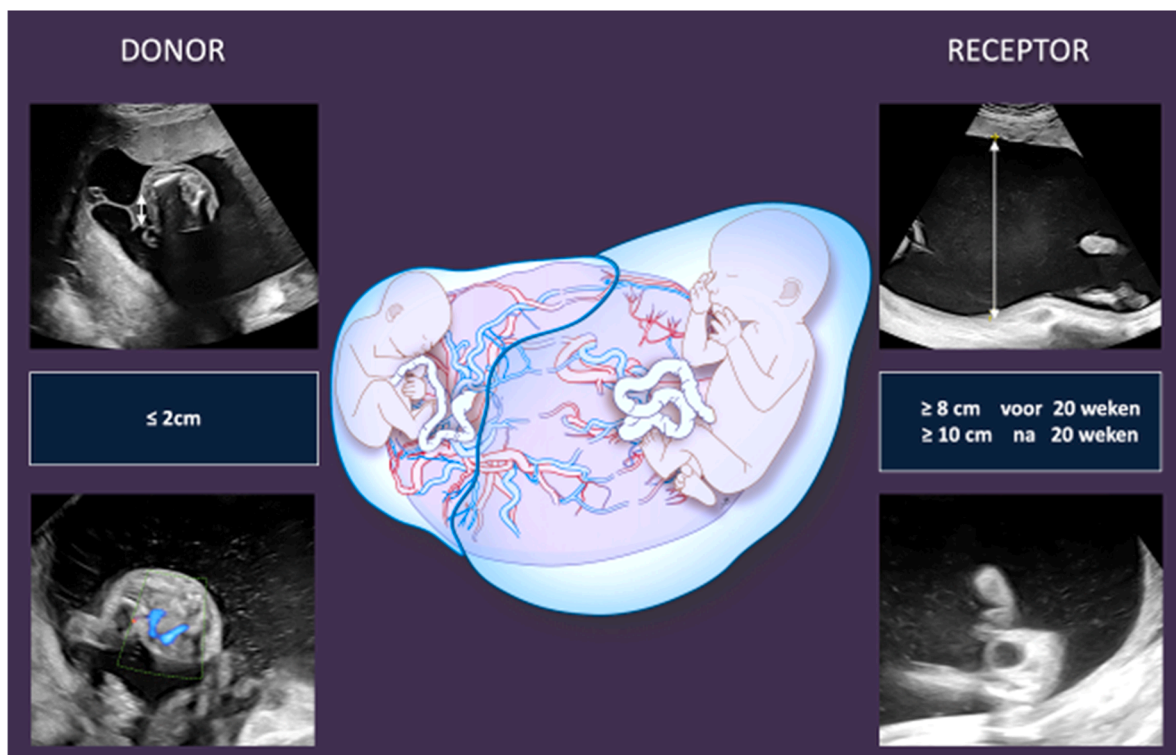


Fig. 8. Twin-to-twin transfusion syndrome is characterized by a severe difference in amniotic fluid with a deepest vertical amniotic fluid loge less than 2 cm in the donor who has a small or empty bladder and more than 8 cm (before 20 weeks) or more than 10 cm (after 20 weeks) in the receptor who has a distended bladder

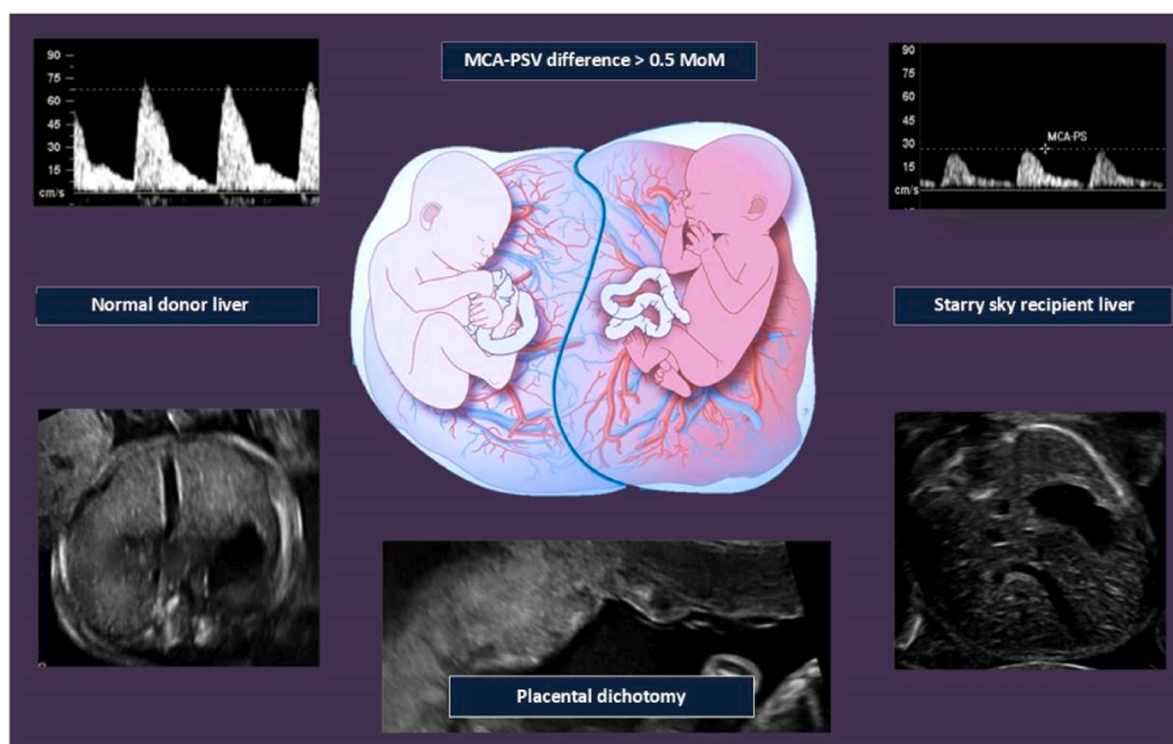


Fig. 9. Twin anemia polycythemia sequence is characterized by a severe difference in hemoglobin with an increased peak velocity in the middle cerebral artery (MCA PSV) of 1.5 MoM (multiples of the median) or more in the anemic donor and 0.8 MoM or less in the polycythemic receptor. A difference of 1 MoM or more is also considered diagnostic. Often there is also an echogenicity difference of the placenta and the receptor has a dark congested liver in which the small venules light up ("starry sky")

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