MANAGEMENT OF MULTIPLE PREGNANCY

Júlia Ponce, Mar Bennasar, Montse Palacio, Francesca Crovetto, Anna Goncé

1. INTRODUCTION

Multiple gestation has experienced a significant increase over recent years. It is associated with a higher risk of maternal and fetal complications compared to singleton pregnancies and this will determine its antenatal and intrapartum management. Chorionicity is the main determinant of gestational prognosis and management.

2. CLASSIFICATION

- Dizygotic: 70-75%: all dichorionic-diamniotic (DCDA)
- Monozygotic: 25-30%.
  - o Dichorionic-diamniotic (DCDA) (20-25%)
  - o Monochorionic-diamniotic (MCDA) (70-75%)
  - o Monochorionic-monoamniotic (MCMA) (1-2%)
  - o Conjoined twins (<1%)

3. COMPLICATIONS

Zygosity determines the risk of genetic diseases. Chorionicity determines the risk of perinatal complications and, therefore, the prognosis, follow-up and gestational management.

3.1 Fetal complications

Associated with prematurity**:** this is the most frequent complication of multiple pregnancy. It is due to various pathophysiological mechanisms that include uterine overdistension. Table 1 shows the prevalence of premature birth according to the number of fetuses:

Table 1. Preterm birth prevalence in multiple pregnancy

Twin pregnancies	**Triplet pregnancies**
< 37 weeks: 50-60% < 34 weeks: 15-20% < 32 weeks: 10% < 28 weeks: 5%	< 35 weeks: 75% < 32 weeks: 25-50% < 28 weeks: 20-30%

Associated with chorionicity: due to the presence of vascular anastomoses between fetuses within a single placenta, monochorionic twins present unique and specific complications that determine the management and follow-up of these pregnancies. The most frequent complications are:

- Twin-to-twin transfusion syndrome (TTTS): affects 10-15% of monochorionic pregnancies.

- Selective fetal growth restriction (sFGR): it is more frequent in multiple pregnancies, but especially in monochorionic pregnancy, with an overall prevalence of 10-15%.
- Intrauterine fetal death: due to the presence of vascular anastomoses, intrauterine death of a monochorionic twin carries a higher risk of death or neurological sequelae in the survivor, between 15-25% and 20-30%, respectively, depending on gestational age.
- Twin Anaemia-Polycythemia Sequence (TAPS): affects 3-5% of monochorionic pregnancies.
- Twin Reversed Arterial Perfusion (TRAP) Sequence: affects 1% of monochorionic pregnancies.

Discordant fetal anomaly:

- Structural anomalies: regardless of chorionicity, in > 80% of cases it will be a discordant anomaly, affecting only one twin. In dichorionic pregnancies, the risk of presenting a structural anomaly is two times higher than in singletons, as there is an individual risk for each foetus, similar to that in singleton pregnancy. In monochorionic twins, there is also an increased risk for each foetus in contrast to singletons, attributable to the process of postzygotic division, presenting a risk 2-3 times higher for dichorionic twins.
- Chromosomal abnormalities: in dichorionic twins, the risk is independent for each foetus, leading to a 2 times higher respect compared to singleton pregnancy. In monochorionic twins, the risk is similar to that in singletons and affects both fetuses, except in the very exceptional cases of heterokaryotic anomaly.

Fetal/perinatal death: in multiple pregnancies, there is an increased risk of overall perinatal mortality compared to singleton pregnancies (2-3 times higher in dichorionic and 5-6 times higher in monochorionic pregnancies).

3.2 Maternal complications

Maternal complications are more frequent than in singletons and include gestational, as well as during labour and delivery, and puerperal complications. Maternal mortality is 2-3 times higher than in singletons. The increase in maternal morbidity and mortality is conditioned by hormonal, haemodynamic (increased cardiac output and plasma volume) and mechanical factors, as well as by the higher prevalence of fertility treatments and advanced maternal age in these pregnancies. Gestational complications condition a greater need for hospitalisation, bed rest, fluid therapy, tocolytic treatments and corticosteroids for fetal lung maturation. The most frequent maternal complications are:

- Hyperemesis gravidarum
- Oedema due to fluid retention and venous stasis. There is also an added risk of acute pulmonary oedema. Particular care should be taken with fluid balance during hospitalisation, in situations of fluid overload and the use of corticosteroids.
- Hypertensive pregnancy disorders, in particular increased risk of preeclampsia in nulliparous women.

- Anaemia and/or iron deficiency.
- Intrahepatic cholestasis of pregnancy
- Thromboembolic disease: twin pregnancy is considered a risk factor itself, increased by the frequent need for bed rest. Thromboembolic prophylaxis should be assessed if coexisting thromboembolic factors.
- Acute fatty liver of pregnancy, very rare, but extremely serious, more common in multiple pregnancy, especially during the third trimester.
- Obstetric haemorrhage: placenta previa, placental abruption, postpartum haemorrhage.

3.3 Complications associated with delivery

Apart from the increased risk of postpartum haemorrhage, there is also an increased risk of obstetric trauma, especially for the second twin.

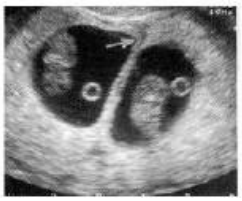
4. ULTRASOUND DIAGNOSIS: DETERMINING CHORIONICITY AND AMNIONICITY. DATING OF PREGNANCY. TWIN LABELLING

4.1 Determining chorionicity and amnionicity

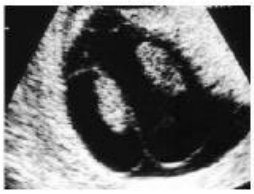
In order to make the diagnosis of chorionicity and amnionicity with utmost reliability, it is mandatory to perform an ultrasound scan before 14 weeks.

4.1.1 Ultrasound ≤ 14 weeks

- Early ultrasound < 11 weeks:
    - Dichorionic pregnancy: view of two enveloping chorion images separating 2 embryos, with their own yolk sac in each foetus sac (Picture 1).
    - Monochorionic pregnancy: view of 2 amniotic sacs (thin membrane) and single exocoelomic cavity with 2 embryos, with a yolk sac in each foetus sac (Picture 2). Before 8-10 weeks, the intertwin membrane may not be visible, making it difficult to diagnose amnionicity until 10 weeks. Early diagnosis of amnionicity considering the number of yolk sacs (1 = monoamniotic and 2= diamniotic) is not always accurate.

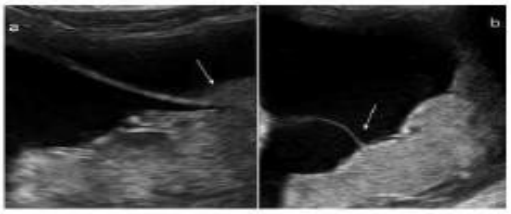


Picture 1



Picture 2

- Ultrasound 11-13.6 weeks:
    - Dichorionic pregnancy: 2 placentas or, if placentas apparently fused, always present lambda sign (Picture 3a).
    - Monochorionic-diamniotic pregnancy: 1 placenta with T-sign at the amniotic junction (Picture 3b).
    - Monochorionic-monoamniotic pregnancy: Single amniotic cavity without view of intertwin membrane. Usually cord entanglement is observed.



Lambda sign (Picture 3a) T sign (Picture 3b)

4.1.2 Ultrasound > 14 weeks

The diagnosis of chorionicity may be uncertain. Same ultrasound signs will be used, although the lambda sign may disappear. If in doubt, and if fetal sex is identical, follow-up should be performed as a monochorionic pregnancy. When intertwin membrane is not visible, it is necessary to rule out a TTTS, in which the oligohydramnios of one foetus (stuck twin) could give the wrong image of absence of intertwin membrane. It should be remembered that the probability of observing a TTTS (10-15%) is clearly higher than the probability of having a monoamniotic pregnancy (1%).

4.2 First trimester pregnancy dating

4.2.1 Dating

In both spontaneously conceived twins and triplets, pregnancy dating is done from the larger of the 2 crown-rump length (CRL) measurements (between 45-84 mm), to avoid underestimation in the case of an early restricted grown foetus. Since it is often not possible to determine the embryonic age at the time of the embryo transfer, and given the little benefit of dating by embryonic age, multiple pregnancies conceived by assisted reproductive technology will be dated by the largest CRL measurement also.

4.2.2 CRL discordance > 10%: associated risks and management

Average first trimester CRL discordance is 3-5%. CRL discordance > 10% (and especially > 15%), increases the risk of adverse perinatal outcomes in both monochorionic and dichorionic pregnancies (fetal death, fetal loss < 24 weeks, preterm delivery < 32 weeks, chromosomal or structural abnormalities, > 20% weight discordance and sFGR or need for foetoscopy treatment in monochorionic twins), although the predictive value is low. Management if CRL discordance is > 10% at 11-13.6:

<u>Dichorionic pregnancy</u>

- Screening for aneuploidy (combined test in twin pregnancy/nuchal translucency (NT) thickness + maternal age in triplets). If the result is low risk for all fetuses, an isolated CRL discordance is not considered an indication for an invasive procedure.
- Early morphological ultrasound (14-16 weeks) in the smallest foetus.
- Early echocardiography (14-16 weeks) in the smallest foetus.

<u>Monochorionic pregnancy</u>

- Screening for aneuploidy (combined test in twin pregnancy/NT + maternal age in triplets), giving a single gestational risk. If low risk, an isolated CRL discordance is not considered an indication for an invasive procedure. In monochorionic pregnancies

with discordant CRL, the possibility of a non-concordant (or heterokaryotic) aneuploidy is unlikely.

- Early morphological ultrasound (14-16 weeks) in the smallest foetus.
- Early echocardiography (14-16 weeks) of both fetuses as in any monochorionic pregnancy

Some studies have also reported an association between intertwin NT discordance or the presence of reversed a-wave in the ductus venosus (DV) in the first trimester scan and the development of TTTS, but its predictive value is low and does not modify the usual ultrasound follow-up of monochorionic pregnancies.

4.3 Twin labelling

In multiple pregnancy, it is important to label appropriately each foetus in the first trimester scan. It is recommended to record the site of each foetus in relation to the maternal abdomen, the location of the placenta and the insertion of the umbilical cords. Once identified, it is recommended that no changes are made in subsequent ultrasound examinations, to ensure adequate follow-up of each foetus, regardless of the fetal presentation, which may vary.

5. PRENATAL DIAGNOSIS

5.1 Aneuploidy screening

The screening of choice is the combined first trimester test: maternal biochemistry (PAPP-A and free ß-hCG) between 7.6-13.6 weeks (preferably between 8-10 weeks) and ultrasound (NT) between 11.2-13.6 weeks (CRL 45-80 mm), preferably at 12 weeks, associated with maternal age. In case of oocyte donation, the maternal age to be considered is the age of the donor. When CRL of the larger foetus is between 80 and 84 mm, a combined test is still feasible, but only if maternal biochemistry has been obtained before 13.6 weeks (CRL up to 80 mm).

In dichorionic pregnancies, a combined test allows a risk estimation of trisomy 21 and trisomy 18/13 for each foetus based on its NT, assuming they are dizygotic. Whereas in monochorionic pregnancies, because the risk of aneuploidy is the same for both fetuses (monozygotic), the combined test estimates a single gestational risk of trisomy 21 and trisomy 18/13, calculated using the mean of both NT. The combined first trimester test has a detection rate for trisomy 21 close to 90%, similar to singleton detection, with a slightly higher false positive rate of 5-6%.

5.1.1 Special situations:

- Multifetal pregnancy (3 or more fetuses) with CRL 45-84 mm: Maternal biochemistry is not applicable. Ultrasound screening using NT + maternal age will be performed.

- Twin pregnancies and largest CRL between 80-84 mm without the possibility of applying first trimester biochemistry: ultrasound screening using NT + maternal age will be performed.

Isolated ultrasound screening with NT + maternal age has a lower detection rate for trisomy 21 (75%) and a higher false positive rate (5% for each foetus in dichorionic, 8% in monochorionic, and 15% in a triple trichorionic pregnancy).

- Twin pregnancies starting gestational follow-up > 14.0 weeks (CRL > 84 mm): Second trimester biochemical screening will be applied, preferably the quadruple test (free ß-fraction of chorionic gonadotropin (fß-hCG), alpha-fetoprotein (AFP), conjugated estriol (uE3) and Inhibin A (inhA)) associated with maternal age.
  Preferably it will be performed between 15-18 weeks, but be applicable up to 19.6 weeks. It gives an estimated risk of trisomy 21 and trisomy 18/13 for the entire pregnancy, applying a correcting factor for each of the markers. It has lower sensitivity than in singleton pregnancies (65%) and a higher false positive rate (10%). It is not applicable in pregnancies with 3 or more fetuses.

- Vanishing twin: if a measurable fetal pole is found, only NT + maternal age will be used for risk calculation, as PAPP-A values may be significantly altered by the presence of an embryonic remnant. If no fetal pole is found, a combined test as a singleton pregnancy is performed.

5.2 Second trimester genetic sonogram

It is applicable in twin pregnancies between 20.0-24.6 weeks without previous screening, to estimate the risk of trisomy 21. Each foetus will be assessed for the presence of second trimester ultrasound markers related to trisomy 21. The risk will be calculated according to maternal age by multiplying or dividing the risk according to the presence or absence of these markers. The second trimester genetic sonogram is also applicable to fetuses in which one or more ultrasound marker(s) are observed during a morphology scan, modifying the risk previously estimated in the first or second trimester screening.

5.3 Cell-free DNA (cfDNA)

In dichorionic pregnancies, sensitivity may be lower since, to obtain a result, the fetal fraction of each twin must be at least 4%. Recent studies have shown a slightly lower detection rate for trisomy 21 compared to singletons: 98.2% (with false-positive 0.05%) while, for trisomy 18, the detection rate is significantly lower 88.9% (false-positive 0.03%), and there are no conclusive results for trisomy 13.

It is now accepted that the performance of cfDNA in maternal blood for trisomy 21 would be similar to that for singleton pregnancy in monochorionic twins, and higher than the combined test in both dichorionic and monochorionic pregnancies, with an additional advantage of reducing the false positive rate, thus avoiding unnecessary invasive procedures. However, the rate of non-informative results is higher, especially in dichorionic pregnancies (non-informative result up to 12%) probably also influenced by assisted reproduction techniques. If SNP genotyping is used, zygosity can also be determined. Cell-free DNA (cfDNA) will be offered in:

- High-risk result of trisomy 21 or trisomy 18-13 (1/11-1/250) in the combined test or second trimester biochemical screening as an alternative to the invasive procedure.
- Intermediate risk of trisomy 21 or trisomy 18-13 (1/251-1/1100)

cfDNA is not applicable in multifetal pregnancies (3 or more fetuses), and its indication is doubtful in case of a vanishing twin, since DNA from the non-survivor foetus can be found beyond 15 weeks, causing a high increase in the false positive rate.

5.4 Indications for invasive procedure

- Risk ≥ 1/250 of trisomy 21 or trisomy 18/13 (First trimester combined test) in one or both fetuses.
- Risk ≥ 1/250 of trisomy 21 or trisomy 18/13 (Second trimester biochemical screening).
- Risk ≥ 1/250 of trisomy 21 or trisomy 18/13 (NT + maternal age) in multifetal pregnancies.
- Confirmation of a high-risk result of trisomy 21, 18 or 13 in the cfDNA test.
- Second trimester genetic sonogram with risk ≥ 1/250 in one or both fetuses.

5.4.1 Type of invasive procedure

Chorionic villus sampling: First choice, except in individual cases.

- In dichorionic pregnancies, 2 samples (one for each foetus) must be obtained. After a discordant high-risk result in the first trimester screening, it is important to obtain the karyotype as early as possible by chorionic villus sampling. If selective termination is a potential option for the progenitors, referral to a tertiary centre is recommended, so that the invasive diagnostic procedure and the eventual termination are performed in the same unit, thus minimising the risks of confusion between twins. The associated procedure-risk decreases significantly if it is performed early.
- In monochorionic pregnancies, a single sample is obtained. In the case of a high-risk result in the first trimester screening, referral to a tertiary centre is recommended for an early anatomic, cardiac and NT assessment of both fetuses, before performing an invasive procedure, in order to decrease the number of procedures and related risks if fetal surgery will be needed.
  As in dichorionic pregnancy, if a selective termination cannot be performed in the centre of origin, referral to a tertiary centre is recommended before performing an invasive procedure. If there is a discordant malformation or NT discordance, it would be advisable to postpone the genetic study by amniocentesis, or to perform it during the fetal surgery, in order to obtain a sample from each foetus due to the possibility of heterokaryotic twins.

Amniocentesis: Above ≥ 16 weeks.

- In dichorionic pregnancies: 2 samples will be obtained by 2 punctures or single puncture. However, when the indication for karyotyping is a discordant malformation with different fetal sex (exclusion of monozygotic gestation), obtaining a single sample from the affected foetus can be assessed on an individual basis to reduce the risk of the procedure.
- In monochorionic pregnancies: especially if performed due to gestational risk of aneuploidy, a single puncture will be made. If it is indicated to obtain 2 samples, a double puncture should always be made. Obtaining 2 samples by a single transamniotic puncture is contraindicated because of the risk of septostomy.

If selective termination is an eventual option for the progenitors, referral to a tertiary centre is recommended, so that the invasive diagnostic procedure and the eventual termination are performed in the same unit, thus minimising the risk of confusion between twins.

5.4.2 Risk of invasive procedure:
Several studies have shown that, when performed by experienced operators, both amniocentesis and chorionic villus sampling present a similar risk of fetal loss, between 1.5-2%, although the risk is higher than in singletons (0.1-0.2%).

6. PREECLAMPSIA PREVENTION

Combined screening for preeclampsia for singleton gestation is not applicable in multiple pregnancy at the present time. Since multiple pregnancy is considered a risk factor for preeclampsia (especially late preeclampsia) and is considered a major epidemiological criterion according to the US Preventive Services Task Force (USPSTF) recommendation, prevention with aspirin 150 mg/24 h should be given to all multiple pregnancies. Ideally, it should be initiated between 12-16 weeks (and no later than 20 weeks), until 36 weeks.

In a multiple pregnancy, angiogenic factors (sFlt-1/PlGF ratio) will be used to rule out preeclampsia, since an sFlt-1/PlGF ratio < 38 pg/mL has a high negative predictive value. There is not enough evidence on the usefulness of angiogenic factors for the diagnosis of preeclampsia, so, to date, this will be established in case of maternal blood pressure > 140/90 mmHg and signs or symptoms of target organ involvement, not attributable to another more likely diagnosis.

7. PRENATAL CONTROL

7.1 General recommendations
Similar general recommendations as in singleton pregnancy care will be followed, but with some particularities due to the increased risk of complications.

- Maternal weight gain up to 16-20 kg is recommended.
- Dietary recommendations: in multiple pregnancies, the need for nutrients and vitamins increases. A varied and balanced diet with low saturated fat intake and rich in fruit, oily fish and vegetables, is recommended. Omega-3 fatty acids seem to act on the inflammatory factor of prematurity (they inhibit the production of arachidonic acids and therefore decrease cytokine concentrations), so in the case of insufficient dietary intake, supplementation through multivitamin preparations (200 mg/day of DHA) is recommended.
- Iron and folic acid supplementation until the end of pregnancy. There is a higher incidence of anaemia in this population.
- Calcium supplementation (> 1 g/d) is recommended in women with low calcium intake (less than 600 mg or 2 servings/day).

- Adaptation of physical activity, considering the occurrence of complications and based on cervical length measurement. Strict bed rest has not been shown to reduce prematurity, either in multifetal pregnancies or in case of cervical dilatation, and instead, increases the risk of thromboembolic disease, osteoporosis, and decreases maternal muscle mass. Nevertheless, it seems acceptable to recommend relative rest in patients with a significant short cervical length. In a situation of strict bed rest, thromboembolic disease prophylaxis should be taken into consideration.

7.2 Antenatal visits and ultrasound assessment

The frequency of visits and ultrasound examinations will depend on chorionicity:

7.2.1 Antenatal visits

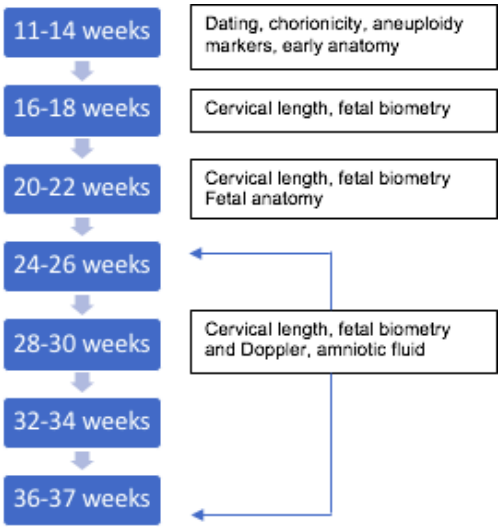
- Uncomplicated dichorionic pregnancy: visits every 4 weeks after first trimester ultrasound until 32 weeks, then every 2 weeks until 36 weeks, then weekly.
- Uncomplicated monochorionic pregnancy: visits every 2 weeks after first trimester ultrasound until 34 weeks, then weekly.
- Uncomplicated triplet pregnancy: visits every 4 weeks after first trimester ultrasound until week 24, then visits every 2 weeks until week 32, then weekly. In triple pregnancies and monochorionic component, check-ups will be fortnightly from the beginning until 32 weeks, then weekly.

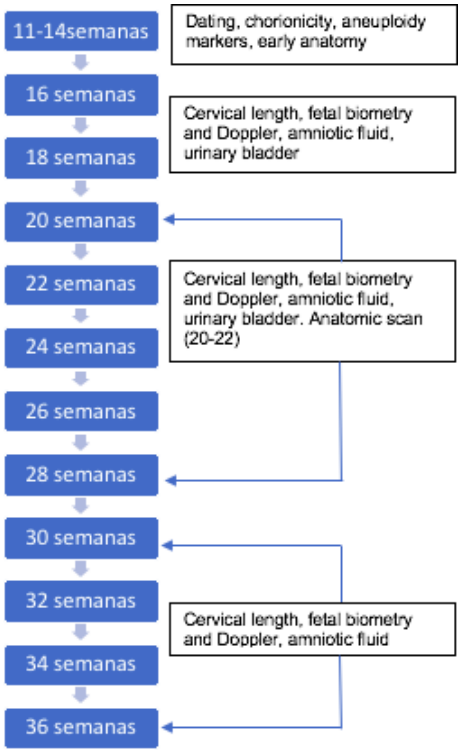
Laboratory tests do not vary from singleton pregnancy, with the exception of the third trimester laboratory test. In addition to the usual laboratory test, a preeclampsia screening profile including liver function test, lactate dehydrogenase, renal profile, uric acid and urine protein/creatinine ratio should be requested.

Due to the increased risk of intrapartum caesarean section and anaesthetic complications, we schedule a follow-up visit with the anaesthesiologist at around 32 weeks, regardless of the intended mode of delivery.

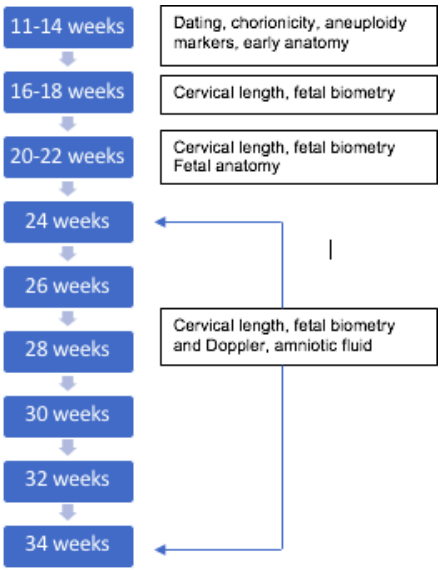
7.2.3 Ultrasound assessment

Dichorionic pregnancy Monochorionic pregnancy





Triplet pregnancy*



* In triplet pregnancies with monochorionic component, ultrasound recommendations apply as in monochorionic twin pregnancy.

Ultrasound objectives are:

- Assess fetal statistics
- Fetal growth monitoring: due to the increased risk of fetal growth restriction (FGR), percentiles and intertwin weight discordance should be reported at each ultrasound scan. Customised growth charts for multiple pregnancy (differentiating dichorionic from monochorionic charts) should be used.
- Rule out specific complications of monochorionic pregnancy: early diagnosis of TTTS by monitoring amniotic fluid, urinary bladders, fetal Doppler and biometry from 14-16 weeks onwards. Early diagnosis of TAPS by monitoring middle cerebral artery (MCA) peak systolic velocity (PSV) from 20 weeks onwards.
- In all monochorionic pregnancies, a fetal echocardiography will be requested from 13-14 weeks, and another at 20-22 weeks, due to the increased risk of heart defects.

7.3 Prediction and prevention of prematurity

A cervical length < 25 mm, at 20-24 weeks, in asymptomatic patients with twin pregnancy is a moderate-to-good predictor of spontaneous preterm birth < 28, < 32 and < 34 weeks. For this reason, cervical length is also the tool used to predict preterm birth in twins. Cervical length decreases notably with respect to singletons, especially after 24 weeks.

Weeks	5th percentile	Median	95th percentile
12	35,6	41,9	48,1
13	34,1	41,3	48,5
14	32,9	40,8	49,7
15	31,6	39,9	49,3
16	30,1	39,6	49
17	28,7	38,9	49,1
18	27,3	38,2	49,2
19	25,8	37,5	49,1
20	24,4	36,7	49
21	22,9	35,9	48,8
22	21,5	35	48,5
23	20	34,1	48,1
24	18,6	33,1	47,7
25	17,1	32,1	47,1
26	15,6	31	46,4
27	14,2	29,9	45,5
28	12,7	28,6	44,6
29	11,2	27,4	43,5
30	9,7	26	42,3
31	8,3	24,6	41
32	6,8	23,2	39,5
33	5,3	21,6	37,9
34	3,8	20	36,1
35	2,4	18,3	34,2
36	0,9	16,5	32,2

7.3.1 Preventive strategies

- Progesterone: its systematic use in asymptomatic twins has not shown any benefit. In contrast, in asymptomatic twins with cervical length < 25 mm, between 18-24 weeks, vaginal progesterone administration has shown a trend towards reducing preterm delivery and improves perinatal outcomes. Based on the available evidence, in multiple pregnancies with cervical length < 25 mm before 24 weeks, treatment with 400 mcg/24 h vaginal progesterone should be initiated and maintained until 34 weeks. There are no data on the strategy to follow when an asymptomatic patient presents a cervical length less than 5th centile beyond 24 weeks. However, in the absence of data, it is proposed to follow the same strategy as that for before 24 weeks.

- Cervical cerclage:
    - Routine cervical cerclage has not been shown to be of benefit and there are data pointing to its harmfulness if performed without indication.
    - Cerclage indicated by previous obstetric history has not shown to be beneficial in patients with twin gestation and a history of preterm delivery. Its indication should be assessed, as in singleton pregnancy, in pregnant women with a history of two or more fetal losses in second or early third trimester suggestive of cervical insufficiency.
    - Cerclage indicated for cervical shortening, with the available evidence; it should not be offered systematically to all these patients, and its use should be individualised in cases of progressive shortening (especially in cervical length < 15 mm) despite vaginal progesterone.
    - Cerclage indicated for cervical dilatation will be indicated in cases of cervical insufficiency, when a physical examination identifies asymptomatic cervical dilatation > 1 cm and < 5 cm, before 24 weeks of gestation.
- Cervical pessary: its routine use in twin pregnancies has not demonstrated any benefit. Results in selected pregnancies with cervical length < 25 mm are contradictory and current meta-analyses do not recommend its use.

8. TIMING OF BIRTH

Uncomplicated multifetal pregnancies should be delivered earlier than singleton pregnancies so as to reduce fetal and maternal morbidity and mortality. In the absence of complications, the recommended timing of delivery will be:

- Dichorionic pregnancy: preferably between 37.0-38.0 weeks.
- Monochorionic-diamniotic pregnancy: preferably between 36.0-37.0 weeks.
- Monochorionic-monoamniotic pregnancy: preferably between 32.0-32.6 weeks. Fetal lung maturation (betamethasone 12 mg/24 h 2 doses) and fetal neuroprotection (MgSO4) should be administered prior to delivery by elective caesarean section.
- Triplet pregnancy: preferably between 34.0-35.0 weeks, depending on chorionicity (trichorionic 35.0 weeks and triplets with monochorionic component 34.0 weeks). If delivery occurs before 35.0 weeks, a course of fetal lung maturation will be administered prior to delivery by elective caesarean section.
  In twin or triplet pregnancies with a monochorionic component that are delivered before 34.0 weeks, fetal neuroprotection with MgSO4 prior to birth is recommended, regardless of the mode of delivery. Neuroprotection will also be recommended in cases of monochorionic pregnancy and previous history of fetal surgery (cord occlusion, laser) if delivered before 34.0 weeks.

8.1 Induction of labour

Precautions during cervical ripening and oxytocin use to induce labour are similar to those for singletons, but taking into consideration that there is a higher risk of uterine rupture, especially in patients with previous caesarean section.
Cervical ripening is performed following our guidelines for patients at high risk of uterine hyperstimulation by using controlled-release vaginal dinoprostone.
If there is a history of previous caesarean section, there is a relative contraindication for cervical ripening with prostaglandins, and mechanical and/or induction with oxytocin will be considered if obstetric conditions are favourable (Bishop > 6).
In monochorionic twins that meet criteria for attempted vaginal delivery, it is advisable to perform a Doppler study of MCA-PSV (middle cerebral artery peak systolic velocity) upon admission in order to rule out TAPS, in which case pregnancy should be delivered by elective caesarean section.

9. DELIVERY

9.1 Mode of delivery

It is determined by the number of fetuses, amnionicity, fetal statistics, gestational age and estimated fetal weight. The mode of delivery should always be assessed individually with the patient, also considering the criteria and experience of the specialists attending to the delivery.

Recent studies have shown that selectively indicated vaginal birth does not increase the risk of fetal or maternal morbidity and mortality compared to a planned caesarean section. However, the patient should be informed that, if attempting a vaginal delivery, the chance of caesarean section at the onset of or during labour is about 35-40% and the chance of caesarean section for the second twin is 5-10%. It is important to report factors that increase the risk of caesarean section: nulliparity, high BMI, advanced maternal age, non-cephalic presentation of the second twin.

- Gestation age ≥ 32 weeks and estimated fetal weight > 1500 g:
  - Both fetuses in cephalic presentation: attempt vaginal birth
  - 1st cephalic / 2nd non-cephalic: attempt vaginal birth.

- Gestational age < 32 weeks or estimated fetal weight < 1500 g:
  - Both fetuses in cephalic presentation: attempt vaginal birth.
  - 1st cephalic/2nd non-cephalic: the literature shows discordant results as to whether caesarean section improves neonatal outcomes. In elective birth situations, it would seem reasonable to perform a caesarean section in order to minimise the risk of injury to the 2nd twin during breech extraction; however, in non-elective situations, especially in advanced labour conditions, or if there is an intention of delayed-interval delivery of the second twin, a vaginal delivery may be chosen, always on an individual basis with the patient and according to the criteria and experience of the obstetric team attending to the delivery.
  - Gestational age < 26 weeks: Consider the possibility of delayed-interval delivery of the second twin. The mode of delivery should be assessed on an individual basis, given that there is not enough evidence on the potential risks/benefits to make a firm recommendation. Gestational age, progression of labour and the experience in breech delivery of the specialists attending to the delivery should be taken into account.

Indications for elective caesarean section:

- Monoamniotic twins.
- Multifetal pregnancy (3 or more fetuses).
- Non-cephalic first foetus.
- Larger second twin (weight discordance > 25%), especially in non-cephalic presentation.
- Other indications for caesarean section due to maternal, fetal or placental pathology.

9.2 Management of labour

This is considered a high-risk delivery. It should be remembered to assess fetal statistics by ultrasound and obtain a maternal blood sample for blood banking upon admission.

Loco-regional anaesthesia is recommended, especially for the management of the delivery of the second twin. Continuous and simultaneous fetal heart rate monitoring

of both fetuses is recommended until delivery. In case of a non-reassuring fetal heart rate status of one or both foetus(es), and difficulty to achieve proper cardiotocographic or biochemical monitoring, caesarean section is recommended. In case of uterine hypodynamia, controlled oxytocin stimulation is allowed.

First stage of labour can take place in a standard delivery room, but the second stage should take place in an operating room with an ultrasound available. The multidisciplinary team at the time of delivery should comprise:

- o 2 obstetricians.
- o 2 midwives.
- o An anaesthesiologist.
- o Neonatologists (1 or 2 according to gestational age).
- o 2 auxiliary nurses.

After delivery of the first foetus, and after clamping the umbilical cord, a vaginal examination to check the presentation of the second twin, keeping the sac intact, is recommended. In case of monochorionic pregnancy, clamp the umbilical cord immediately to reduce the risk of acute transfusion phenomenon of the second twin.

In case of hypodynamia between delivery of the first and second foetus, start oxytocin stimulation. Once the second twin's presenting part is engaged, perform a controlled amniorrhexis of the second sac. Maintain fetal heart rate monitoring during the delivery of the second twin.

In case of a transverse or oblique lie during the hypocontractile period and guided by ultrasound, perform an external cephalic version. Depending on the experience of the obstetrician, an internal podalic version and total breech extraction could be assessed. Internal podalic version and total breech extraction criteria:

- Gestation age ≥ 32 weeks and estimated weight > 1500 g.
- Intact amniotic sac before performing the procedure.
- Administer uterine relaxant (nitroglycerin 50-100 µg in intravenous bolus) prior to procedure.
- Second foetus with estimated weight no more than 25% higher than the first.

In case of failure of any of the manoeuvres or non-reassuring fetal heart rate status, an emergent caesarean section of the second twin is recommended.

Delivery time between twins: in 70% of deliveries, birth of the second foetus takes place within 30 minutes. However, a maximum time for the delivery of the second twin is not established, as long as there are no signs of fetal distress, cord prolapse and/or excessive bleeding.

Concerning the third stage of labour, there is an increased predisposition to uterine atony due to uterine overdistention. Preventive measures for postpartum haemorrhage:

- Perform an active management of the third stage of labour after the delivery of the second twin
- Intravenous Oxytocin 3-5 IU + 10-20 IU in perfusion (0.9% saline solution 500 cc at 125 ml/h) after delivery.
- Carbetocin 100 µg intravenous will be administered in case of elective caesarean section.
- Check complete placental delivery. If not, manual removal (+/- curettage) under antibiotic prophylaxis is recommended.
- Blood bank available if blood transfusion is needed

10. SPECIFIC SITUATIONS

10.1 Monochorionic-monoamniotic twins

They represent 1% of twin pregnancies but are associated with very high risk of fetal loss (50% < 16 weeks and 5-10% > 24 weeks). In addition to the complications of monochorionic pregnancy, there is also the increased risk of fetal demise associated with cord entanglement.

Follow-up visits and ultrasound scans prior to viability are the same as for monochorionic diamniotic twins. Management after viability is controversial, although inpatient management based on daily monitoring of fetal well-being has not been demonstrated to improve perinatal outcomes compared to outpatient management. From 26-28 weeks onwards, an intensive weekly or twice-weekly ultrasound and cardiotocographic monitoring is advisable. If fetal well-being is threatened, hospital admission will be recommended and management (delivery, fetal therapy, expectant management) will be agreed with the parents according to the specific complication and gestational age.

Delivery by elective caesarean section is recommended from 32 weeks (preferably between 32-33 weeks). A course of fetal lung maturation (betamethasone 12 mg/24 h, 2 doses) and fetal neuroprotection ($MgSO_4$) will be administered prior to delivery.

10.2 Fetal growth defects

Fetal growth is assessed using specific growth charts for multiple pregnancy and according to chorionicity.

Discordant growth is considered when the estimated weight difference is > 20-25% based on the estimated weight of the larger twin: (larger weight - smaller weight) x 100/larger weight. A weight discordance ≥ 25% is an independent poor prognostic factor associated with increased perinatal mortality and morbidity, especially in monochorionic twins.

Fetal growth is considered restricted when the estimated fetal weight is below the 10th percentile. When establishing a diagnosis of fetal growth restriction, chorionicity should always be considered, as management and treatment differ according to chorionicity.

In a dichorionic twin pregnancy with selective intrauterine growth restriction, the stage classification is based on the degree of growth restriction and Doppler abnormalities, excluding uterine artery flow. Diagnostic criteria, monitoring of fetal well-being and criteria for admission and lung maturation are the same as for a singleton pregnancy. Selective FGR in monochorionic pregnancy management will be detailed in a specific chapter.

When it comes to the time of delivery, the decision should be individualised, always after prenatal counselling by an expert neonatologist. Provide information on the risks, considering gestational age, severity of Doppler abnormalities and try to agree with progenitors an expectant attitude in benefit of the normally grown twin.

Criteria and gestational age for delivery are:

- **SGA** (Estimated Fetal Weight, EFW ≥ p3 and < p10) **or stage I FGR** (EFW < p10 + CPR < p5 [in two determinations > 12 h apart] or fetal middle cerebral artery (MCA) pulsatility index (PI) MCA-PI < p5 [in two determinations > 12 h apart])**:** Delivery from 37 weeks onwards. Vaginal delivery not contraindicated if an optimal intrapartum control of fetal well-being can be assured.
- **Stage II FGR** (EFW < p10 + absent end-diastolic flow (AEDF) in the umbilical artery (UA) in > 50% of the cycles measured in a free loop in both arteries, in two determinations > 12 h apart): Delivery from 34 weeks. Elective caesarean section.
- **Stage III FGR** (EFW < p10 + reverse end-diastolic flow in UA in > 50% of the cycles measured in a free loop in both arteries, in two determinations > 6-12 h apart or PI in DV > p95 or absent diastolic flow in DV in two determinations > 6-12 h apart): Delivery from 30 weeks. Elective caesarean section.
- **Stage IV FGR** (EFW < p10 + pathological CTG tracing (variability <5 in the absence of sedative drugs and/or decelerative pattern) or reverse diastolic flow in DV (in two determinations > 6-12 h apart)). Offer delivery from 28 weeks onwards. Elective caesarean section.

Prior to termination, assess the need for lung maturation and neuroprotection.

10.3 Delayed-interval delivery

Delayed delivery of the second twin is a justified management with the aim of increasing and improving the survival of the remaining twin, when the delivery of the first foetus occurs at a previable or extremely premature gestational age.

Recent studies report an increased perinatal survival of the remaining foetus compared to the first foetus, with a median interval delivery between the first and second twin of 29 days and a failure rate of 32% (immediate delivery of the second twin). Maternal morbidity has been reported at 39%, although the percentage of severe morbidity is less than 11%: local infection or endometritis (11%), sepsis (5.5%), chorioamnionitis (13%), postpartum haemorrhage (6.6%), placental abruption (4.4%), hysterectomy (1.1%). There are no reported cases of maternal death.

10.3.1 Indications

- Dichorionic and monochorionic diamniotic twin pregnancies.

- Delivery of first twin before 30 weeks (between 30-32 weeks, decision should be individualised, considering the lower success rate, the associated risk factors, maternal morbidity and completed lung maturation).
- If the first twin is in breech presentation and < 26 weeks: consider delivery of the first twin in breech with the aim of delaying the delivery of the second twin. If the first twin is in breech presentation ≥ 28 weeks, elective caesarean section of both twins is recommended. Between 26 and 28 weeks, assess the best option on an individual basis.

10.3.2 Contraindications

- Suspected loss of fetal well-being, congenital anomalies or premature rupture of membranes in the second twin.
- Significant haemorrhage after delivery of the first twin.
- Suspected chorioamnionitis. If there are signs of intraamniotic infection, and it is feasible, it is recommended to perform an amniocentesis.

10.3.3 Management during delivery of the first twin

It is important that the decision to attempt a delayed-interval delivery is made before the delivery of the first twin, by explaining to both progenitors the main objective of this management and the procedure itself. Obtain verbal consent and record it in the medical record.

- Epidural anaesthesia for the delivery of the first twin, whenever possible.
- Intrapartum intravenous tocolytic administration (atosiban).
- Intrapartum intravenous antibiotic therapy (Ampicillin 2 g/6 h + ceftriaxone 1 g/12 h + clarithromycin 500 mg/12 h (oral).
- Avoid episiotomy.
- Early cord clamping and umbilical cord ligation as high as possible.
- Take vaginal and endocervical cultures.
- Vaginal and cervical washing with chlorhexidine.
- Administer 1500 IU of anti-D globulin, if the patient is rhesus-negative.

10.3.4 Attitude towards interval

- Epidural anaesthesia could be maintained, initially, for up to 48-72 hours.
- Intravenous tocolytic treatment will be maintained for the first 48 hours after delivery of the first twin and, if there is clinical stability, it will be replaced by oral tocolytic treatment for the next 48 hours; finally, it may subsequently be withdrawn if absence of uterine contractions.
- Fetal lung maturation with betamethasone from 24.0 weeks, if not received before. Assess its administration between 23.0 and 23.6 weeks after parental counselling by an expert neonatologist
- Empiric intravenous antibiotic therapy should be maintained until definitive culture results. Antibiotics should be withdrawn if cultures are negative. If positive, antibiotic treatment should be adapted according to the antibiogram.

- Absolute bed rest for 48 hours, allowing relative rest afterwards, if patient is clinically stable.
- Strict clinical and analytical control: serial haemogram and C-reactive protein (CRP). In absence of clinical changes, blood tests will be performed: daily for the first 3 days and, subsequently, every 48-72 hours. From the third week onwards, an analytical control will be performed weekly.
- In case of the need for re-evaluation of cervical conditions, avoid vaginal examinations and use ultrasound assessment of cervical length.
- Amniocentesis and cervical cerclage should not be performed systematically, as there is controversy. Each case should be considered on an individual basis according to clinical situation and laboratory test results. Cervical cerclage may be considered if there is evidence of progressive cervical shortening or membrane exposure. Prior to performing it, subclinical intraamniotic infection in the remaining sac must be ruled out by an amniocentesis.
- The patient will remain hospitalised during the acute period, with possibility of hospital discharge and outpatient management, if there is clinical stability.

10.4 FETAL DEATH OF ONE TWIN DURING THE SECOND AND THIRD TRIMESTER

Stillbirth study protocol should be applied. Given that the most recent literature has not demonstrated the hypothetical risk of disseminated intravascular coagulation (DIC) suggested in the past, expectant management seems justified. Chorionicity is the most important condition in pregnancy prognosis:

- Dichorionic: there is an increased risk of prematurity. Recommend home rest and serial cervical length assessment. Expectant management until term and elective delivery between 37.0 - 38.0 weeks, according to dichorionic criteria, is recommended.
- Monochorionic: in addition to the increased risk of prematurity, there is a high risk of intrauterine death (20-25%) or severe neurological sequelae (20-30%) for the surviving twin. Referral to a tertiary centre is recommended. MCA-PSV should be assessed to rule out signs of fetal anaemia due to exsanguination. If MCA-PSV Doppler is normal, expectant management with weekly ultrasound monitoring is recommended.

  If there are signs of fetal anaemia, cordocentesis and intrauterine transfusion can be considered, although this has not demonstrated a significant reduction in the risk of neurologic injury. It is recommended to rule out the presence of central nervous system abnormalities in the surviving foetus by neurosonography and MRI around 30-32 weeks (preferably 4-6 weeks after diagnosis of intrauterine fetal death). Elective termination at 34-36 weeks is recommended, always on an individual basis considering the causes and gestational age of demise of the other twin.

10.5 EMBRYO OR FETAL REDUCTION/SELECTIVE FETAL TERMINATION

Fetal reduction at parental request may be considered in the following situations

- Elective embryo reduction in triple or higher gestation.
- Selective fetal termination in discordant anomaly.