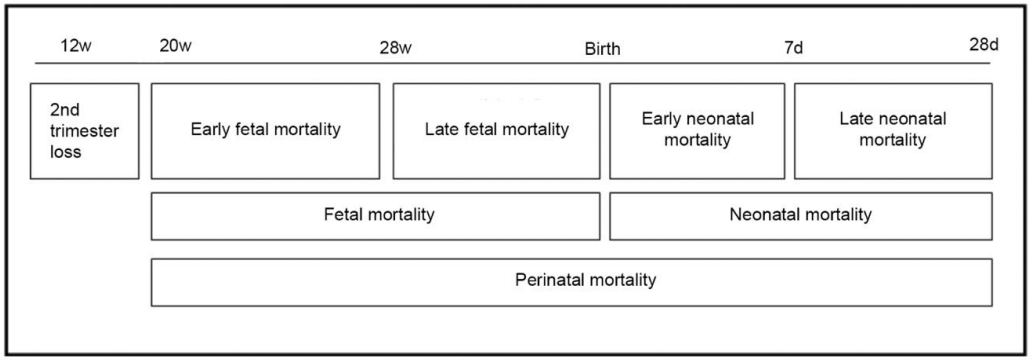
SECOND TRIMESTER PREGNANCY LOSS AND FETAL DEATH

A.Toro, O. Gómez, N. Masoller, A. Peguero,
M. Illa, C. Esteve, A M. González F.

1. DEFINITIONS

Classically, fetal mortality has been defined as that which occurs > 22 weeks of gestation or > 500 g (WHO). However, following international initiatives (CDC, ACOG and the "Stillbirth Collaborative Research" group), the ICD-10 coding system has defined fetal mortality as that which occurs after 20 weeks of gestation. Given that the coding system is mandatory in Spain, the Catalan Society of Gynaecology and Obstetrics (SCOG, Societat Catalana d'Obstetrícia i Ginecologia) has accordingly adopted the new definition. This new cut-off point will also be applied to the definition of perinatal mortality, which will be considered as those cases that occur from 20.0 weeks of gestation to the first 28 days of life (< 28); and those cases in which the fetal death occurs between week 12.0 and 19.9 of gestation will be considered a second trimester loss.



- **Second trimester pregnancy loss**: absence of signs of fetal vitality between 12.0 – 19.6 weeks.
- **Intrauterine fetal demise/death (IUFD)**: absence of signs of fetal vitality after 20.0 weeks of gestation or with a fetus > 350 grams if the gestational age is unknown. This death can occur during labour (intrapartum fetal death) or it can be diagnosed prior to the onset of labour (antepartum fetal death). According to gestational age, we differentiate:
  - **Early IUFD**: between 20.0 – 27.6 weeks.
  - **Late IUFD**: between 28.0 – 36.6 weeks.
  - **Full term IUFD**: from 37.0 weeks.
- **Born alive**: regardless of gestational age, any fetus born with signs of vitality. The presence of gasping or ventricular extrasystoles are not considered signs of vitality.
- **Neonatal death**: occurs before 28 days of life.
  - **Early neonatal death**: between 0 – 7 days postpartum.
  - **Late neonatal death**: between 8 – 27 days postpartum.
- **Perinatal mortality**: includes both IUFD (from 20.0 weeks of pregnancy to delivery) and neonatal death (27 days after birth).

2. SECOND TRIMESTER PREGNANCY LOSS

Given the diagnosis of a pregnancy loss in the second trimester, patients can be offered an informative brochure if your clinic has one.

2.1 STUDY PROTOCOL

It is necessary to inform patients of the study protocol and request their oral and written consent in order to carry it out.

When diagnosing a second trimester pregnancy loss (12.0 – 19.9 weeks) the study protocol will include:

1. **Medical history**: anamnesis aimed at identifying risk factors and physical exploration.
2. **Ultrasound study**: to confirm the diagnosis and assess the presence of fetal abnormalities.
3. **Blood test**: to evaluate complete blood count (CBC), coagulation test, blood type and Rh factor, Coombs test, blood biochemistry test (including liver function test).
4. *During the COVID-19 situation, a maternal nasopharyngeal swab will be performed for COVID-19 PCR, even if the patient does not present symptoms compatible with infection.*
5. **Maternal serology test**: IgM and IgG antibodies of toxoplasma, Rubella, CMV and parvovirus B19. Syphilis VDRL and Elisa. HIV, HBV and HCV serology test should be performed in case it has not been done before.
6. **Antiphospholipid antibodies** (lupus anticoagulant, IgG and IgM anti-cardiolipin, IgG and IgM antibeta-2-glycoprotein).
7. **Urine drug test**.
8. **Kleihauer–Betke test**: quantification of fetal haemoglobin or RhD cells in maternal bloodstream for the identification of feto-maternal haemorrhage. It will be requested preferably before delivery and in all cases, since feto-maternal haemorrhage (FMH) can occur in the absence of maternal symptoms. The aim of this study is to diagnose FMH as a possible cause of pregnancy loss and to determine the required dose of Rho(D) immune globulin (RhIg) to be administered to Rh negative patients.
9. **Genetic study**: amniocentesis will be offered in all cases. Depending on the technical difficulty, it may be performed at the time of diagnosis or it can be scheduled in the ultrasound unit.
    a. If amniocentesis is technically feasible:
        i. Molecular karyotyping (CMA-chromosomal microarray analysis) will be performed in amniotic fluid in those cases in which the study has not been previously done. In all cases, prior to performing the CMA, a QF-PCR will be performed, and the CMA will only be carried out if the QF-PCR does not present anomalies.
        ii. A sample of fetal skin will be obtained (5 x 5 mm from the inner side of the thigh or forearm including subcutaneous tissue, after disinfection with alcohol) to get a DNA sample with the intention of having genetic material to carry out further studies if required.
    b. If amniocentesis is not technically feasible or the parents refuse to perform it:
        i. Two fetal skin samples will be obtained to perform CMA (in those cases in which the study has not been previously done) and DNA storage.

    It is recommended to obtain samples as close as possible to the time of pregnancy loss. Samples must be obtained and shipped under sterile conditions and must be stored at room temperature.

10. **Infection study**: placental culture will be performed (sample collection between amnion and chorion).
    a. If amniocentesis is technically feasible, the following will be performed: amniotic fluid PCR for cytomegalovirus and parvovirus B19 and amniotic fluid culture. *Also, during the Covid-19 episode, PCR COVID-19 will be added*.

   b. If amniotic fluid is not available, a 1 cm^3 placental fragment will be obtained for PCR study of cytomegalovirus, parvovirus B19 and COVID-19.

11. In case of symptoms suggestive of threatened preterm labour, PROM, intraamniotic infection or maternal infection, request complementary examinations according to specific protocols and assess the performance of fetal cultures.
12. **Anatomopathological study**:
    a. **Placenta**: recommended in all cases. Send the placenta in formaldehyde to the Pathological Anatomy Service. Assess in advance the need to obtain samples to carry out additional studies.
    b. **Fetus**:
        i. If < 14.0 weeks, send the fetus together with the placenta as a Pathological Anatomy sample.
        ii. If ≥ 14+0 weeks, request a necropsy study if the family authorises it. Specify relevant data and the need for complementary examinations. If parents refuse to perform a necropsy, permission will be requested to perform a post-mortem MRI in those cases >17.0 weeks.

3. INTRAUTERINE FETAL DEATH (IUFD)

Antepartum fetal death contributes to 50% of perinatal mortality. In our centre there is a Perinatal Mortality Committee whose objective is to define the most probable cause of death of the fetus or newborn and to define future recommendations.

Given the diagnosis of antepartum fetal death, patients should be offered the possibility to have an informative brochure about perinatal grief.

3.1 **STUDY PROTOCOL**

The systematic study of the possible causes of antenatal death is essential to achieving correct perinatal and future advice. The autopsy of the fetus, the anatomopathological study of the placenta and the fetal genetic study are the most relevant tests for determining the cause. However, before the diagnosis of antepartum fetal death, all the examinations detailed below must be performed, given that in some cases the fetal death may be due to the interaction or the sum of several causes.

It is essential to inform patients of the study protocol to be carried out and to request their oral and written consent.

*3.1.1 **ANTEPARTUM STUDY***

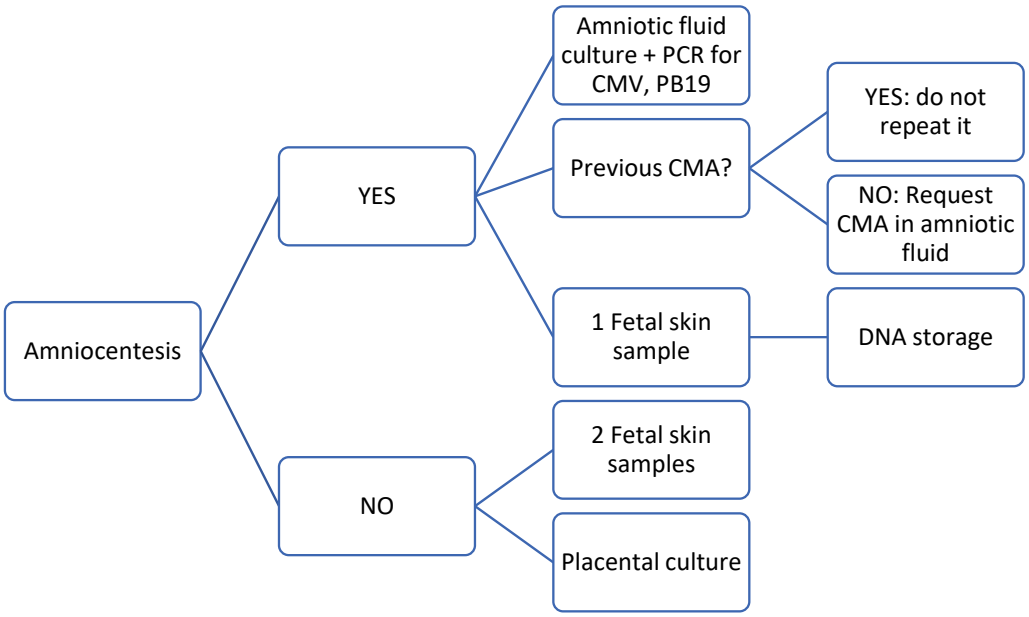
1. **Medical history**: including perinatal and familiar data. Anamnesis aimed at identifying risk factors. Physical examination including determination of blood pressure and measurement of fundal height.
2. **Ultrasound study**: to confirm the diagnosis, assess fetal presentation, estimated fetal weight, amniotic fluid, placenta (assessment of pathologic imaging and rule out placenta previa), and the presence of fetal abnormalities.
3. **Blood test**: to evaluate complete blood count (CBC), coagulation test, blood type and Rh factor, Coombs test, blood biochemistry test (including liver function test).
4. *During the COVID-19 situation, a maternal nasopharyngeal swab will be performed for COVID-19 PCR, even if the patient does not present symptoms compatible with infection.*
5. **Maternal serology test**: IgM and IgG antibodies of toxoplasma, Rubella, CMV and parvovirus B19. Syphilis VDRL and Elisa. HIV, HBV and HCV serology test should be performed in case it has not been done before.

6. **Antiphospholipid antibodies** (lupus anticoagulant, IgG and IgM anti-cardiolipin, IgG and IgM antibeta-2-glycoprotein).
7. **Urine drug test**.
8. **Kleihauer–Betke test**: quantification of fetal haemoglobin or RhD cells in maternal bloodstream for the identification of feto-maternal haemorrhage. It will be requested preferably before delivery and in all cases, since fetal-maternal haemorrhage (FMH) can occur in the absence of maternal symptoms. The aim of this study is to diagnose FMH as a possible cause of pregnancy loss and to determine the required dose of Rho(D) immune globulin (RhIg) to be administered to Rh negative patients.
9. **Urine protein/creatinine ratio** (UPCR) test. Especially when suspecting preeclampsia and/or IUGR.
10. **Amniocentesis.** In those cases, in which it is technically possible, an amniocentesis with will be offered:
    a. **Genetic study:** Molecular karyotype (CMA-chromosomal microarray analysis) will be carried out in amniotic fluid in those cases in which the study has not been previously performed. In all cases, prior to carrying out the CMA, a QF-PCR will be carried out and the CMA will only be performed if QF-PCR does not present abnormalities.
    b. **Infection study:** In all cases, PCR will be performed on amniotic fluid for cytomegalovirus and parvovirus B19, as well as culture of amniotic fluid. Also, during the COVID-19 episode, PCR for COVID-19 will be added.

    It is recommended to obtain samples as close as possible to the time of pregnancy loss. Samples must be obtained and shipped under sterile conditions and must be stored at room temperature.

3.1.2 IMMEDIATE POSTPARTUM STUDY

1. **Fetus and placenta assessment:** record the weight of the fetus and placenta in the clinical history. Highlight remarkable macroscopic findings.
2. **Anteroposterior/lateral X-ray** of the fetus may be requested.
3. A **sample of fetal skin** will be obtained in all cases (5 x 5 mm from the inner side of the thigh or forearm, including subcutaneous tissue, after disinfection with alcohol).
    a. If CMA has been performed in amniotic fluid: ONE fetal skin sample will be sent for DNA extraction and storage with the intention of having genetic material available for further studies if necessary.
    b. If CMA is not available: TWO fetal skin samples will be sent, one for CMA study and another one for DNA extraction and storage.
4. In selected cases (due to medical history or ultrasound findings), request the collection of specific samples of fetal tissues for the study of metabolic diseases.
5. In selected cases of suspected maternal or fetal infection (compatible clinical signs or ultrasound findings), the study of DNA in the placenta or fetal tissues using the PCR technique may be requested. In cases in which amniocentesis could not be performed (due to non-acceptance or absence of amniotic fluid), a 1 cm^3 fragment of placenta will be obtained for a PCR study of cytomegalovirus, parvovirus B19 and COVID-19. Additionally, placental culture (collecting the sample between amnion and chorion) will be performed.
6. In case of symptoms suggestive of threatened preterm labour, PROM, intraamniotic infection or maternal infection, request complementary examinations according to specific protocols and assess the performance of fetal cultures.
7. **Necropsy**: it is recommended in all cases. Parents must authorise it. It is important to detail the relevant clinical information in the necropsy request. The fetus should not be stored in formalin or frozen. Given the refusal of the parents to perform a necropsy, permission will be requested to perform a post-mortem MRI.
8. **Anatomopathological study of the placenta:** it is recommended in all cases. Placenta should be sent in formaldehyde to the Pathology Department. Previously assess the need to obtain samples to carry out complementary studies.



3.1.3 STUDY AND POSTPARTUM MANAGEMENT IN THE OBSTETRICS WARD:

1. **Lactation suppression**: cabergoline 1 mg single dose in pregnancies > 16 weeks. Remember that this drug is contraindicated in patients with hypertension. In this case, only physical measures and water restriction will be recommended.
2. In **Rh-negative patients**, a standard intramuscular dose of **300 mcg (1500 IU) of Rho(D) immune globulin** will be administered within the first 72 hours postpartum. This dose is capable of protecting the mother in case of fetomaternal haemorrhage of up to 30 ml (which corresponds to 0.6% fetal haemoglobin, HbF, in maternal blood or RhD-positive cells).
   In case of significant fetomaternal haemorrhage, it will be necessary to adjust the dose according to the estimated haemorrhage. 200 mcg Rho(D) immune globulin will be administered for every 10 ml of fetomaternal haemorrhage. The calculation for the equivalence of the % of fetal red blood cells into ml of fetomaternal haemorrhage is: % red blood cells x 50 = ml of fetomaternal haemorrhage.
3. Check that all the **required documents have been completed**. Record in the patient history the decision of the parents regarding the burial and the autopsy. Reference, if it were the case, if this decision is pending or if there has been a change of decision.
4. Request oral glucose tolerance test (**OGTT)** (75 g), if the fetal weight at birth > 90th percentile, to be performed at the post-discharge visit, except in those cases with a basal glycemia > 126 or pregnant women with a previous diagnosis of diabetes.
5. Favour **early discharge** when the patient's condition allows it. Schedule an appointment in 6 weeks to close the case and assess future advice.

3.1.4 *STUDY IN THE FOLLOW-UP VISIT*

- **Study thrombophilia in selected cases**: IUGR, placental abruption, placental lesions, personal history of thrombosis and recurrent fetal loss. Antiphospholipid antibodies, anticardiolipin antibodies (IgG and IgM), antibeta2-glycoprotein antibodies, G-20210-A mutation of the prothrombin gene, activated Protein C resistance, V Leiden mutation, Protein C (functional and antigen) and protein S (free and total) will be requested.

- **Parents' karyotype study:** in cases of recurrent fetal loss (>= 2 fetal losses) or due to findings from the fetal death study.

4.7 MANAGEMENT IN THE IMMEDIATE PUERPERIUM

It is important to favour a correct environment for mourning, so it should be offered in all cases that the parents (or other relatives if they request it) stay with the newborn for as long as they need. In the event that the parents do not want to see the newborn, the possibility of holding it properly wrapped can be offered. It is favourable to offer the possibility of taking photographs and/or obtaining footprints, which will be offered to the parents on cardboard designed for this purpose. If there is a demand to do a brief farewell ritual, attempt to favour the appropriate space. Record in the history a brief summary of what happened (whether the family has seen the fetus, whether or not they want a necropsy and whether or not they will take charge of the burial).

4.7 INTERBIRTH INTERVAL

The recommended birth interval period after the end of pregnancy in case of fetal death is 6 months. The data available in the literature establish that shorter interbirth periods are associated with a slight increase in the risk of spontaneous abortion, prematurity and low birth weight.

In all cases, the results of the different tests carried out (genetic study, necropsy, etc.) will be evaluated to establish future pre-pregnancy advice and the presence of risk factors related to prematurity (history of preterm birth, PROM, etc.), in which case a pre-pregnancy visit can be made in the Prematurity Unit to define future measures and establish the recommended interbirth interval period (9-12 months according to data available in the literature).

3.4 PREGNANCY CONTROL WITH A HISTORY OF FETAL DEATH OF UNKNOWN CAUSE

It is important to evaluate the study carried out in the previous pregnancy and complete the study before recommending a new pregnancy.
The risk of recurrence of antenatal death as well as presenting other obstetric complications (preeclampsia/IUGR/early pregnancy loss) increases between 2-10 times compared to the general population. The risk of recurrence will depend on the cause and the gestational age at the time of death. Globally, the recurrence of death of unknown cause stands at 3% and rises to 11% if there are two previous instances.

A pregnancy control will be carried out as for a high-risk pregnancy. There is no evidence that greater pregnancy control reduces the risk of recurrence, although the patient's anxiety levels can be reduced with more frequent prenatal visits and fetal well-being assessments. Ultrasound will be recommended to assess fetal growth at 28 weeks (± 2w), 32 weeks (± 2w) and 36 weeks (± 2w). It is also recommended to perform a nonstress test (NST) one or two weeks before the time of the previous fetal death (in cases of more than 32 weeks of gestational age). It is important to insist on the control of fetal movements from 28 weeks.
Evaluate ending the pregnancy from week 39, in agreement with the parents, based on the obstetric history, cervical conditions and the emotional state of the parents.

4. TERMINATION OF PREGNANCY

4.1 TERMINATION OF PREGNANCY METHODS

- **Uterine curettage**

- When requested by the patient, and provided the **femoral length is < 12 mm**, surgical evacuation of the uterus can be considered.
- Perform cervical ripening by administering 400 µg of misoprostol (2 Cytotec® tablets in the posterior vaginal fornix 4 hours before the procedure). In case of contraindication to misoprostol, administer 200 mg of mifepristone (1 tablet per os in the 24 hours prior to the intervention).

- **Pharmacological method**: is considered the method of choice.
  - Use the combined regimen of mifepristone-misoprostol (best safety and effectiveness profile).
  - Perform outpatient cervical ripening using 200 mg of mifepristone (hospital dispensing drug) in all cases. Up to 5% of patients may present bleeding during the first 24 hours after the administration of mifepristone, which may cause the expulsion of the pregnancy (less than 3% of cases).
  - Optimal time interval between mifepristone and misoprostol:
    - 12 - 23.6 weeks of pregnancy: 12 - 24 hours.
    - ≥ 24 weeks of pregnancy: 12 hours.
      Although these are the recommended intervals in our centre, mifepristone must ALWAYS be administered since it is also effective at shorter time intervals.
  - The misoprostol administration regimen will vary depending on the gestational age.
  - First dose: administer the first dose of misoprostol always vaginally and then continue orally.
  - When presenting regular uterine contractions (> 2 contractions/10 minutes), do not administer successive doses of misoprostol.
  - Do not start treatment with IV oxytocin until > 4 hours after the last dose of misoprostol (concomitant use of misoprostol and oxytocin increases the risk of uterine hyperdynamics and consequently uterine rupture).

  <u>In case of non-expulsion of the fetus on the first day of treatment:</u>
  - Repeat dose of mifepristone (200 mg per os) at 00:00, which will be administered if the patient is pain-free and regardless of whether the misoprostol course has been completed.
  - Intracervical balloon placement. There is also the option of using intracervical Dilapan® in those cases in which it is considered more appropriate. The intracervical balloon can be maintained for 24 hours. After this time, it is recommended to reassess the case.
  - Explain the process to the patient and allow the pregnant woman a few hours to rest after finishing the course of misoprostol.
  - Repeat new misoprostol regimen. See table below (maximum 5 doses). It is recommended to administer all doses vaginally since it offers greater effectiveness (higher plasma levels of the drug) and a better safety profile.

Gestational age		No previous uterine surgery
12 – 24.6 weeks	**Day 1**	800 mcg vaginally; at 3 hours start: 400 mcg/3h po
	Day 2	800 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
25 – 31.6 weeks	**Day 1**	400 mcg vaginally; at 3 hours start: 200 mcg/3h po
	Day 2	400 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
≥ 32 weeks	**Day 1**	50 mcg vaginally; at 3 hours start: 50 mcg/3h po
	Day 2	50 mcg vaginally; at 4 hours start: 50 mcg/4h vaginally

Treatment in case of non-expulsion of the fetus in 48 hours:

- <25 weeks: depending on the gestational age and the clinical situation of the patient, one can opt for:
  - Prostaglandin F2α intraamniotic. An amniocentesis will be performed with evacuation of amniotic fluid and instillation of 10 x 1 ml vials of carboprost (2500 µg, in total).
  - Prostaglandin E2 IV. An infusion pump will be used. Dilution in 500 cc of 5% glucose serum of one vial of PG E2 (5 mg each vial), obtaining a concentration of 10 micrograms/mL. The infusion will begin at 15 ml/h = 5 drops/min and will increase every 30 minutes as tolerated up to a maximum of 60 ml/h = 20 drops/min. The infusion can be interrupted for overnight rest.
- > 25 weeks: based on the Bishop score, assess the initiation of oxytocic stimulation according to the labour induction protocol in viable gestation.
  Previously reassess the analgesic regimen with the Anaesthesiology team.

4.2 **GENERAL CONSIDERATIONS TO ASSESS:**

- Determine placental insertion by ultrasound prior to the start of pharmacological treatment: rule out the presence of a low insertion placenta (5-7% of cases in the second trimester of pregnancy) and insertion on the previous caesarean section scar (assess risk of placental accreta).
- During treatment with prostaglandins, carry out clinical control: appearance of systemic symptoms and control of blood pressure, temperature and pulse.
- In order not to increase the risk of uterine hyperdynamics, avoid concomitant use of oxytocin and misoprostol. Do not start treatment with oxytocin IV until 4 hours after the last dose of misoprostol.

4.3 **ANALGESIC REGIMEN AND TREATMENT OF SIDE EFFECTS**

1. Administer an anxiolytic at the start of treatment: Diazepam 5 mg sublingually. It can be continued with 5 mg/12-24 hours according to tolerance.
2. Start intravenous analgesia with elastomeric/volumetric pump of Tramadol + Dexketoprofen (or Metamizole if contraindication to NSAIDs) + Methadone + Ondansetron. The elastomeric pump is a non-electronic system for continuous drug infusion that allows the perfusion rate to be preset (constant or variable).
3. Allow the intake of a liquid diet, as well as the mobilisation of the patient.
4. In case of diarrhoea, administer loperamide 2 mg per os.

FIRST ANALGESIC LEVEL: it will start simultaneously with the start of the misoprostol regimen. Dexketoprofen 50 mg IV single dose will be administered + start of elastomeric/volumetric pump (24 h):

- Pregnancy of < 25 weeks: 100 mL pump (Dexketoprofen 100 mg+ Tramadol 100 mg+ methadone 5 mg+ ondansetron 4 mg+ rest of volume of saline solution) to be administered at a constant rate of 4 mL/h.
- Pregnancy of ≥ 25 weeks: A 100 mL pump will be prepared (Dexketoprofen 150 mg+ Tramadol 200 mg+ methadone 5 mg+ ondansetron 8 mg+ remaining volume of saline solution) to be administered at a rate of 4 mL/h.

- If allergic or intolerant to NSAIDs (a frequent situation in atopic or asthmatic patients), start analgesia with paracetamol 1 g IV and replace Dexketoprofen with metamizole in an elastomeric pump, 4 g if gestational age < 25 weeks and 8 g if gestational age ≥ 25 weeks.
- Complementary analgesia: if pain control is insufficient, 1 g of paracetamol IV/6h can be administered (maximum dose of 4 g/24h, contraindicated in patients with liver dysfunction).
- Rescue analgesia:
    - If VAS > 6 – 7: 20 minutes after the administration of paracetamol, administer 3 mg of methadone subcutaneously under pulse oximetry monitoring.
    - If VAS > 6-7, 20 minutes after methadone administration, it is recommended to transfer the pregnant woman to the Delivery Room to start the second level of analgesia.

SECOND ANALGESIC LEVEL: after checking if a dose of methadone has been administered and at what time, 1 mg midazolam + 50 mcg fentanyl will be administered IV under clinical and respiratory monitoring (respiratory rate and pulse oximeter). If pain persists, fentanyl doses can be repeated up to a maximum dose of 1 mcg/Kg. If the pain persists, start the third level of analgesia.

THIRD ANALGESIC LEVEL: epidural analgesia.

4.4 **ANTIBIOTIC PROPHYLAXIS**

Perform antibiotic prophylaxis only in case of surgical curettage. Antibiotic prophylaxis is not indicated if the termination method is pharmacological.

Antibiotic regimen: cefazolin 3 g IV + Metronidazole 500 mg IV in pre-induction of anaesthesia. In case of allergies to penicillin, cefazolin will be replaced by tigecycline 100 mg IV.

4.5 **CONDUCT IN THE IMMEDIATE POSTPARTUM**

Medical conduct similar to that detailed in the Protocol for Assistance to normal childbirth.

Do not perform systematic ultrasound after expulsion of the fetus and placenta if the patient is asymptomatic (high false positive rate). In case of significant bleeding and/or suspicion of retained placenta, perform an ultrasound to establish the need for curettage.

If the placenta is not delivered after expulsion of the fetus, a new dose of 400 mcg of misoprostol will be administered PO (in gestations of <22 weeks) or 5-10 IU of oxytocin IV or IM (in gestations of > 22 weeks). If the placenta has not been delivered in the following 2 hours, a suction curettage will be performed.

4.6 **CLINICAL ATTITUDE IN CASE OF RETAINED PRODUCTS OF CONCEPTION (RPOC) POST-DISCHARGE**

In the event that the patient explains abnormal bleeding and/or pain after discharge, an ultrasound will be performed.

- If the ultrasound suggests the presence of retained products of conception (heterogeneous ultrasound pattern and/or endometrial thickness > 15 mm), the therapeutic option will be:
    - A uterine suction curettage on a scheduled basis, although depending on the professional criteria, expectant management may be considered or administering misoprostol 800 mcg vaginally with painkillers (Paracetamol-Codeine 500/30 mg + Ibuprofen 600 mg 30-40 minutes before Misoprostol. Then Misoprostol 800 µg, single dose, vaginally. Painkillers can be administered every 6-8 hours if the pain persists).
- In all other cases (endometrial thickness ≤ 15 mm without a heterogeneous ultrasound pattern suggesting RPOC), 1) expectant management will be recommended, although depending on the professional criteria, 2) administration of vaginal misoprostol 800 mcg with prescribed analgesia may be considered.

In all cases, a follow-up visit will be scheduled in 2 - 3 weeks for clinical follow-up. If there is still doubt of the presence of RPOC when performing the ultrasound:

- If a suction curettage has not been previously performed → it will be scheduled within the next days.
- If a suction curettage has already been performed → the patient will be referred to the Gynaecology Service for ultrasound and hysteroscopic evaluation.

In cases where surgical curettage is performed, antibiotic prophylaxis will be administered with Cefazolin 3 g + Metronidazole 500 mg IV before induction of anaesthesia. In case of allergy to penicillin, Cefazolin will be replaced by Tigecycline 100 mg IV.

4.7 SPECIAL SITUATIONS

4.7.1 PREVIOUS CAESAREAN SECTION OR PREVIOUS UTERINE SURGERY

There is evidence that the use of misoprostol increases the risk of uterine rupture in pregnant women with a history of a previous lower-segment transverse caesarean section. In non-viable gestation the risk is between 0.3 - 1.1% for pregnancies < 29 weeks and between 1 - 5% when ≥ 29 weeks. Although the data from the medical literature are limited, the use of misoprostol for the induction of a non-viable pregnancy with a history of a lower-segment transverse caesarean section is generally accepted.

<u>History of 1 previous lower-segment transverse caesarean section or uterine surgery:</u>

- Inform the patient about all the risks in detail and record it in her medical history. The patient must sign the specific informed consent.
- Locate the insertion of the placenta by ultrasound to assess the risk of accreta in the case of a placenta located on a previous uterine scar.
- Request blood reservation at the time of admission.
- Cervical ripening:
  - < 25 weeks: outpatient pharmacological treatment (mifepristone 200 mg).
  - ≥ 25 weeks: cervical ripening balloon. It can be placed upon admission and can be kept for 24 hours. After this time the case will be reassessed.
- It is recommended to decrease the misoprostol dose based on gestational age. See table below (maximum 5 doses)

Gestational age		**Previous uterine surgery**
12 – 24.6 weeks	**Day 1**	800 mcg vaginally; at 3 hours start: 400 mcg/3h po
	Day 2	800 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
25 – 31.6 weeks	**Day 1**	200 mcg vaginally; at 3 hours start: 100 mcg/3h po
	Day 2	200 mcg vaginally; at 4 hours start: 100 mcg/4h vaginally
≥ 32 weeks	**Day 1**	25 mcg/4h vaginally
	Day 2	25 mcg/4h vaginally

- First dose: administer the first dose of misoprostol always vaginally:
  - If gestational age < 32 weeks: continue orally.
  - If gestational age ≥ 32 weeks: continue vaginally since it offers a more stable plasmatic level with higher safety profile.
- During treatment with prostaglandins, carry out clinical control: appearance of systemic symptoms and control of blood pressure, temperature and pulse.
- When presenting regular uterine contractions (> 2 contractions/10 minutes), do not administer successive doses of misoprostol.
- Control of symptoms suggestive of uterine rupture: appearance of pain that persists between contractions, pain at the level of the previous scar, pain radiating to the shoulders or chest, cessation of contractions, change in fetal presentation, vaginal bleeding or haematuria, appearance of dyspnoea, tachycardia, hypotension, or shock.

- In case of non-expulsion of the fetus on the first day of treatment:
    - If gestational age < 25 weeks:
        - Repeat dose of mifepristone (200 mg per os) to be administered at 24:00 if the patient is pain-free and regardless of whether the misoprostol regimen has been completed.
        - Intracervical balloon placement. There is also the option of using intracervical Dilapan® in those cases in which it is considered more appropriate. The intracervical balloon can be maintained for 24 hours. After this time, it is recommended to reassess the case.
    - If gestational age ≥ 25 weeks: remove intracervical balloon and assess cervical conditions. There is the option of using intracervical Dilapan® in those cases in which it is considered appropriate.
- Explain the process to the patient and allow the pregnant woman a few hours to rest after finishing the regimen of misoprostol.
- Repeat a new regimen of misoprostol (see the previous table on day +2). It is recommended to administer all doses vaginally since it offers greater effectiveness (more stable plasma levels of the drug) and better safety profile.
- In case of non-expulsion with a second round of treatment, reassess the case individually.

<u>History of > 1 previous lower-segment transverse caesarean section, other uterine surgeries, caesarean delivery and subsequent childbirth interval < 18 months</u>:

- There are very few data in the literature regarding the safety profile of misoprostol in pregnant women with more than 1 previous lower-segment transverse caesarean section or with a history of other uterine surgeries, and it is currently not possible to establish a specific risk of uterine rupture.
- Given that there is no fetal risk, most clinical guidelines do NOT contraindicate attempted vaginal delivery in this group of pregnant women, although the prostaglandin induction regimen is not well defined.
- In all cases, individualised counselling will be carried out, assessing different factors, such as age, the existence of previous vaginal deliveries and the future reproductive desire of the pregnant woman.
- In case of induction, follow the same pharmacological regimen as in pregnant women with a history of 1 previous lower-segment transverse caesarean section.

4.7.2 ***PREGNANCY WITH PREECLAMPSIA***

Misoprostol is contraindicated in viable pregnancy complicated with preeclampsia due to its potential association with the appearance of acute intrapartum complications such as uterine hyperdynamics, urgent caesarean sections due to FHR abnormalities, and abruptio placentae. Recent studies have not confirmed this association and establish that misoprostol is a safe option in the clinical context of preeclampsia, with higher rates of vaginal delivery and shorter expulsion intervals. In non-viable pregnancy there are no clear recommendations on induction with misoprostol and for the moment there is no contraindication for its use.

In our centre, the induction of a non-viable pregnancy with misoprostol is not contraindicated, although it should be taken into account that misoprostol affects the contractility of vascular smooth muscle, which can condition the appearance of side effects such as hypotension, which are dose-dependent and that may become more relevant in the clinical context of severe preeclampsia.

When having a patient with preeclampsia, the following points should be taken into account:

- Specific information on previously detailed risks, recording this in the medical history. The pregnant woman must sign the specific informed consent form.
- A feticide will be recommended in all cases, including pregnancies of < 23 weeks to reduce the risk of bleeding in the event of an obstetric complication.
- Admission of the patient in the Delivery Room area.

- Clinical control according to the Preeclampsia protocol.
- Blood reservation (2 PRBC) at the time of admission.
- Outpatient pharmacological cervical ripening with 200 mg of mifepristone.
- Adjust misoprostol dose according to gestational age. Do not use doses of misoprostol > 400 mcg due to the increased risk of side effects.
- Always use the vaginal route as it has a better safety profile.
- Recommended regimen based on gestational age and the presence or not of previous uterine surgery:

Gestational age		**Preeclampsia + NO previous uterine surgery**
12 – 24.6 weeks	**Day 1**	400 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
	Day 2	400 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
25 – 31.6 weeks	**Day 1**	400 mcg vaginally; at 4 hours start: 200 mcg/4h vaginally
	Day 2	400 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
≥ 32 weeks	**Day 1**	100 mcg vaginally; at 4 hours start: 50 mcg/4h vaginally
	Day 2	> 34 weeks: induction protocol

Gestational age		**Preeclampsia + AND previous uterine surgery**
12 – 24.6 weeks	**Day 1**	400 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
	Day 2	400 mcg vaginally; at 4 hours start: 400 mcg/4h vaginally
25 – 31.6 weeks	**Day 1**	200 mcg vaginally; at 4 hours start: 100 mcg/4h vaginally
	Day 2	200 mcg vaginally; at 4 hours start: 100 mcg/4h vaginally
≥ 32 weeks	**Day 1**	25 mcg/4h vaginally
	Day 2	50 mcg/4h vaginally; > 34 weeks: induction protocol

- In pregnancies ≥ 34 weeks, induction will be recommended according to the preeclampsia protocol with a viable gestation.

4.7.3 ***OCCLUSIVE PLACENTA PREVIA***

Low-lying placenta (< 10 mm from the internal cervical os or completely beyond it) occurs in 5-7% of pregnancies in the second trimester and constitutes a risk factor for obstetric bleeding. The location of the placenta is therefore an important point when planning the termination of a non-viable pregnancy. There are studies that show that performing a pharmacological induction with mifepristone and misoprostol is a valid option in the context of non-viable pregnancy with low-lying placenta or placenta previa beyond the internal cervical os. In all cases, individualised counselling will be carried out, assessing different factors such as gestational age, the existence of previous vaginal deliveries and the reproductive desire of the pregnant woman.

In the event that the pregnant woman requests the option of attempted vaginal delivery:

- Specific information on the previously detailed risks, recording this in the pregnant woman's clinical history. The pregnant woman must sign the specific informed consent form.
- Blood reservation (2 PRBC) at the time of admission.
- Pharmacological cervical ripening with 200 mg of mifepristone according to the standard regimen and with an optimal mifepristone-misoprostol interval of 24-36 hours. Mechanical cervical ripening is contraindicated.
- Follow the usual induction regimen based on gestational age and the existence of previous uterine surgery.

4.7.4 ***PREGNANT WOMAN WITH PULMONARY HYPERTENSION OR MATERNAL CARDIOVASCULAR DISEASE TYPE III-IV (WHO CLASSIFICATION)***

The management of the termination of pregnancy process in a pregnant woman with pulmonary hypertension (see specific protocol "Obstetric-gynaecological Management of Pulmonary Hypertension)

or with relevant maternal cardiovascular disease (type III-IV according to the modified WHO classification) must be carried out in a multidisciplinary way, with the involvement of the specialist in Maternal-Fetal Medicine, the reference doctor on the specific pathology of the patient and the Anaesthesia team.

- Always schedule a pre-anaesthetic visit.
- Carry out the termination of pregnancy at the lowest possible gestational age to avoid maternal complications and inform about the option of medical and surgical treatment based on gestational age.
- Treatment with misoprostol can favour the appearance of coronary vasospasm, haemodynamic changes, and arrhythmias, so doses > 400 mcg should be avoided, and it is recommended to use the vaginal route (better safety profile). The recommended regimen will be the same as that of the pregnant woman with preeclampsia

4.7.5 CONTRAINDICATIONS FOR THE ADMINISTRATION OF PROSTAGLANDINS

Although it is a rare situation, in the event that there is a contraindication to the use of prostaglandins when planning the termination of a non-viable pregnancy:

- You can choose:
  - Induction of labour with mifepristone 600 mg/day per os for 2 days. See contraindications of mifepristone in the next section.
  - Mechanical cervical ripening by placing an intracervical balloon.
- Assess the need to use other methods for mechanical cervical ripening (intracervical Dilapan®).
- Perform artificial rupture of membranes/amniotomy as soon as cervical conditions allow it.
- Perfusion with oxytocin, according to the labour induction protocol.

4.8 **PHARMACOLOGICAL CONSIDERATIONS**

<u>Mifepristone</u>: (Mifegyne ®, 1 tablet = 200 mg):
Acts as a competitive progesterone receptor antagonist at the receptor level, thus altering the endometrium and producing necrosis of the decidua and favouring the trophoblast's separation from it. It also sensitises the myometrium to the effect of prostaglandins and increases uterine contractility. In the first trimester of pregnancy, it favours cervical ripening.

Contraindications:

- Chronic adrenal insufficiency or chronic corticosteroid use (mifepristone decreases the effect of corticosteroids. In general, the use of a single dose of mifepristone is not contraindicated in pregnant women under chronic corticosteroid treatment. In all cases, the need to adjust the dose of the base treatment will be assessed with the pregnant woman's referral doctor or with the Anaesthesia Service).
- Severe asthma not controlled with treatment.
- Bleeding disorders.
- Treatment with anticoagulant drugs.
- Porphyria.

Its use is not recommended in patients with hepatic insufficiency, renal insufficiency and during lactation. Up to 5% of patients may present bleeding during the first 24 hours after the administration of mifepristone, which may cause the termination of the pregnancy (less than 3%). Perform an ultrasound before misoprostol administration if in doubt. 10-45% of pregnant women may present dysmenorrheal pain in the first hours after drug administration. It is not known whether mifepristone has teratogenic effects on the fetus.

Mifepristone is a hospital administration drug. In all cases, an emergency telephone number should be provided to the patient, and it should be recommended that she stays close to a hospital.

Prostaglandin Analogues Drugs:

- **PGE_1: Misoprostol** (Cytotec® 200 µg tablets: Route of administration: vaginal, oral, sublingual and rectal).
- **PGE_2: Dinoprostone** (Propess®, 10 mg dinoprostone. Vaginal delivery system). Each vaginal delivery system contains 10 mg dinoprostone (prostaglandin E2).
- **$PGF_{2\alpha}$: Carboprost** (Hemabate® solution. Each 1 ml ampoule contains 250 mcg of carboprost). Route of administration: intraamniotic and intramuscular.

They are powerful stimulants of uterine contractility at all stages of gestation and are also involved in cervical ripening. They favour the contractility of the intestinal smooth muscle and have vascular effects, which conditions the appearance of dose-dependent side effects: nausea, vomiting, skin redness, arterial hypotension, fever, diarrhoea, abdominal pain, tremor and chills. There is a greater possibility of these side effects in case of IV or intra-amniotic administration.

In case of cervical administration, the vagina must be asepticised. Do not exceed the internal cervical os in order not to favour the appearance of uterine hypertonia. In case of significant systemic symptoms (fever...) strict control of vital signs and analytical follow-up (blood count, PCR and coagulation with FDPs) will be performed.

Contraindications:

- Allergy or hypersensitivity to prostaglandins.
- Presence of arterial hypotension.
- Inflammatory bowel disease not controlled with treatment.
- Glaucoma
- Asthma (misoprostol does not cause bronchoconstriction so it can be administered in asthmatic patients).

There are data that confirm the possibility of teratogenicity of misoprostol (cranial defects, limb defects and Moebius sequence: micrognathia, facial anomalies and cranial nerve VI and VII defects).