# HYPERTENSION AND PREGNANCY

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## 1. DEFINITIONS

- **Hypertension:** systolic blood pressure (SBP) ≥ 140 mmHg or Diastolic blood pressure (DBP) ≥ 90 mmHg, in two occasions at least 6 hours apart while the patient is at rest. At the first gestational control, blood pressure (BP) should be assessed in both arms, and the worst should be considered for clinical purposes. To avoid overestimating BP, a cuff of at least 1.5 times the diameter of the arm will be used. Two measurements of SBP ≥ 160 mmHg or DBP ≥ 110 mmHg separated by 15 minutes will also be considered diagnostic.

- **Proteinuria:** urine protein/creatinine ratio ≥ 30 mg/mmol (or 0.3 mg/mg) or excretion of ≥ 300mg of protein in a 24-hour urine collection. In both cases, it must be in the absence of urine infection. Preferentially the urine protein/creatinine ratio will be used.

- **Abnormal uterine artery Doppler:** Median pulsatility index (PI) above 95th centile. (Reference values: Gómez O, UOG 2008;32:128).

- **Signs or symptoms of organ dysfunction:**
    - Abnormal uterine artery Doppler (uteroplacental dysfunction).
    - Proteinuria
    - Thrombocytopenia (platelet count less than 100,000/microliter)
    - Haemolysis (lactate dehydrogenase more than twice normal concentration)
    - Impaired liver function (elevated liver transaminase levels in the blood more than twice normal concentration or abnormal coagulation tests) with or without right upper quadrant or epigastric pain (in the upper abdomen).
    - Renal insufficiency (serum creatinine concentrations greater than 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease)
    - Pulmonary oedema

- Neurological symptoms (eclampsia, altered mental state, stroke, clonus, severe headache unresponsive to medication, persistent visual scotoma)

- **Chronic hypertension:** hypertension predating the pregnancy or recognised at <20 weeks of gestation. The majority of cases are due to essential hypertension, secondary causes are uncommon.
- **Pregnancy induced hypertension:** hypertension > 20 weeks of gestation. Includes gestational hypertension and preeclampsia (PE).

| | **< 37 weeks' gestation** | **≥ 37 weeks' gestation** |
|---|---|---|
| **Gestational hypertension** | BP ≥ 140/90<br>+<br>sFlt-1/PlGF < 38<br>+<br>Absence of organ dysfunction | BP ≥ 140/90 and < 160/110<br>+<br>Absence of organ dysfunction |
| **Preeclampsia** * | BP ≥ 140/90<br>+<br>sFlt-1/PlGF ≥ 38 | BP ≥ 140/90<br>+<br>Organ dysfunction not accounted for by alternative diagnoses |
| | BP ≥ 140/90<br>+<br>Organ dysfunction not accounted for by alternative diagnoses | BP ≥ 160/110 |

*****In case of multiples pregnancies there is no evidence on the use of the sFlt-1/PlGF ratio for the diagnosis of PE, so the diagnosis of PE will be established if BP ≥ 140/90 and organ dysfunction not accounted for by alternative diagnoses. The determination of sFlt-1/PlGF < 38 can be used to rule out PE due to its high negative predictive value.

- **PE superimposed upon chronic hypertension:** In patients with chronic hypertension:

  < 37 weeks: rises in blood pressure (up to 20%) or maternal organ dysfunction consistent with PE not accounted for by alternative diagnoses and sFlt-1/PlGF ratio ≥ 38.

  ≥ 37 weeks: rises in blood pressure (up to 20%) or maternal organ dysfunction consistent with PE not accounted for by alternative diagnoses.

- **Eclampsia:** a convulsive condition associated with PE.
- **HELLP syndrome:** haemolysis (lactate dehydrogenase more than twice normal concentration), **E**levated **L**iver enzymes (transaminases more than twice normal concentration) and **L**ow **P**latelet count (less than 100,000/microlitre). The syndrome is considered incomplete when any of the 3 criteria is missing.

## 2. SEVERE FEATURES

The presence of one or more of the following criteria establishes the diagnosis of PE with severe features:

- Severe hypertension (SBP $\geq$ 160mmHg or more and/or DBP $\geq$ 110 mmHg on two occasions at least 4 hours apart or SBP $\geq$ 180mmHg and/or DBP $\geq$ 120 on two occasions 30 minutes apart.
- Neurological symptoms (eclampsia, altered mental status, stroke, clonus, severe headache unresponsive to medication, persistent visual scotoma)
- Severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses.
- Liver enzymes more than twice normal concentration.
- Renal insufficiency (serum creatinine concentration more than 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease) or oliguria ($\leq$ 500 ml in 24 hours or < 90 ml in 3 hours).
- Pulmonary oedema.
- Thrombocytopenia (platelet count less than 100,000/ml)
- Haemolysis (lactate dehydrogenase level more than twice the normal upper limit)
- Altered coagulation tests (PT <60%, aPTT > 40 sec, etc.)

## 3. MANAGEMENT

### 3.1. CHRONIC HYPERTENSION

Management in a specific high risk unit is recommended, especially if a co-morbidity coexists, like diabetes or target organ involvement (heart disease, kidney disease, known retinopathy,

etc.). In the cases of secondary hypertension, combined screening with the reference specialist is recommended.

**Baseline study** (recommended before the gestation or in the first trimester):

1. Blood test (creatinine, uric acid, blood count, liver enzymes, lactate dehydrogenase, sodium, potassium, glucose, urine protein/creatinine ratio).
2. Electrocardiogram (ECG): during the third trimester, the interpretation is limited by physiological changes in the cardiac axis. The presence of electrocardiographic changes suggestive of left ventricular hypertrophy (S in V1 + R in V5 or V6 > 3.5 mV or R in aVL > 1.1mV) requires echocardiography.
3. In cases where hypertension coexists with pregestational diabetes, an ocular fundus examination is recommended (except if one has been performed in the previous 6 months).
4. Stop antihypertensive treatment in women taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), hydrochlorothiazide and Atenolol; and offer alternatives if necessary. During the first trimester of pregnancy, it may be necessary to reduce the dose of drugs.

**General measures:**

1. In women with low calcium intake (less than 600 mg per day), calcium supplementation (1 g/day) is recommended. In patients with a high risk of PE according to the first trimester combined screening, Acetylsalicylic acid (ASA) at a dose of 150 mg/day is also recommended before 16 weeks to 36 weeks' gestation.
2. Low sodium or hypocaloric intake is not required.
3. Restriction of activity during the third trimester (maternal rest)
4. Information about symptoms of eclampsia and PE.

**Management and controls:**

- Self-monitoring of BP 2-3 times/weeks. Medical checkup every 2-4 weeks if there is no co-morbidity (diabetes or target organ disease) that indicates another frequency.
- Proteinuria: urine dipstick at each checkup and urine protein/creatinine ratio every month or if clinical changes. If the urine protein/creatinine ratio is > 0.3 mg/mmol, 24-hour proteinuria is requested.
- Blood test: monthly or if clinical changes (creatinine, uric acid, blood count, liver enzymes, lactate dehydrogenase, sodium, potassium, glucose).

- Monitoring of foetal growth by ultrasound at 28, 32 and 36 weeks of gestation. If the median Uterine Artery PI in the second trimester is above 95$^{th}$ percentile, it is recommended to assess the foetal growth at 24, 28, 32 and 36 weeks of gestation.

Superimposed PE should be suspected when there is a sudden worsening in BP (20% increase) or if there is an appearance/worsening of signs/symptoms of target organ involvement not accounted for by alternative diagnoses. In case of suspicion of superimposed PE between 22-36.6 weeks of gestation, measurement of the sFlt-1/PlGF ratio in the maternal blood could be helpful, PE will be ruled out if the sFlt-1/PlGF ratio is < 38.

**Treatment of hypertension**

In pregnant women with uncomplicated chronic hypertension, the aim is to keep SBP between 130-145 and DBP between 80-95, and it is necessary to start antihypertensive treatment in those patients who present BP above this range.

Acceptable anti-hypertensives include alpha/beta blockers such as labetalol, calcium antagonists such as nifedipine, vasodilators such as hydralazine, or drugs that act on the nervous system such as methyldopa.

**Timing of birth**

From 37 to 40 weeks of gestation, depending on the Bishop score, the delivery prognosis and clinical situation. At 34 weeks, offer referral for a first hospital visit to open the clinical history and assess the need for a pre-anaesthetic visit.

**Postpartum care**

In women with chronic hypertension who have given birth, the goal is to keep BP lower than 140/90 mmHg.

Alpha-methyldopa is associated with postpartum depression, and it is recommended to substitute it with another drug within 2 days of birth. Annex 4 details the drugs and therapeutic escalation for managing hypertension recommended in our centre.

The postpartum period is an ideal time to promote lifestyle modifications in hypertensive women for the prevention of cardiovascular diseases and to establish the necessary controls in the field of primary care.

### 3.2 GESTATIONAL HYPERTENSION

Hospital admission is not essential if the foetus presents correct foetal wellbeing tests and the patient performs correct home blood pressure controls and follow-up.

**General measures:**

1. Information on the prodromal symptoms of eclampsia and PE (it is recommended to go to the emergency room when they appear).
2. Restriction of the pregnant woman's activity (maternity rest and/or sick leave) and normal diet (normal caloric, normal sodium and normal protein) unless another pathology contraindicates it.
3. ASA 100 mg/24 h from diagnosis until 36 weeks.

**Management and controls:**

- Self-monitoring of BP 2-3 times/week.
- Medical control every 1-2 weeks if there is no co-morbidity.
- Proteinuria: urine dipstick at each control and urine protein/creatinine ratio every month or if clinical changes. If the urine protein/creatinine ratio is > 0.3 mg/mmol, 24-hour proteinuria is requested.
- Blood test: every 2 weeks or if clinical changes (creatinine, uric acid, blood count, liver enzymes, lactate dehydrogenase, sodium, potassium, glucose).
- Monitoring of foetal wellbeing every 2 weeks or if clinical changes (monitoring of foetal growth by ultrasound, amniotic fluid and umbilical artery Doppler).

**Treatment of hypertension**

The aim is to keep SBP between 130-145 and DBP between 80-95 and it is necessary to start antihypertensive treatment in those patients who present BP above this range.

Different drugs can be used, the choice depends on the experience and the existence of contraindications (*Table 1*).

*Table 1*

| |
|---|
| - Labetalol 50-100 mg/6 h. Maximum dose 2400 mg/day. |
| - Hydralazine. Maximum dose 200 mg/day. |
| - Nifedipine immediate-release 10 mg [10 mg/6-8 h], Nifedipine extended-release [30 mg/12-24 h]. Not to exceed 90 mg/day (conventional) or 120 mg/day (extended release). Immediate release nifedipine is recommended only in the treatment of urgent blood pressure control. |
| - Methyldopa 250 mg/8h. Maximum dose 2-3 g/day. |

**Timing of birth**

From 37 to 40 weeks of gestation depending on the Bishop score, the delivery prognosis and clinical situation.

### 3.3 PREECLAMPSIA WITHOUT SEVERE FEATURES

Women with PE should be assessed in hospital upon first diagnosis, therefore hospital admission is not essential. Patients may be managed as outpatients once it is established that their condition is stable, and they can perform correct home blood pressure control and follow-up.
Close follow-up is mandatory as the disease can worsen abruptly.

- At diagnosis:
    - Blood test (creatinine, uric acid, blood count, liver enzymes, lactate dehydrogenase, sodium, potassium, glucose).
    - sFlt-1/PlGF ratio if the gestational age is < 37 weeks.
    - 24-hour proteinuria (repeat assessment is not recommended).
    - Clinical assessment
- Self-monitoring of BP 2-3 times/day
- Medical follow-up in a specific Unit at least 1-2 times per week.
- Every 2 weeks (or if clinical changes):
    - Blood test: (creatinine, uric acid, blood count, liver enzymes, lactate dehydrogenase, sodium, potassium, glucose).
    - Foetal monitoring (foetal biometry, amniotic fluid and umbilical artery Doppler).
- Ratio sFlt-1/PlGF once a week since 33-34 weeks of gestation.
- General measures:
    1) Information on the prodromal symptoms of eclampsia and PE (it is recommended to go to the emergency room when they appear).
    2) Restriction of the pregnant woman's activity (maternity rest and/or sick leave) and normal diet (normal caloric, normal sodium and normal protein) unless another pathology contraindicates it.

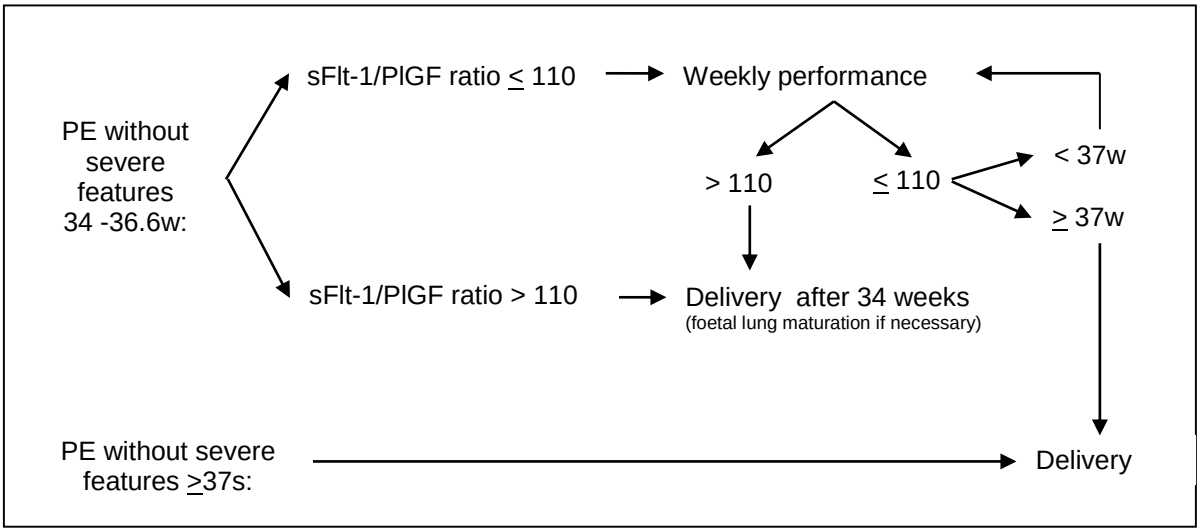
If there is no co-morbidity, the objective is to maintain the SBP between 130-155 and the DBP between 80-105. Initiate treatment in those patients who present BP above this range in a sustained manner.

If there is co-morbidity, the objective is to maintain the SBP between 130-145 and the DBP between 80-95.

Different drugs can be used, the choice of which depends on the experience and the existence of contraindications (Table 1).

**Timing of birth**

In those patients with a diagnosis of PE without severity criteria between 34 and 36.6 weeks, the sFlt-1/PlGF ratio will be determined. In cases with a sFlt-1/PlGF ratio ≤ 110, we recommend repeating it weekly until 37 weeks, when delivery is indicated. If the sFlt-1/PlGF ratio is > 110, delivery is recommended after 34 weeks, prior to foetal lung maturation in those cases of < 35 weeks.




## 3.4 PREECLAMPSIA WITH SEVERE FEATURES

The diagnosis of PE with severity criteria will be established in those cases with: SBP ≥ 160 mmHg or DBP ≥ 110 mmHg on two separate occasions for 6 hours with the patient at rest; SBP > 180 or DBP > 120 on two occasions 30 minutes apart; persistent prodromes of eclampsia; oliguria or renal failure; abnormal liver tests (ASAT and/or ALAT x2 the normal upper limit); Thrombocytopenia; Haemolysis (LDH x2 the normal upper limit); abnormal coagulation tests and/or pulmonary oedema.

Hospital admission to assess the maternal and foetal wellbeing and establish the need for antihypertensive treatment and prevention of eclampsia.

**Initial assessment**

- BP control every 5 minutes until stabilisation, then we can monitor and record BP every hour.
- General obstetric examination (includes cardiotocographic [CTG] monitoring, estimation of foetal growth and uterine and umbilical artery Doppler).
- Laboratory test: blood count, renal function (uric acid, creatinine, urea, Na, K), liver function (ASAT, ALAT, bilirubin, glucose, alkaline phosphatase), lactate dehydrogenase, lactate, sFlt-1/PlGF ratio and coagulation test.
- Group B streptococcus test if > 32 weeks of gestation.
- Foetal lung maturation between 24-34.6 weeks (according to specific protocol). The administration of repeated doses of corticosteroids for lung maturation when there is no medical need for it is not recommended, the lung maturation course will only be repeated when there are foetal or maternal clinical changes that may indicate the end of pregnancy.
- Normal caloric, normal protein and normal sodium diet.

**Anti-hypertensive treatment**

Treatment of severe hypertension (BP > 160/110) is the main objective in severe PE. The main aim is to keep SBP between 140-155 and the DBP between 90-105 with the lowest possible effective dose. It is important to avoid sudden drops in BP due to the risk of placenta hypoperfusion. Different drugs can be used, the choice of which depends on the experience and the existence of contraindication (*Table 2*).

*Table 2*

| Labetalol IV. |
|---|
| ▪ Dosage: start with a slow 20 mg intravenous (iv) bolus (1-2 minutes). Repeat after 20 minutes if BP is not controlled by doubling the dose (40, 80, 80 mg. Do not exceed 200 mg). Continue with continuous infusion (dose between 50-400 mg/6h). If BP is not controlled, the infusion can be doubled every 15 minutes until a maximum dose of 600 mg/6 h is reached, although with doses >300 mg/6 h it is advisable to combine nifedipine before increasing the labetalol infusion. |
| ▪ Maximum daily dose: 2400 mg (600 mg/6 h) |
| ▪ Side effects: foetal bradycardia. In premature babies, the maximum possible latency to delivery should be kept. |
| ▪ Contraindications: congestive heart failure, maternal bradycardia < 60 beats/minute, and asthma. |

Nifedipine

- Dosage of immediate-release: 10 mg orally; it can be repeated in 30 minutes. Maintenance dose: 10-20 mg/6-8 h. Not to exceed 90 mg/day.
- Dosage of extended-release: 30 mg/12-24 h. Not to exceed 120 mg/day.
- The sublingual route is contraindicated due to the risk of severe hypotension.
- Side effects: headache, flushing, tachycardia and oedema.
- Relative contraindication in patients with intestinal stenosis (possibility of obstructive symptoms).

Hydralazine

- Dosage: start the medication with a 5 mg slow iv bolus (1-2 minutes). A maximum of 4 boluses can be repeated at 20-minute intervals. Continue infusion of 3-7 mg/h.
- Maximum daily dose: 200 mg.
- Side effects: maternal tachycardia and headache.
- Contraindications: tachycardia, coronary disease and heart disease.

Nitroglycerin

- Dosage: 5 mcg/min and gradually increase, doubling the dose every 5 minutes if necessary (maximum dose of 100 mcg/min).
- Contraindicated in hypertensive encephalopathy since it can increase cerebral blood flow and intracranial pressure.
- It is a good option for the hypertension associated with pulmonary oedema.

Sodium nitroprusside

- Dosage: 0.25 mcg/kg/min increasing the dose 0.25 mcg/kg/min every 5 minutes if necessary (maximum dose 10 mcg/kg/min)
- Only indicated if the other treatments have failed, since it is fetotoxic due to cyanide accumulation if used for more than 4 hours. Therefore, it is an agent of last resort for the urgent control of severe and refractory HT and for a maximum of 4 hours.

**Pharmacological prevention of seizures**

Pharmacological prevention of seizures will be indicated in those cases that meet the severity criteria.

Drug of choice: SO4Mg (1 amp=10ml=1.5 gr):

- Dosage: 2-4 g of IV bolus (1 g/5 min) + IV infusion of 1-2 g/h with the aim of obtaining plasma Magnesium levels between 3.5 – 7 mEq/L (4.2 - 8.4 mg/dL).
- Side effects: visual accommodative insufficiency. Risk of cardiorespiratory arrest if the drug accumulates. It can interact with other drugs such as curatives or calcium channel blockers (there are studies that support the safe use of nifedipine as a hypotensive agent associated

with magnesium sulphate, although, due to the potential synergistic effect of neuromuscular blockers in these patients, the osteotendinous reflexes will be checked every 2 hours).

- Contraindicated in patients with myasthenia gravis.
- During administration (every 2-3 h): assessment of the knee-jerk reflex (must be present). Magnesium tests will not be routinely performed. It will only be indicated when there is clinical suspicion of intoxication (obtundation, bradypnea or absent knee jerk reflexes), oliguria, renal failure (creatinine > 1.2 mg/dL or progressive worsening of renal function > 20%) or suspicion of an infratherapeutic dose.
- Treatment of poisoning with magnesium sulphate: Calcium glutamate (1g iv bolus in 3-4 min [10 ml of 10% calcium glutamate). Appendix 1.

**Following controls in expectant management**

- Maternal weight and water balance/24 hours. Hourly diuresis control (with Foley catheter)
- Control of foetal wellbeing: foetal cardiotocographic control/24 hours (it must be taken into account that the variability decreases in the presence of treatment with magnesium sulphate). Doppler ultrasound at least every 2-3 days (in the case of type III or more Intrauterine Growth Restriction the control must be daily)
- Blood test:
    - Weekly: complete blood count, renal function (uric acid, creatinine, urea, ionogram), liver profile (ASAT, ALAT, bilirubin), LDH, Lactate, sFlt-1/PlGF ratio and coagulation. Determination of fibrinogen is recommended prior to delivery.
    - Daily: complete blood count, ASAT, ALAT, LDH and creatinine.
    - In those patients with a sFlt-1/PlGF ratio <300 (low tercile according to our centre's own data) analytical control may be done every 48-72 hours.
    - In all cases, the need of other analytical determinations and another frequency of follow-up must be individually assessed.
- Quantitative proteinuria will only be performed at the time of diagnosis.
- Hemodynamic monitoring:
    - Blood pressure every hour. In case of haemodynamic instability or repeated arterial blood sampling, invasive BP monitoring by arterial catheterisation (preferably the radial artery) will be necessary.
    - Continuous electrocardiography (3 leads)
    - Variations in Central Venous Pressure and Pulmonary Artery Pressure do not correlate with the level of vascular filling, so they are not currently recommended.

    - Respiratory monitoring: arterial oxygen saturation or respiratory rate. In case of respiratory failure, an imaging test will be requested (Chest X-ray or lung ultrasound*), the need for arterial blood gases will be assessed and oxygen therapy will be initiated.

      * In case of suspicion of pulmonary oedema, lung ultrasound allows its identification, quantification and assessment of its evolution. The presence of B-lines has an excellent correlation with the presence of extravascular water and increased ventricular filling pressures. The presence of 3 or more B-lines in any of the spaces is suggestive of pulmonary congestion.

- Control of foetal wellbeing: foetal cardiotocographic control/24 hours (it must be taken into account that the variability is decreased in the presence of treatment with magnesium sulphate). Doppler ultrasound at least every 2-3 days (in the case of stage III or more Intrauterine Growth Restriction the control must be daily)
- Fluid therapy: it must be individualised in all cases, taking into account the oral intake, the contributions of hypotensive solutions and magnesium sulphate, presence of oedema, respiratory symptoms, renal failure, etc. The objective will be to maintain a neutral water balance (inputs between 2.5-3 L/24 hours). In the case of absolute diet, crystalloid solution will be administered at a rate of 80 ml/hour (500 ml/6 h) with the minimum objective of maintaining diuresis >30 ml/h. The total intake of liquids cannot exceed 2.5-3 L/24 h.
    - Volume replacement is not recommended to increase plasma volume or treat oliguria in patients with normal renal function and normal creatinine values.
    - Diuretic treatment is indicated if there is persistent oligoanuria (<90 ml/3 h) despite correct fluid therapy, acute pulmonary oedema, cerebral oedema or indication for heart disease or nephropathy. Although it must be individualised in each case.
- Prophylaxis of thromboembolic disease with Low Molecular Weight Heparin whenever there is a minimum of three associated thrombotic risk factors.

**Timing of birth**

The treatment of PE with severe features is the termination of pregnancy, which will be carried out taking into account the gestational age:

- < 24 weeks: given the poor gestational prognosis in these cases, termination of pregnancy is recommended.
- 24 – 31.6 weeks: expectant management with intensive maternal and foetal control.
- 32 – 33.6 weeks: expectant management or delivery based on the PIERS predictive model and the determination of the sFlt-1/PlGF ratio.
- ≥ 34 weeks: delivery prior to lung maturation with corticosteroids.

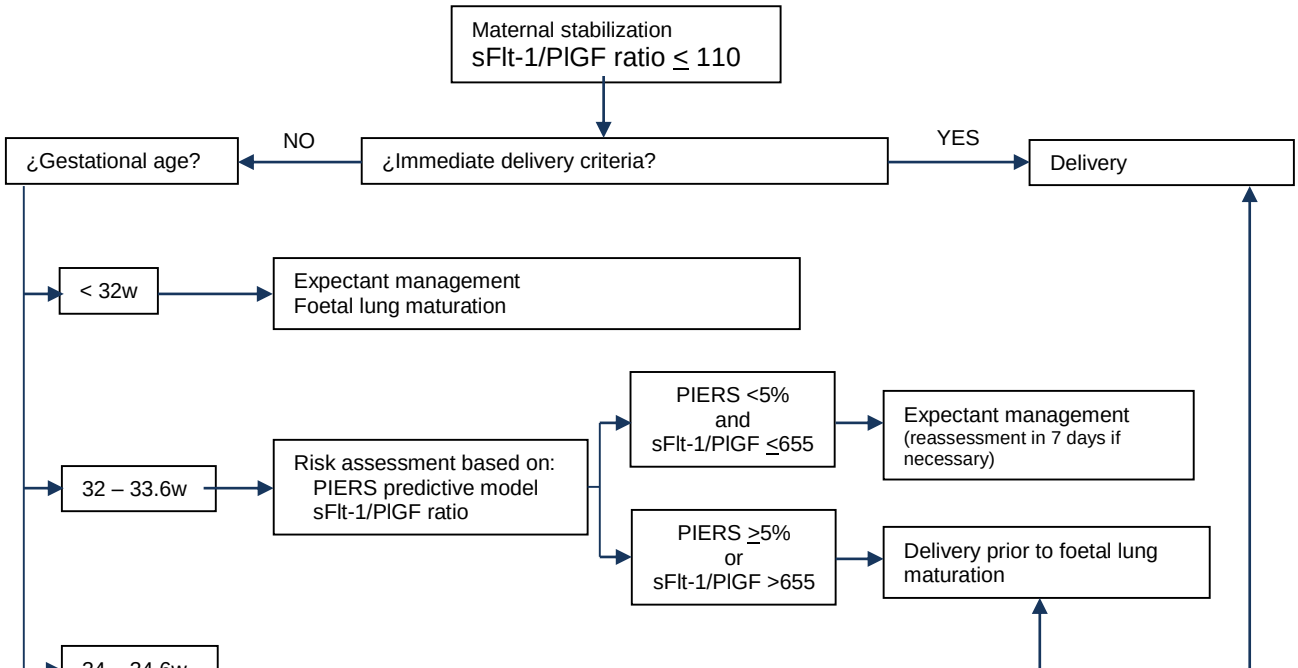
After 32 weeks' gestation, the timing of birth will be indicated based on:

1) Risk of presenting an adverse outcome according to the PIERS (Preeclampsia Integrated Estimate of RiSK) predictive model: the PIERS predictive model will be applied to predict the probability of developing an adverse outcome in the next 7 days. If the risk is less than 5% (NPV 91% and PPV 69%) and there are no criteria for immediate delivery, expectant management will be continued, with a risk reassessment after 7 days. If, after 32 weeks' gestation, the risk of presenting an adverse outcome is greater than or equal to 5%, we will recommend delivery (prior lung maturation with corticosteroids).
2) sFlt-1/PlGF ratio: if the patient has a sFlt-1/PlGF ratio > 655 at 32 weeks, we will indicate delivery (prior lung maturation with corticosteroids) since, in these cases, the risk of presenting a complication in the next weeks is 90%, and 70% in the following 48 hours.

**Immediate delivery criteria** (regardless of gestational age)

- Severe hypertension, uncontrollable pharmacologically (despite the combination of 3 hypotensive drugs at maximum doses).
- Persistent prodromes of eclampsia that do not subside with initiation of magnesium sulphate (hyperreflexia with clonus, intense headache, visual disturbances, stupor, epigastric pain, pain in the right upper quadrant and/or nausea and vomiting).
- Signs of loss of foetal wellbeing.
- Progressive maternal organ involvement: impaired renal function, persistent oligoanuria, impaired liver function and/or progressive thrombocytopenia.
- Onset of serious maternal complications: cerebral haemorrhage, pulmonary oedema that does not respond to treatment, liver rupture or placental abruption.

The following algorithm will be followed:



The time of delivery must be determined in coordination with the Anaesthesia and Paediatric services in order to optimise the maternal and foetal management. The preferred route of delivery is vaginal, as long as it does not involve inductions of more than 24 hours. We recommend performing an elective caesarean section if gestational age is less than 32 weeks and the Bishop score is less than 5, or if there is a maternal or foetal condition that requires a c-section.

Neuraxial analgesia will always be a priority, regardless of the mode of delivery, since it allows better control of maternal BP and avoids the risks of general anaesthesia in PE.

**Postpartum control in PE with severe features:**

During the first 24-48 hours:

- Strict fluid balance and monitoring of oxygen saturation (this is the period of maximum risk of pulmonary oedema)
- In the immediate postpartum period, the definition of oliguria must be more tolerant, and diuretic treatment is not required if the diuresis is above 60 ml/3 hours, as long as renal function is normal.
- Adjustment of hypotensive treatment: 24-48 hours postpartum; if the patient is haemodynamically stable, it is recommended to change the medication to oral route.
- Maintain the magnesium sulphate treatment a minimum of 24 hours postpartum. In those patients with neurological symptoms or severe hypertension it will be maintained for 48 hours postpartum.
- Prophylaxis of thromboembolic disease with Low Molecular Weight Heparin is always recommended in case of caesarean section and when there is a risk factor associated with thrombosis in case of vaginal delivery.
- The use of ergot-derived drugs is contraindicated. In case of postpartum haemorrhage, oxytocin, carboprost or misoprostol can be used. For lactation suppression, we recommend using physical measures instead of cabergoline.

- The use of non-steroidal anti-inflammatory drugs (NSAIDs) during the puerperium should be avoided as far as possible, especially in patients with poorly controlled hypertension, oliguria, renal failure, coagulopathy or thrombocytopenia.

An increase in blood pressure is common from the third day postpartum, so it may be necessary to adjust oral drugs to achieve BP below 160/110 mmHg before discharge. The goal is to achieve SBP < 140mmHg and DBP < 90 mmHg with the lowest effective dose.
During the postpartum period, the following considerations regarding the usual antihypertensive drugs should be taken into account:

- Alpha-methyldopa is associated with postpartum depression and its replacement with another hypotensive agent is recommended.
- Angiotensin-converting enzyme inhibitors are contraindicated during pregnancy and in case of breastfeeding in premature infants (< 32 weeks) but are a good option in other clinical scenarios.
- In case of use of calcium blockers, prolonged release ones are recommended.

Annex 4 details the drugs for the management of hypertension recommended in our centre.

Hypertension that responds to the described regimen is not sufficient to reinstate anticonvulsant treatment with magnesium sulphate. Indications to restart magnesium sulphate are:

- Hypertension resistant to treatment despite the combination of 3 hypotensive drugs at maximum doses.
- Prodromal symptoms of eclampsia (hyperreflexia with clonus, severe headache, visual disturbances, epigastric pain, pain in the right hypochondrium or vomiting)
- Worsening of signs of endothelial dysfunction: haemolysis, hepatic function, renal function or thrombocytopenia.

In these scenarios, treatment with magnesium sulphate will be reinstated.

The use of NSAIDs during the puerperium should be avoided as far as possible, especially in patients with poorly controlled hypertension, oliguria, renal failure, coagulopathy or thrombocytopenia.

### 3.5. ECLAMPSIA

The presence of seizures or coma in a pregnant woman makes it necessary to rule out eclampsia as soon as possible.

In 50% of cases, it will occur in preterm gestations, and approximately 59% will occur antepartum, 20% intrapartum and 21% postpartum (90% of postpartum cases occur in the first week). 20-25% of cases present with a minimal increase in BP levels and without proteinuria.

The immediate objectives are:

- Prevent hypoxia and maternal trauma.
- Treatment of arterial hypertension if it exists.
- Prevention of recurrences.
- Evaluation of foetal extraction.

We will proceed in this order:

1. Request help from a multidisciplinary team (obstetrics, anaesthesiology and nursing). Record actions.
2. Avoid maternal trauma, protect the tongue, and place in left lateral decubitus (to avoid aspiration).
3. Maintain a patent airway (asses the use of a Mayo tube depending on the state of consciousness) and aspiration of pharyngeal secretions. Start administering oxygen at a rate of 6 L/min (30% mask)
4. Seizure control:
    a. Insert a peripheral catheter and start intravenous treatment with magnesium sulphate (initial bolus of 4.5 g (3 vials of 1.5 g) at a rate of 1 vial/5 min + continuous infusion at 2 g/h. If no response, repeat with a second 2 g bolus of magnesium sulphate or increase the rate of continuous infusion to 4 g/h). The route of choice will always be intravenous but, if this is not possible, intramuscular administration may be chosen (5 g in each buttock, making a total of 10 g) and then continue with continuous intravenous infusion.
    b. If there is no response, one of the following drugs can be added:
        i. Diazepam (5-10 mg intravenous in 1-2 minutes, up to maximum dose of 30 mg)
        ii. Phenytoin (15 mg/kg intravenous in 1h + 250-500 mg/12 h)
    c. If the above-mentioned measures fail, induction of anaesthesia and airway protection by endotracheal intubation should be considered.
    d. The use of diazepam, other benzodiazepines or phenytoin as an alternative to magnesium sulphate is not recommended (unless magnesium sulphate is not available).
5. Treatment of hypertension.
6. Assessment of maternal status (BP monitoring, heart rate, oxygen saturation, electrocardiography, double peripheral pathway)
7. Acid-base balance, blood gases and coagulation study: after neurological and haemodynamic stabilisation of the patient.

8. Chest X-Ray: recommended to rule out the existence of a bronchial aspiration.
9. Cardiotocographic foetal control. It must be taken into account that the presence of pathological patterns of foetal heart rate during the seizure are not an indication for urgent caesarean section, since they usually recover in 3-15 minutes. The persistence of alterations should lead to suspicion of placental abruption or loss of foetal wellbeing.
10. Delivery once the symptoms have stabilised and during the first 24 hours after the seizure. The vaginal route is recommended in patients with favourable obstetric conditions.
11. Postpartum imaging (computed tomography or magnetic resonance imaging) is recommended, especially if there are neurological focal signs. In 90% of cases, we will observe posterior reversible encephalopathy syndrome (PRES).

### 3.6. HELLP SYNDROME

Given the finding of an analytical alteration compatible with HELLP syndrome, a differential diagnosis should be made with thrombotic thrombocytopenic purpura (TTP), haemolytic-uremic syndrome (HUS), acute fatty liver, hepatitis, lupus, antiphospholipid syndrome, etc. (appendix 2).
In 10-15% of cases of HELLP syndrome there may be no hypertension.

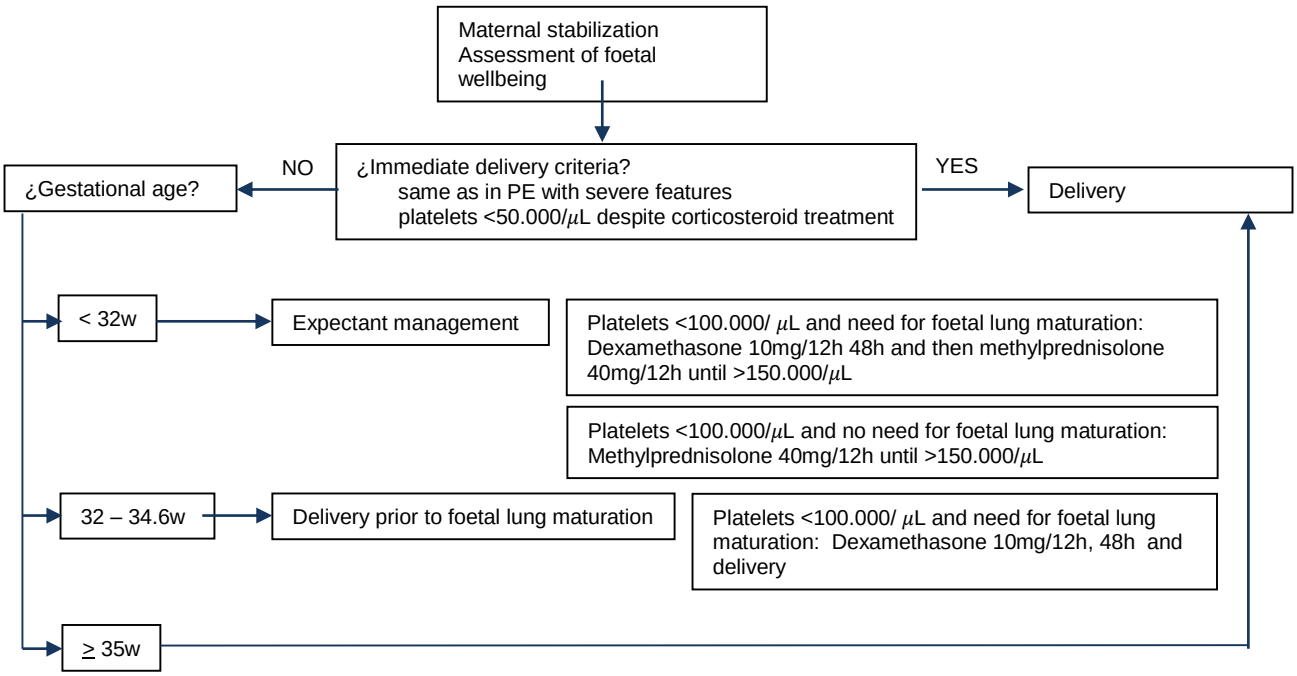
Clinical management:

- Initial assessment and subsequent controls: same as PE with severe features (prophylaxis of seizures with magnesium sulphate, treatment of severe hypertension, fluid therapy and control of foetal wellbeing)
- Antepartum treatment with high-dose corticosteroids. Data available demonstrate a transient clinical and analytical improvement, which allows the use of regional anaesthesia and improves the prognosis of vaginal delivery. Start the treatment only if platelet count < 100,000/μL:
    - If foetal lung maturation is necessary: dexamethasone 10 mg/12 h for 48 hours and then methylprednisolone 40 mg/12 h intravenous until platelet count > 150.000/μL. In case of no response after 8-10 hours from the start of the treatment, increase the dose to 40 mg/6 h.
    - If foetal lung maturation is not necessary: methylprednisolone 40 mg/12 h until platelet count > 150.000/μL. If no response after 8-10 hours from the start of the treatment, increase the dose to 40 mg/6 h.

- Platelet transfusion: immediately before delivery if platelets < 40.000/μL in case of caesarean section; or if platelets < 20.000/μL in case of vaginal delivery; and in the first 24 hours postpartum if there are symptoms of bleeding.
- Treatment with magnesium sulphate will be maintained for a minimum of 24 hours postpartum. In those patients with neurological symptoms or severe hypertension it will be maintained for 48 hours.
- Imaging studies (computed tomography or magnetic resonance imaging) are only indicated if the symptoms are suggestive of hepatic haematoma (severe epigastric pain, pain in the right upper quadrant or shoulders, hypotension, disseminated coagulopathy or evidence of ascites).

Maternal stabilisation and assessment of foetal wellbeing will be carried out following the same criteria described for PE with severe features.

The timing of delivery will depend on the existence or not of criteria for immediate delivery (see section on PE with severe features) and on the gestational age, following the algorithm:




- In case of caesarean section, it is necessary to leave subaponeurotic and subcutaneous drainage.
- Withdrawal of the epidural catheter will always be performed after normalisation of the coagulation tests and with a platelet count > 80,000/μL.
- Given the little evidence currently available on the benefit of treatment with corticosteroids during puerperium in patients with HELLP syndrome, this will only be maintained during the

firsts 48 hours postpartum, regardless of the platelet count: Dexamethasone 2 doses of 10 mg/12 h and then 2 doses of 5 mg/12 h, thereafter the treatment will be discontinued. A more gradual reduction in treatment (halving the dose every 48 hours) will be only necessary in those cases in which the treatment has been administered for more than two weeks.

## 4. ANGIOGENIC FACTORS IN PATIENTS WITHOUT HYPERTENSION

The usefulness of the angiogenic factors has been demonstrated, especially in the exclusion of PE and in the prediction of adverse outcomes associated with the disease.

As explained above, the sFlt-1/PlGF ratio will be determined in patients with de novo hypertension or in patients with chronic hypertension and worsening of pre-existing hypertension. However, in the absence of hypertension we also recommend its determination in the following clinical scenarios:

- At 22-36.6 weeks of gestation for singleton pregnancies:
    1) In the absence of hypertension and presence of two or more of the following criteria:
        - New onset proteinuria.
        - Abnormal uterine artery Doppler.
        - Persistent and severe headache, stupor or neurological symptoms.
        - Hyperreflexia with clonus.
        - Visual disturbances.
        - Epigastric pain, pain in the right hypochondrium or nausea and vomiting.
        - Creatinine > 1.2 mg/dL.
        - ASAT and/or ALAT and/or LDH x2 the normal upper limit.
        - Thrombocytopenia (< 100.000/μL)
        - Alteration of coagulation parameters.
        - Signs of increased capillary permeability (significant subcutaneous oedema or ascites, or suspicion of pulmonary oedema).
    2) Worsening of pre-existing proteinuria (empirically using x2 the initial value)

In these cases, PE will be diagnosed when the sFlt-1/PlGF ratio is > 85 in gestations of < 34w and > 110 in gestations of 34-36.6 weeks; and PE will be excluded when it is < 38. When the value of the ratio is between 38-85 or 38-110 according to gestational age, the patient will be called in a week's time for reassessment and the determination will be repeated.

In cases of twin pregnancies, we can benefit from determining whether the sFlt-1/PlGF ratio < 38 to rule out PE given its high negative predictive value. Given the few studies on multiple pregnancies we do not recommend its use for the diagnosis of PE.

## 5. LONG-TERM ASSESSMENT

- In most patients, blood pressure normalises during the first days of the puerperium, although in severe cases it may take 2-4 weeks. It is mandatory to assess the need for hypotensive treatment and decrease the dose every 48 hours if the patient maintains normal BP.
- Analytical control with protein/creatinine urine ratio included, approximately 6 weeks postpartum.
- The study of thrombophilia will be done in those cases or early-onset PE (< 32 weeks' gestation), placental abruption or recurrent PE. It will include antiphospholipid antibodies, prothrombin mutation, factor V Leiden mutation, antithrombin, resistance to activated protein C, protein S (free and total) and protein C; at 6 weeks postpartum.
- It is important to inform the patient of the risk of recurrence: 20% if diagnosed after 37 weeks' gestation, 30% if diagnosed between 34 and 37 weeks, 40% if 28-34 weeks and 50% if < 28 weeks. In case of history of HELLP syndrome, a recurrence risk of 3% for HELLP syndrome and 20% for PE is estimated; and in the case of eclampsia, an estimated 2% recurrence for eclampsia and 20% for PE.
- Patients with a history of PE should be informed that they are at greater risk of developing chronic hypertension and cardiovascular disease in the future (approximately 2-3 times compared to the general population), so healthy lifestyle habits should be encouraged.

## 6. PREVENTION OF PREECLAMPSIA

In all women with low calcium intake (less than 600 mg or 2 servings/day), calcium supplements (> 1 g/day) are recommended.

All women will be screened for early PE, according to gestational age:

a) Screening for early PE in the 1st trimester (<14 weeks)

The estimation of risk in singleton pregnancies will be made in the first trimester ultrasound, with the combination of personal history, blood pressure and Doppler of the uterine arteries.

High risk of PE will be considered in those cases with a result > 1/100; the outcome of this risk will prevail over individual epidemiological risk factors.

b) Screening for early PE in 2nd trimester (14.0 – 16.6 weeks)

In those singleton pregnancies between 14 and 16.6 weeks in which it has not been possible to perform the screening in the first trimester, it is recommended to perform screening based on individual epidemiological risk factors and Doppler of the uterine arteries. High risk of PE will be considered in those cases with ≥ 1 high risk factors or ≥ 2 moderate risk factors (adaptation of the NICE Guidelines and US Preventive Services Task Force Recommendation Statement).

| | |
|---|---|
| High risk factors | Personal history of PE<br>Chronic kidney disease<br>Autoimmune disease (Systemic Lupus Erythematosus, Antiphospholipid Syndrome)<br>Pregestational diabetes<br>Chronic hypertension<br>Mean pulsatility index of Uterine Arteries > 95$^{th}$ centile<br>Multiple pregnancy |
| Moderate risk factors | Nulliparity<br>Maternal age > 40 years<br>Interval with previous pregnancy > 10 years.<br>BMI > 35Kg/m$^2$ at the first gestational control<br>Family history of PE (First degree) |

In those cases, with high risk of PE, it is recommended to start treatment with acetylsalicylic acid (ASA) 150 mg/day (preferably at night), ideally before 14 weeks' and no later than 16 weeks gestation, continuously until 36 weeks. It is not necessary to start ASA before 11 weeks of gestation. Contraindication for ASA treatment are as follows:

- Chronic duodenal or stomach ulcer.
- History of gastrointestinal bleeding.
- Allergy or hypersensitivity to salicylates or NSAIDs.
- Bleeding diathesis.
- Coagulation disorders.
- Severe asthma or asthma induced by salicylates or similar medication.
- Severe renal or hepatic insufficiency.

In the case of metrorrhagia/haematoma, cessation of ASA is not indicated, although this decision must be individualised.

If 150mg ASA is not available, the tablets can be divided to obtain the appropriate dose (100 mg or 300 mg) but the portion of the tablet that is not used must be discarded and cannot be kept for the next intake.

c) Screening for early PE in the 2nd trimester (17-22.6 weeks)

In low-risk pregnancies, the use of uterine artery Doppler in the second trimester does not improve perinatal outcomes. Doppler imaging of uterine arteries is recommended only in the high-risk population:

- History of early PE, intrauterine growth restriction, placental abruption and/or intrauterine death.
- Chronic hypertension
- Renal disease
- Type I diabetes with vascular complications.

In these patients it is not recommended to start treatment with ASA, but specific follow-up will be carried out following the recommendations detailed in section "7. Follow-up of pregnant women at high risk of early PE".

## 7. FOLLOW-UP OF PREGNANT WOMEN AT HIGH RISK OF EARLY PREECLAMPSIA

The follow-up that we recommend for these pregnant women is:

- Normal mean pulsatility index of uterine artery Doppler (< 95$^{th}$ centile) in week 20:
  - 28 weeks: Ultrasound (with estimated foetal weight) + analysis with liver profile and urine protein/creatinine ratio.
  - 32 weeks: Ultrasound (with estimated foetal weight) + Third trimester analysis adding liver profile and urine protein/creatinine ratio.
  - 37 weeks: Routine 3$^{rd}$ trimester ultrasound + Analysis with liver profile and urine protein/creatinine ratio.
- Abnormal mean pulsatility index of uterine artery Doppler (>95$^{th}$ centile) in week 20:
  - 24 weeks: Ultrasound (with estimated foetal weight) + analysis with liver profile and urine protein/creatinine ratio.
  - 28 weeks: Ultrasound (with estimated foetal weight) + analysis with liver profile and urine protein/creatinine ratio.

- 32 weeks: Ultrasound (with estimated foetal weight) + Third trimester analysis adding liver profile and urine protein/creatinine ratio.
- 37 weeks: Routine 3rd trimester ultrasound + Analysis with liver profile and urine protein/creatinine ratio.

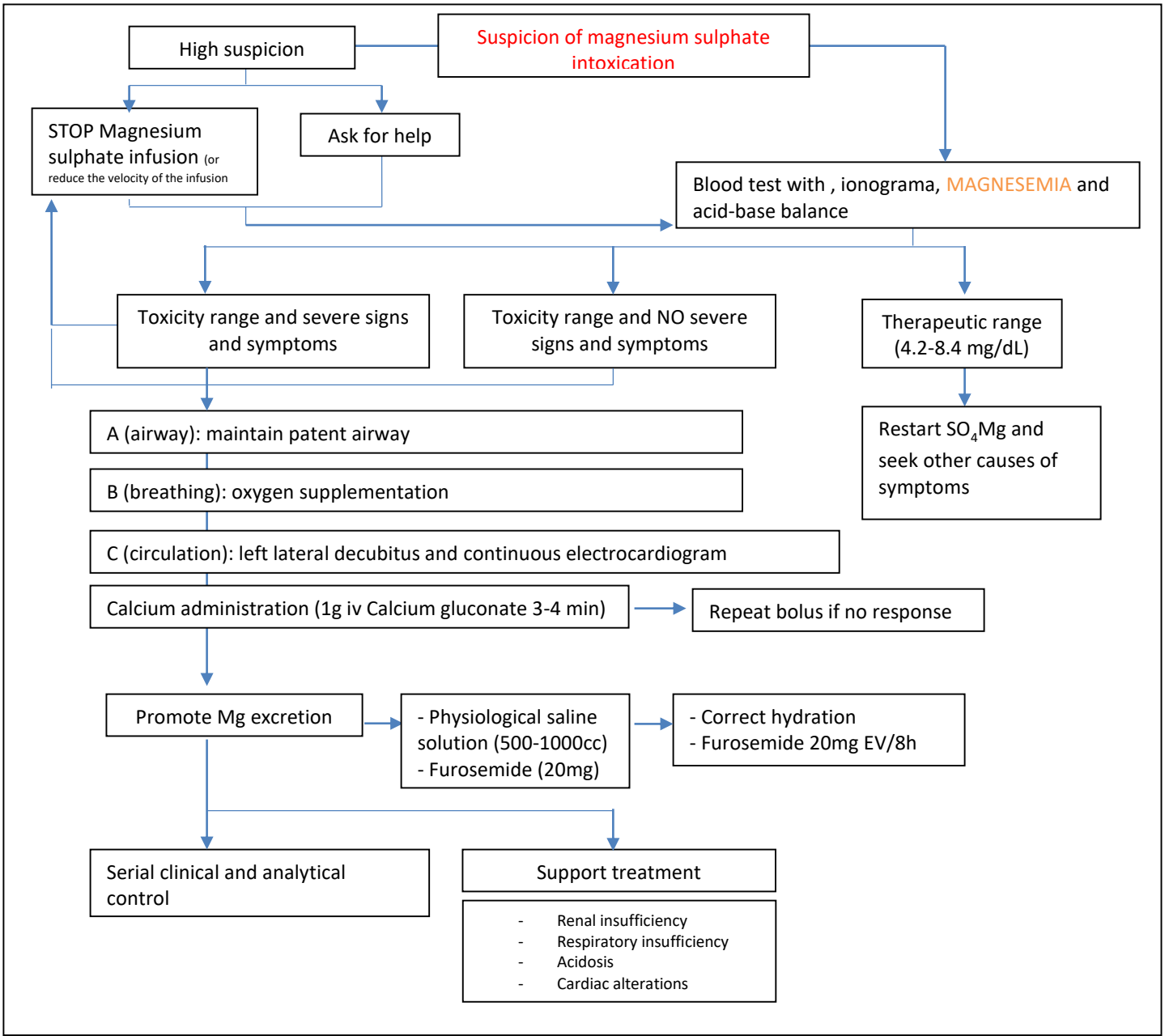
Moment of delivery for patients at high-risk of early PE did not differ with respect to the high-risk population.

APPENDIX 1- **Suspicion and management of magnesium sulphate intoxication**

WHEN TO SUSPECT MAGNESIUM SULPHATE INTOXICATION

| | SYMPTOMS AND SIGNS | [Mg] (mg/dL) |
|---|---|---|
| | Asymptomatic (therapeutic range) | 4.2-8.4 |
| | Nausea, drowsiness, double vision, slurred speech, generalised weakness, sudden hypotension, low-grade fever, flushing, loss of tendon reflexes, oliguria. | 9-12 |
| Severe features | Bradypnea and cardiac conduction disorder. | >12 |
| | Muscular paralysis and respiratory arrest. | 15-17 |
| | Complete auriculoventricular block and asystole | >18 |

¿WHAT TO DO IF YOU SUSPECT MAGNESIUM SULPHATE INTOXICATION?



APPENDIX 2- **Differential diagnosis of HELLP Syndrome**

| | HELLP | AFL | TTP | HUS |
|---|---|---|---|---|
| Thrombocytopenia | > 20,000/mm$^3$ | > 50,000/mm$^3$ | ≤ 20,000/mm$^3$ | > 20,000/mm$^3$ |
| Haemolysis | 50-100% | 15-20% | 100% | 100% |
| Anaemia | < 50% | Absent | 100% | 100% |
| DIC | < 20% | 73% | Rare | Rare |
| Hypoglycaemia | Absent | 61% | Absent | Absent |
| LDH | ≥ 600 | Variable | > 1.000 | > 1.000 |
| Hyperbilirubinemia | 50-60% | 100% | | |
| Kidney failure | 50% | 90-100% | 30% | 100% |
| vW factor multimers | Absent | Absent | 80-90% | 80-90% |
| ADAMST-13 <10% | Absent | Absent | 33-100% | Absent |
| Proteinuria | 90-95% | 30-50% | With haematuria | 80-90% |
| Hypertension | 85% | 50% | 20-70% | 80-90% |

AFL: acute fatty liver of pregnancy; TTP: thrombotic thrombocytopenic purpura; HUS: Haemolytic-uremic syndrome; DIC: disseminated intravascular coagulation; LDH: Lactate dehydrogenase, vW: von Willebrand

**Acute Fatty Liver in pregnancy:**

The diagnostic suspicion of acute fatty liver in pregnancy is clinical and is based on the presence of gastrointestinal symptoms (vomiting, nausea, abdominal pain, fainting and/or anorexia) in a pregnant woman with significant liver dysfunction in the second half of pregnancy, after excluding other possible causes. There is a large clinical overlap between AFL and HELLP syndrome.

For the diagnosis of AFL, the use of the Swansea criteria can be useful.

| | |
|---|---|
| • Vomiting.<br>• Abdominal pain.<br>• Polydipsia/Polyuria.<br>• Encephalopathy.<br>• Ascites or increased liver echogenicity by ultrasound.<br>• Microvesicular steatosis in liver biopsy. | • Increased bilirubin (>0.8 mg/dl or >14 micromol/L)<br>• Hypoglycaemia (glucose <72 mg/dl or <4 mmol/L)<br>• Leukocytosis (>11,000 cells/microL)<br>• Increased transaminases (ASAT or ALAT >42 UI/L)<br>• Hyperammonaemia (>47 micromol/L)<br>• Hyperuricemia (>5.7 mg/dL or >340 micromol/L)<br>• Acute renal failure or creatinine > 1.7 mg/dL (>150 micromol/L).<br>• Coagulopathy or prothrombin time > 14 sec. |

The presence of ≥ items have a positive predictive value of 85% and a negative predictive value of 100%.