ANAEMIA DURING PREGNANCY AND POSTPARTUM PERIOD

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1. INTRODUCTION

Anaemia is one of the most significant medical problems during pregnancy. Because of the increase in nutritional requirements in response to the synthesis and maintenance of the fetoplacental unit, the risk of developing anaemia increases as gestational age advances.

As a frequent cause of adverse maternal and foetal outcomes, especially if Hb <7 g/dL, it is necessary to investigate and treat any anaemia detected during pregnancy.

1.1 CAUSES OF ANAEMIA DURING PREGNANCY

The most common cause of anaemia during pregnancy is iron deficiency anaemia. More than 50% of anaemias during this period are attributed to iron deficiency, followed in frequency by folic acid deficiency anaemias. Anaemia due to vitamin B12 deficiency is very infrequent because its deposits in the body are sufficient to cover the needs for 3-5 years.

Haemoglobinopathies are characterized by an alteration on the synthesis of globin chains. Usually, they are diagnosed before pregnancy and require a joint follow-up with Haematology department. The most frequent haemoglobinopathies in pregnancy are

- Sickle cell disease or sickle cell anaemia: is the most frequent haemoglobinopathy. It is the consequence of an inherited (autosomal recessive) mutation in the β chain of haemoglobin that originates Hb S, which is unstable and causes the erythrocyte to acquire a sickle morphology. The clinical manifestations vary from asymptomatic forms (sickle cell trait) to severe cases (homozygotes).

- Thalassaemia: this is an inherited defect (autosomal recessive) in the synthesis of some globin chains (α or β), differentiating α-thalassaemia and β-thalassaemia. Depending on the number of alleles affected we will have different manifestations of the disease. As mild forms we will find Thalassaemia minor (α or β) or silent carrier, and as more severe and symptomatic forms we would have Thalassaemia major (β0 homozygotes) and Thalassaemia intermedia (β+ homozygotes, β+ double heterozygotes or, in the case of α, Hb H disease where there is the functional involvement of three of the four α genes).

There are other less frequent causes during pregnancy. Although some of these pathologies may debut during pregnancy, usually they are diagnosed previously, and require a joint management with different medical specialties.

- Anaemias secondary to haemorrhage.

- Haemolytic anaemias, whether of autoimmune aetiology, due to congenital erythropathies (membranopathy such as spherocytosis or enzymopathy such as G6FD enzyme deficiency), paroxysmal nocturnal haemoglobinuria or microangiopathic anaemias.

- Anaemias secondary to clonal haemopathies.

- Anaemias secondary to inflammatory/chronic processes (renal failure, active infection, etc).

- Other causes (e.g., hypothyroidism).

1.1 CLINIC

Anaemia during pregnancy may be **asymptomatic** and be a casual finding in routine laboratory tests, or it may present with nonspecific symptoms, with **asthenia** being the most frequently reported symptom. Other frequent signs and/or symptoms are mucocutaneous pallor, headache, dizziness, dyspnoea, palpitations, increased sensitivity to cold and/or restless legs syndrome. Depending on the origin of theanaemia we can find characteristic symptoms:

- Iron deficiency: fatigue, irritability, decreased ability to concentrate and/or hair loss.
- Vitamin B12 and/or folic acid deficiency: rough skin, glossitis and/or cheilosis. Vitamin B12 deficiency may also produce neurological symptoms due to demyelination.
- Haemolytic anaemias: usually present with jaundice and choluria as general manifestations. Depending on the type of haemolytic anaemia, we will have other specific manifestations (petechiae in microangiopathies such as thrombotic thrombocytopenic purpura).
- Sickle cell disease or sickle cell anaemia: severe cases are characterised by anaemic syndrome,vascular occlusion phenomena and repeated infections due to hyposplenism. It is associated with maternal and foetal complications, highlighting: Intrauterine growth restriction (IUGR), premature detachment of the placenta, thromboembolic events,hypertensive disorders and preeclampsia and infections (especially urinary tract and pneumonia).
- Thalassaemia: *Minor* forms usually present asymptomatically or with mild forms of anaemia. In contrast, *major* forms are associated with more severe anaemias that may be transfusion-dependent clinical manifestations secondary to multisystem involvement by haemosiderosis (cardiac, hepatic, and endocrine) and bone malformations (increased risk of osteopenia - increased risk of osteoporosis). They also present an increased risk of maternal and foetal complications, of which the following are highlighted: Intrauterine growth restriction; thromboembolic events and preeclampsia.

2. DIAGNOSIS OF ANAEMIA DURING GESTATION

Although it is possible to suspect anaemia based on the clinical manifestations, the diagnosis will be analytical. A **complete blood count should be** requested **in each trimester of pregnancy** and always in the presence of symptoms suggestive of anaemia or iron deficiency. During gestation, physiological anaemia is produced by the expansion of maternal plasma volume (30-50%) compared to the increase in erythrocyte mass (20- 30%), generating a state of haemodilution. For this reason, the threshold for establishing the diagnosis of anaemia varies with respect to the general population. We will diagnose gestational anaemia when:

- Hb < 11 g/dL during the first and third trimesters, and
- Hb < 10.5 g/dL during the second trimester.

Depending on the Hb level, **degrees of severity are** differentiated:

- Mild anaemia: 10-10.9 g/dL
- Moderate anaemia: 7-9.9 g/dL
- Severe anaemia: <7 g/dL

In addition, some risk factors for iron deficiency or iron deficiency anaemia have been identified during pregnancy, in the presence of which **serum ferritin** should also be routinely requested (Table 1), since a state of iron deficiency requires the initiation of treatment. In general, we will diagnose **iron deficiency** with **ferritin** levels **< 30 µg/L**.

Related to gestation	Other circumstances
Pre-pregnancy anaemia Multiple pregnancy Short inter-pregnancy interval (< 18 m) Multiparity	Iron-poor diets (strict vegetarian, malnutrition) Diabetes Obesity or underweight Young people (≤16 years) Abundant menstruation Malabsorptive pathology Known haemoglobinopathy (e.g., thalassaemia, sickle cell anaemia).

Table 1: Risk factors for iron deficiency

2.1 PROTOCOL OF STUDY

Due to the high prevalence of iron deficiency anaemia during pregnancy, in the presence of a mild anaemia with compatible characteristics (normo-microcytic and in the absence of clinical signs that suggest other aetiologies), empirical iron supplementation treatment will be performed, without the need to perform a complete analytical study at the outset. The diagnostic protocol is now essential in the case of **moderate or severe anaemia** or anaemia not responding to empirical iron therapy and should be carried out according to Annex 1. **It will be performed while fasting and without taking iron and/or folic acid in the last 7-10 days.**

- **Basic study**:
  - Haemogram
  - Reticulocyte count
  - Ferritin
  - Iron
  - Transferrin
  - Transferrin saturation index: to be calculated by dividing iron/transferrin (at the Clínic site it will be calculated automatically by the laboratory).
  - Folic acid or folate
  - Vitamin B12 or Cobalamin
  - Thyroid hormones

If the basic study is normal, if there is no response to treatment, or if there is suspicion of a specific pathology, an **advanced study will be** performed. This study will be directed according to the level of reticulocytes of the basic study:

2.1 Reticulocytes > 100,000/µL:

- Rule out bleeding
- Haemolysis study:
  - Reticulocyte count
  - Haptoglobin
  - Total bilirubin and fractions (free and conjugated)
  - LDH
  - Direct Coombs' test or direct antiglobulin test

2.2 Normal reticulocytes or < 75000/µL:

- Study of haemoglobinopathies:
  - Basic haemoglobin study
  - Haemoglobin electrophoresis
- If suspected by haemogram and epidemiological context, a molecular or of α-thalassaemia will also be requested.
- Inflammatory parameters: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

2.2 DIAGNOSIS AETIOLOGY

The aetiologic diagnosis is important to be able to adjust the treatment. The reticulocyte count allows us to differentiate between two types of anaemia:

- Anaemias with **adequate marrow response** (reticulocytes >100,000/µL): they are usually secondary to haemorrhage or haemolysis. In haemoglobinopathies and thalassaemia (especially in the case of α) there may be a haemolysis component and slightly elevated reticulocytes.

- **Hyporegenerative** anaemias (normal or decreased reticulocytes <75000/µL): deficiency anaemias (iron, vitamin B12 and/or folic acid deficiency) or secondary to haemopathies, inflammatory/chronic processes or haemoglobinopathies.

The following table (Table 2) summarises the laboratory parameters according to the type of anaemia:

HYPOREGENERATIVE ANAEMIAS (reticulocytes N or <75000/µL)		
Aetiology	**Parameter**	**Expected values**
Iron deficiency	Mean Corpuscular Volume (MCV)	<80 fL
	Ferritin	↓
	Iron	↓
	Transferrin	↑
	Index of saturation from the transferrin	↓
Folic acid deficiency	Mean Corpuscular Volume (MCV)	>100 fL
	Folic acid or folate	↓
B12 vitamin deficiency	Mean Corpuscular Volume (MCV)	>100 fL
	Vit. B12 or cobalamin	↓
Structural haemoglobinopathies (e.g., sickle cell anaemia)	Mean Corpuscular Volume (MCV)	N o <80 fL
	Mean corpuscular haemoglobin (MCH)	N or <27 pg
	Ferritin	N o ↑
	Index of saturation from the transferrin	N
	Basic study Hb	Hb A2 ↑
	Hb electrophoresis	Anomalous band compatible with haemoglobinopathy S
Thalassaemia	Mean Corpuscular Volume (MCV)	<80 fL
	Mean corpuscular haemoglobin (MCH)	<27 pg
	Ferritin	N o ↑
	Index of saturation from the transferrin	N
	Basic study Hb	Hb A2 ↑ In α-thalassaemia may be normal.
	Hb electrophoresis	Presence of anomalous bands In α-thalassaemia may be normal. Requires Haematology evaluation
Chronic processes	Mean Corpuscular Volume (MCV)	<80 fL or N (80-100 fL)
	Ferritin	N o ↑
	Index of saturation from the transferrin	N o ↓
	C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).	↑

ANAEMIAS WITH ADEQUATE MEDULAR RESPONSE (reticulocytes >100000/µL)		
Aetiology	**Parameter**	**Expected values**
Haemolysis	Mean Corpuscular Volume (MCV)	>100 fL
	Reticulocytes	↑
	Haptoglobin	↓
	Total bilirubin	↑
	LDH	↑
	Coombs direct or direct antiglobulin test	+ if immunological origin
	Depending on the suspicion, an evaluation by Haematology will be required.	

Table 2: Laboratory parameters according to the aetiology of anaemia.

2.2.1 SCREENING AND DIAGNOSIS OF HAEMOGLOBINOPATHIES

Screening for haemoglobinopathies in pregnant women will be performed if at least two of the following are met:

- Hemocytometry compatible with Thalassaemia:
  - Microcytosis (MCV <80 fL) and hypochromia (MCH <27 pg)
  - High red blood cell count
  - Normal or decreased reticulocytes. In cases with compensated chronic mild haemolysis we may see slightly elevated reticulocytes.
- Family history of haemoglobinopathy or consanguinity
- History of chronic anaemia not studied
- Patient of high prevalence ethnicities or geographic areas (Africa, Caribbean, South America, Mediterranean, Middle East, Southeast Asia, West Pacific).

The basic study of anaemia and the study of haemoglobinopathies will be requested. Ideally, if there is iron deficiency, this should be corrected before doing the study to avoid falsely normal results.

If suspected by haemogram and epidemiological background, molecular study of α-thalassaemia will also be requested directly (study of the α-thalassaemia gene) because by definition those patients presenta normal haemoglobin study.

If the study is positive, a **confirmatory diagnosis** will be made by molecular diagnosis. One of the following will be requested depending on the results of the haemoglobin study:

- Molecular study of β-thalassaemia.
- Molecular study of Haemoglobinopathy S

In patients from the Middle East, where the coexistence of α-thalassaemia and β-thalassaemia is frequent, even if the haemoglobin study indicates β-thalassaemia and this justifies the clinic, the study will be extended with the molecular study of α-thalassaemia.

It is ~~important to **study the** pregnant **couple** with a diagnosis of Thalassaemia or other haemoglobinop~~athy,

whether homozygous or heterozygous. In these cases, the following will be requested:

- Basic anaemia study
- Study of haemoglobinopathies

Genetic confirmation will be performed following the same indications as in the pregnant woman. Ideally, the study will be performed in two steps, first the basic study of anaemia and haemoglobinopathies and then the molecular study. However, if necessary, everything can be requested at the same time. In this case, the molecular study will be requested depending on the type of haemoglobinopathy that the pregnant woman presents (if the woman has a β-thalassaemia, the molecular study of the β-thalassaemia will be requested). In this way we will have the couple's DNA from the beginning and other tests can be added if necessary.

If the couple also presents Thalassaemia or other haemoglobinopathy, a visit for genetic counselling will be requested.

Any patient with a new diagnosis of haemoglobinopathy will be referred to the Haemotherapy and Haemostasis.

3. PREVENTION OF ANAEMIA DURING GESTATION

3.1. SUPPLEMENTATION WITH IRON

Iron requirements vary according to the trimester of gestation, being higher as gestation progresses. For this reason:

- It will be universally recommended from the second trimester of gestation, even if ferritin or Hb levels are within normal ranges, to administer a **daily dose of iron: 30-40 mg/day**. This dose is covered by most prenatal polyvitamin formulations.
- In patients with **iron deficiency**, the prophylactic dose should be increased to a therapeutic dose, with a minimum intake of **60-100 mg/day.**

Oral iron supplementation in pregnant women should be **discontinued if** the **Hb** level is **> 13 g/dL**.

Oral iron supplementation is **contraindicated** in patients with **haemoglobinopathies** because of the risk of iron overload.

3.2. FOLIC ACID SUPPLEMENTATION

The body's reserves of **folic acid** cover the needs for about 3-6 months.

However, pregnancy is a situation of increased folic acid requirements, and the supply from the diet may be insufficient. For this reason:

- The administration of **400 µg/day of folic acid** from 4 weeks preconception to the end of gestation is universally recommended. This dose is covered by most prenatal vitamin formulations.
- If there is a folic acid deficiency before pregnancy, in patients with antiepileptic treatment, with a diagnosis of haemoglobinopathies or a history of neural tube defect, a dose of 5 mg/day (Acfol®) is recommended.

3.3. VITAMIN B12 SUPPLEMENTATION

There is no recommendation for the administration of prophylactic vitamin B12 supplements to the entire pregnant population. However, we should advise systematic **vitamin B12** supplementation to pregnant women with **vegetarian diets** (both ovo-lacto vegetarians and strict vegetarians). Most prenatal poly-vitamin formulations carry the recommended daily dose of vitamin B12. In these patients, in addition to prenatal vitamins, we will add the following supplementation:

- **1 mg orally per week of vitamin B12**. If no monocomponent oral preparations are available in the market, intramuscular preparations that are also drinkable might be used. (Optovite B12®).

4. TREATMENT OF ANAEMIA DURING GESTATION

Treatment of anaemia during pregnancy will depend on the cause and level of anaemia.

4.1 EMPIRICAL TREATMENT

- Since the main cause of anaemia during pregnancy is iron deficiency anaemia, empirical treatment with oral iron (100-200 mg/day) will be started without the need to perform an aetiological study, in mild anaemias (10-10.9 g/dL). The choice of dose and composition should be made following the indications in the following section.

4.2 TREATMENT OF DEFICIT ANAEMIAS

4.2.1 TREATMENT OF IRON DEFICIENCY ANAEMIA

- **ORAL IRON THERAPY:**

- It is indicated in **mild/moderate anaemias (Hb 7-10)**, If there is no contraindication, it is the treatment of choice. (Table 3).

- Treatment consists of the administration of **100-200 mg/day of oral iron**.

- Iron supplementation will be carried out with **ferrous salts** due to their greater absorption despite the higher incidence of gastric intolerance.

The following table (Table 3) shows the main types of iron marketed for oral administration:

Type of iron		Trade name	Dosage	Comments
FERROUS IRON (Fe2+)	Ferroglycine sulphate	**Ferbisol®**	Capsules 100 mg	Higher absorption and lower cost, but poorer tolerance.
		Ferrosanol	Capsules 100 mg	
	Ferrous sulphate	**Fero-gradumet®**	105 mg tablets	
		Tardyferon	80 mg tablets	
FERRIC IRON (Fe3+)	Iron protein succinylate	**Ferplex®**	Drinkable vial 40 mg	Lower absorption, higher cost, but better tolerated
	Ferrimanitol	**Profer®**	40 mg tablets 40 and 80 mg sachets	
		Kilor®	40 mg tablets 40 and 80 mg sachets	
LIPOSOMAL IRON		**Fisiogen Ferro**	Capsules 14 mg	Bioavailability comparable to ferrous salts, but with better tolerance.
		Fisiogen Ferro Forte®	30 mg Capsules30 mg Sachets	

Table 3: Types of iron marketed in Spain.

- The **most frequent side effects** derive from gastric intolerance (20%):
  - Constipation or diarrhoea
  - Nausea and/or vomiting
  - Epigastric discomfort
  - Pseudomelenas (dark coloration of faeces)

  In case of gastric intolerance, we will initially switch to an extended-release preparation (ferrous glycine sulphate). If, in spite of this, symptoms continue, supplements with a lower iron content can be offered, the administration interval can be modified (alternate day intake), iron can be taken 1-2 hours before dinner or with food (avoiding absorption inhibitors, see Table 4).

- **Recommendations in the intake:**
  - Ferrous salts should be taken with a little water or citrus fruit juice (orange or lemon). It's better to be taken on an empty stomach.
  - Ferric salts can be taken during and after the main meal with the exception of iron ,protein succinylate (Ferplex®), which is recommended to be taken one hour pre-meal.

There are factors that can favour or worsen iron absorption (Table 4).

Absorption enhancers	Absorption depressants *
Vitamin C Citrus fruits	Phytates: whole grain bread, cereals Calcium: milk and milk products Oxalates: spinach and root vegetables Medications: levothyroxine, antacids, α-methyldopa, antibiotics, penicillamine, bisphosphonates, and drugs containing calcium, magnesium, or aluminium Coffee or tea

Table 4: Factors that modify the absorption of oral iron.

* The administration of iron has to be done two hours before or after ingestion of any of these foods/drugs.

- Oral iron administration is **contraindicated** in the following circumstances:
  - Iron overload disease (e.g. haemochromatosis, haemosiderosis, thalassemia, etc.). major, β-intermediate thalassaemia, Hb H disease and sickle cell disease).
  - Recent repeated blood transfusions or concurrent treatment with intravenous iron (oral iron will not be started until 4 weeks post endovenous (ev) treatment)
  - *Minor* forms of congenital anaemias or haemoglobinopathies (*minor* forms, silent carrier or sickle cell trait) are a **relative contraindication**. It requires an identified iron deficiency to initiate iron therapy.

- **INTRAVENOUS IRON THERAPY:**

Treatment with intravenous iron is **indicated** in the following cases:

- Inadequate response to oral iron therapy (Hb increases less than 1 g/dL at 2 weeks or less than 2 g/dL at 4 weeks under treatment with 100 mg/day of ferrous salt).
- Non-adherence or pathologies leading to malabsorption (patients with chronic inflammatory disease or malabsorptive bariatric surgery).
- Absolute intolerance to oral iron (after change of preparation)
- Need for rapid and effective treatment (e.g. Jehovah's witness, moderate iron deficiency anaemia > 34 weeks, transfusion refusal when indicated).

- Before starting intravenous iron therapy, **the necessary iron dose should be calculated** according to the following table (Table 5), based on Ganzoni formula:

Pregestational body weight [kg] x (target Hb [12 g/dL] - current Hb [g/dL]) x 2.4 + 500

Body weight	**35 - 70 Kg**		**≥70 Kg**	
Hb (g/dL)	≥10	<10	≥10	<10
Total Fe dosage	1000 mg	1500 mg	1500 mg	2000 mg

Table 5: Calculation of iron deficiency

- **Precautions** before starting treatment
  - It is recommended to use the pregestational weight for dose calculation.
  - Do not administer > 500 mg in patients < 35 kg, regardless of Hb value.
  - In patients with CKD on haemodialysis, do not exceed a maximum daily dose of 200 mg.
- The administration schedule varies depending on the compound (Table 6):

Ferrous salt - tradename	**Fe content**	**Features**	**Administration**
Ferric carboxymaltose **Ferinject**	Vials 100 and 500 mg Vial concentration: 50 mg/mL	▪ Best choice, but higher cost ▪ Demonstrated effectiveness and safety in pregnancy ▪ Increase and faster increase in Hb ▪ Maximum infusion per dose: 1000 mg ▪ Rapid infusion (15 min per 1000 mg) ▪ Does not cross placental barrier	▪ 500 or 1000 mg of Fe in each administration ▪ If more doses are needed (Table 6), fractionate and administer at intervals of at least 7 days: - 1st set: 1000 mg - 2nd set: 500 or 1000 mg ▪ Max dose 1000 mg/week
Iron sucrose **Feriv®** **Venofer**	Vials 100 and 200 mg Vial concentration: 20 mg/mL	▪ Less efficient, lower cost ▪ Maximum infusion per dose: 200 mg ▪ Slow infusion (30 min per 100 mg)	▪ 100 or 200 mg of Fe in each administration ▪ If more doses are needed (Table 6), fraction the dose and administer at intervals of at least 48 hrs until the required dose is completed, maximum 3 doses per week. ▪ Max. dose 600 mg/week

Table 6: Intravenous iron therapy

- The **side effects** that may appear, apart from anaphylaxis (1% of cases), are generally related to the infusion rate, such as hypotension, headache, dizziness, hot flushes, nausea. Others: phlebitis, hypertransaminasaemia, hypophosphataemia, free radical toxicity.
- **The patient** should be **monitored during the infusion and up to 30 minutes** after the administration of iron ev. In case of hypersensitivity reactions or signs of intolerance during administration, treatment should be discontinued immediately.
- Administration of intravenous iron is **contraindicated** in the following circumstances:
  - Anaemia not attributable to iron deficiency
  - History of previous anaphylaxis with intravenous iron (regardless of the ev iron preparation administered)
  - First trimester of gestation (do not start before 14 weeks)
  - Acute or chronic active infection:
    - Contraindicated in active infection not controlled or correctly treated. Whenever possible, it should be deferred until after antibiotic treatment has been completed.
    - It is NOT contraindicated in well-controlled chronic HIV or HBV/HCV infections.
  - Hepatopathy:
    - Hepatic insufficiency resulting in a x3 increase in normal transaminase values.
    - Hepatopathy when iron overload is the triggering factor (e.g. porphyria cutanea tarda).
  - Same contraindications as for oral iron.

4.2.2 TREATMENT OF FOLIC ACID DEFICIENCY ANAEMIA

It is **indicated** in case of an identified folic acid deficiency. It will be performed by administering **5 mg/day of folic acid** (Acfol®) for a minimum of 4 months or until the end of gestation.

4.2.3 TREATMENT OF ANAEMIA DUE TO VITAMIN B12 DEFICIENCY

It is **indicated** in case of identified vitamin B12 deficiency. The treatment will be performed by administration of **cyanocobalamin intramuscular injection (IM)** and consists of two phases:

- 1 mg three times a week for two weeks or 1 mg weekly for 4 weeks.
- 1 mg every 1-3 months until reserves are restored.

Or If no monocomponent oral preparations are available in the market, intramuscular preparations that are drinkable might be used. (Optovite B12®).

4.2.4 TREATMENT OF MIXED DEFICIENCY ANAEMIAS

Deficits must be made up simultaneously following the indications in the previous sections.

In these cases, there is a higher risk of iatrogenic iron overload than in pure iron deficiency. For this reason:

- If **ENDOVENOUS IRON THERAPY** is required, the maximum dose to be administered will be **500 mg ev**.

4.3 TRANSFUSION OF RED BLOOD CELLS

- During pregnancy it is **indicated** in the following cases:
  - Severe anaemia (Hb <7 g/dL)
  - Hb <9 g/dL with significant anaemic symptoms
  - Any degree of anaemia with haemodynamic instability or symptoms requiring immediate intervention.
  - It will also be assessed in the presence of any degree of anaemia and the presence of signs compatible with tissue hypoxia (tachycardia, syncope, angina, dyspnoea) that cannot be explained by hypovolemia or other causes, or in the presence of cardiovascular risk factors (heart failure, ischaemic or valvular heart disease, cerebrovascular disease).

- The choice of the **number of concentrates** to be administered will depend on the level of anaemia. Approximately, it is estimated that in an adult patient of standard constitution, stable and without haemolysis or active bleeding, each red cell concentrate will increase the Hb level by 1.1 g/dL and the haematocrit by 3 percentage points. The goal is to achieve a minimum Hb level of 8 g/dL (in stable non-cardiac patients). It will be necessary to sign the **informed consent** form.

- **Post-transfusion monitoring** should be performed with a blood count between 1 h and 24 hours after completion of the transfusion. If the expected increase in Hb or haematocrit does not occur, the following possibilities should be investigated:

  - Sample extraction error (haemodilution)
  - Active haemorrhage (visible or occult)
  - Haemolysis of transfused blood

  Depending on the post-transfusion Hb value and the cause of the anaemia, the corresponding treatments will be initiated following the indications in the previous sections.

4.4 TREATMENT OF THE HAEMOGLOBINOPATHIES

4.4.1 MINOR FORMATS (Thalassaemia *minor* (α or β), Silent carrier, Sickle cell trait)

The clinical management of these patients will not differ too much from that of any other pregnant woman. The goal is to maintain Hb levels between 9-10 g/dL.

- **Moderate anaemias** (Hb >7 g/dL):
  - Treatment with iron will only be carried out in case of confirmed iron deficiency (Ferritin < 30 µg/L).
  - First of all, treatment with oral iron will be carried out.
  - Intravenous iron therapy can be used following the same indications as for other pregnant women. However, the specific dose must be calculated considering that the target Hb will be 9-10 g/dL.

    Pregestational body weight [Kg] x (target Hb [9-10 g/dL] - current Hb [g/dL]) x 2.4 + 500

- **Severe anaemia** (Hb < 7 g/dL):
  - Infrequent in the *minor* forms. The study protocol will have to be performed to confirm/rule out other superimposed causes.
  - The need for blood transfusion will be assessed jointly with Haematology. Always perform crossmatching tests due to the risk of alloimmunisation and haemolytic anaemia.
  - In some specific cases in patients with Thalassaemia *minor*, treatment with EPO may be considered in conjunction with the referring haematologist.

It is important to perform a **thrombosis risk** assessment in these patients:

- Thalassaemia *minor*, silent carrier status or sickle cell trait act as low risk factors during pregnancy.

4.4.2 MAJOR FORMS (Thalassaemia *major* (α or β), β-Thalassaemia intermedia, Hb H disease or sickle cell disease).

Patients who, due to the aetiopathology of the disease, have a higher morbidity and mortality during pregnancy and therefore require a multidisciplinary assessment and follow-up by the obstetrician and the referring haematologist.

- Iron treatment is contraindicated.
- The need for transfusions during pregnancy is frequent. This will be indicated with Hb values < 9-10 g/dL. Transfusion of more than 2 red cell concentrates at a time is not recommended. The indication and frequency should be agreed with the referring haematologist.

It is important to perform a **thrombosis risk** assessment in these patients:

- In patients with *major* forms of Thalassaemia and concomitant presentation of some of the following risk factors described in the table (Table 7), treatment with low molecular weight heparin (LMWH) will be indicated during pregnancy in patients with splenectomy; treatment with acetylsalicylic acid (ASA) at antiplatelet doses (100 mg/day) will also be initiated.

Indications for thromboprophylaxis	
• B-intermediate thalassaemia (without other RF) • Splenectomy • No transfusions • Platelets > 500x109/L • Red blood cells > 300x106/L	• Hb < 9 g/dL • Pulmonary hypertension • Ferritin ≥ 800 ng/mL • Family or personal history of thrombosis • Other thrombotic risk factors

Table 7: Indications for thromboprophylaxis in major forms of Thalassaemia

- Sickle cell anaemia acts as an intermediate risk factor during gestation.

2. FOLLOW UP

2.1 FOLLOW-UP OF ANAEMIAS DUE TO DEFICIT

5.1.1 MONITORING OF IRON DEFICIENCY ANAEMIA

Follow-up will be done according to the severity of the anaemia:

- **Mild anaemias:** to be performed every quarter coinciding with the gestational control tests.
- **Moderate-severe anaemias:**
  - To be performed 4-6 weeks after the start of iron therapy.
  - In moderate anaemias > 34 weeks of gestation, monitoring should be performed at 2 weeks to assess the need for further treatment in view of delivery.

- In anaemias that have required transfusion, the control will be performed after 2 weeks to optimise future treatments.

Follow-up will be done with a **complete blood count**. It is important not to include ferritin because it undergoes a rapid increase that would cause a false positive result in terms of remission of iron deficiency.

- Good response if Hb increase 0.5-1 g/dL per week. In these cases, we will maintain the same treatment.
- If poor response (< 0.5 g/dL per week): change type of ferrous component or perform intravenous treatment.
- Iron therapy will be maintained until 3 months after the anaemia was corrected.

In cases in which treatment with **intravenous iron** has been indicated, follow-up will also be carried out at 4-6 weeks. Treatment with oral iron will not be carried out simultaneously with intravenous iron or during the following four weeks.

- If the indication for intravenous iron persists (depending on the clinical manifestations and degree of anaemia), the dosage will be recalculated and a new round of intravenous treatment will be performed.
- If the indication disappears, in case of persistence of anaemia, treatment with oral iron will be completed.
- Once the patient is switched to oral treatment, iron therapy will be maintained until three months after the anaemia was corrected.

5.1.2 MONITORING OF FOLIC ACID OR VITAMIN B12 DEFICIENCY ANAEMIA

The determination of folic acid or vitamin B12 will be added, following the same control cadence as in the previous section:

- **Mild anaemias:** every 3 months.
- **Moderate-severe anaemias:** 6-8 weeks after starting treatment.

In case of normalisation of folic acid and/or vitamin B12 levels, no further follow-up is required. If deficiency persists during gestation, normalisation should be confirmed at the quarantine visit. If vitamin B12 deficiencies persist at the quarantine visit, referral to a haematologist will be necessary to rule out pernicious anaemia.

5.1.3 MONITORING OF MIXED DEFICIENCY ANAEMIAS

In this case, follow-up will be performed **4-6 weeks** after the start of treatment. The control will be carried out with a haemogram, ferric metabolism and the other deficiency factors (folic acid and vitamin

B12). The evaluation of the response will be made following the indications of the previous sections.

2.2 MONITORING OF THE HAEMOGLOBINOPATHIES

5.2.1 MINOR FORM (Thalassaemia *minor* (α or β), silent carrier, sickle cell trait).

The follow-up will be done with a **haemogram**. It is important to not include ferritin in those cases that have been treated with iron.

- **Mild-moderate anaemias:** it will be performed quarterly coinciding with the gestational control tests. Iron treatment will be suspended once the objectives have been reached (Hb between 9-10 g/dL).
- **Severe anaemia:** assess the frequency of follow-up with Haematology according to the treatment established (EPO/transfusion).

5.2.2 MAJOR FORMS (Thalassaemia *major* (α or β), β-Thalassaemia intermedia, Hb H disease orsickle cell disease).

The frequency of follow-up of these patients will be determined by the referring haematologist.

ANAEMIA DURING THE PUERPERIUM

1. INTRODUCTION

One third of women suffer from postpartum anaemia. The most frequent cause is haemorrhage, with minor or major contribution of a possible pre-existing iron deficiency. In 80% of cases, anaemia was present during pregnancy.

2. DIAGNOSIS OF ANAEMIA DURING THE POSTPARTUM PERIOD

Diagnosis of postpartum anaemia will be made by **haemogram**. Postpartum anaemia is defined as an **Hb**concentration **<10 g/dL**.

- **A complete blood count will not be routinely requested**. It will be requested only in the following situations:
  - Uncorrected antepartum anaemia
  - Haemoglobinopathies
  - Signs and symptoms suggesting anaemia.
  - Estimated blood loss > 500 mL
- Note that the minimum postpartum Hb level is reached approximately 48 h after the primary distribution of plasma volume.
- **The determination of ferritin should not be included** in these cases as it may be falsified during at least the first two weeks postpartum, because it is an acute phase reactant. It should be determined either before delivery or at least 6 weeks after delivery.

3. PREVENTION OF ANAEMIA DURING THE POSTPARTUM PERIOD

Prevention of iron deficiency anaemia in the puerperium is recommended with the supplementation of **60-100 mg/day of oral iron**. It can be discontinued at the 6 weeks postpartum visit if the patient is asymptomatic.

In case of **breastfeeding**, supplementation with **15 mg/day of oral iron** should be continued, after the 6 weeks postpartum visit and during the whole breastfeeding period, this being a dose that is covered by most postdelivery vitamin formulations.

Oral iron supplementation is **contraindicated** in patients with **haemoglobinopathies** due to the risk of iron overload.

4. TREATMENT OF ANAEMIA DURING THE POSTPARTUM PERIOD

4.1 TREATMENT OF DEFICIT ANAEMIAS

4.1.1 TREATMENT OF IRON DEFICIENCY ANAEMIA

- **ORAL IRON THERAPY**

With Hb levels between 8 and 10 g/dL, in haemodynamically stable and asymptomatic patients, supplementation with **100-200 mg of** elemental **iron** daily for 3 months is indicated.

- **INTRAVENOUS IRON THERAPY**

- Intravenous iron therapy during admission is **indicated** in the following cases:
  - Hb < 8 g/dL without clinical anaemia.
  - Inadequate response, intolerance or non-compliance with the oral route during pregnancy.
  - Need for rapid and effective treatment (e.g. Jehovah's testimony, refusal of transfusion when indicated).
- The same procedure will be used to **calculate the dose** as during gestation (Table 5).
- After treatment with intravenous iron, treatment with oral iron will not be started until 6 weeks postpartum control.

4.1.2 TREATMENT OF ANAEMIA DUE TO FOLIC ACID OR VITAMIN B12 DEFICIENCY

Rare entity in the postpartum period if there is no antepartum deficit. In any case, the treatment will be the same as during pregnancy.

4.1.3 TREATMENT OF MIXED DEFICIENCY ANAEMIAS

Rare postpartum entity in the absence of antepartum folic acid or vitamin B12 deficiency. In any case, the treatment will be the same as during pregnancy.

4.2 TRANSFUSION OF RED BLOOD CELLS

- Red blood cell transfusion is **indicated** in the following cases:
  - At 6-8 g/dL, transfusion should be considered depending on the patient's clinical and haemodynamic tolerance.

- Hb values < 6 g/dL may make transfusion advisable even in the absence of clear anaemic symptoms.
- In cases of acute blood loss, despite higher Hb levels, transfusion may be indicated if the patient has acute anaemic syndrome.

- Post-transfusion control will be performed following the same indications as for transfusion during pregnancy. Depending on the post-transfusion Hb, oral iron therapy will be started until 6 weeks postpartum.

4.3 TREATMENT OF THE HAEMOGLOBINOPATHIES

The treatment of haemoglobinopathies will be carried out following the same indications as during pregnancy.

It is important to perform a **thrombosis risk** assessment in these patients:

- Thalassaemia *minor*, silent carrier status or sickle cell trait act as low risk factors during the puerperium (see specific protocol).
- In all cases of Thalassaemia *major*, intermedia or H disease, thromboprophylaxis is indicated throughout the postpartum period.
- Sickle cell anaemia acts as an intermediate risk factor during the puerperium (see specific protocol).

5. FOLLOW UP

5.1 FOLLOW-UP OF ANAEMIAS DUE TO DEFICIT

Patients diagnosed with **mild anaemia** during the puerperium do not require a control haemogram at the 6 weeks postpartum visit. Treatment will be maintained until 3 months after the delivery.

In patients diagnosed with **moderate or severe anaemia** during the puerperium, especially those who have required intravenous iron therapy or blood transfusion, a control haemogram will be performed during the 6 weeks postpartum visit to optimise treatment. Patients will be instructed on the signs and symptoms of emergency consultation.

Patients with uncorrected gestational deficiencies of folic acid and/or vitamin B12 will require a control blood count and folic acid and/or vitamin B12 levels at the quarantine visit.

5.2 FOLLOW-UP OF THE HAEMOGLOBINOPATHIES

5.2.1 MINOR FORM (Thalassaemia *minor* (α or β), silent carrier, sickle cell trait).

A control haemogram will be performed at the 6 weeks postpartum visit in those patients who have been started on iron therapy or who have been diagnosed with severe anaemia during the postpartum period.

5.2.2 MAJOR FORMS (Thalassaemia *major* (α or β), β-Thalassaemia intermedia, Hb H disease orsickle cell disease).

The frequency of follow-up of these patients will be determined by the referring haematologist. A postpartum follow-up visit with the referring haematologist is recommended in order to modify/restore treatments.

Responsible for the protocol:	Laura Ribera, Míriam Illa, Elena Monterde, Meritxell Nomdedéu, Jordi Fornells, Jordi Esteve, Ana Belén Moreno
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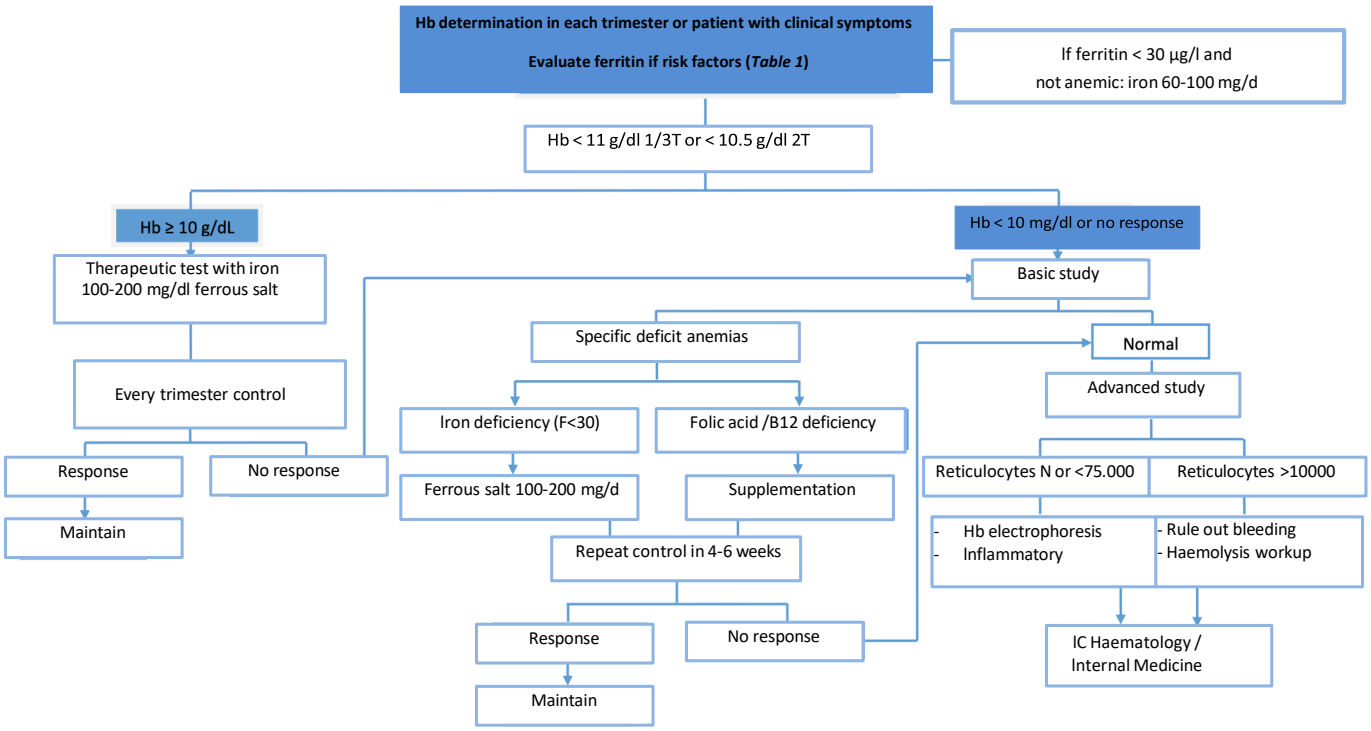
ANNEX 2: DIAGNOSIS AND CLINICAL MANAGEMENT OF IRON DEFICIENCY ANAEMIA DURING THE POSTPARTUM



ANNEX 2: DIAGNOSIS AND CLINICAL MANAGEMENT OF IRON DEFICIENCY ANAEMIA DURING THE POSTPARTUM