“Thrombosis in pregnant women with hemolytic anemia”

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Pregnancy in Thalassemia

- The natural history of thalassemia has drastically changed in recent years thanks to the improvement of transfusion and iron chelation therapy and to the treatment of complications derived from them

- Pregnancy of women with thalassemia major, thalassemia intermedia, and sickle cell disease should be approached by a multidisciplinary team and followed from the preconception phase until the post-partum period with a close monitoring of the maternal and fetal conditions, in order to ensure an optimal outcome

Pregnancy in Thalassemia - Management

Crucial points in the management of pregnancies are:

- iron chelation therapy before and during pregnancy
- antithrombotic prophylaxis
- the management of transfusion therapy according to the modified transfusion requirement

paying particular attention to

- immune-hematological examinations

and a careful cardiologic monitoring for hemodynamic changes that expose an increased risk of heart failure

Iron Chelation Therapy

- In the preconception period, the iron chelation therapy is strictly recommended when dealing with pregnancy forecast, in order to avoid complications due to heart diseases (heart failure and arrhythmias) or liver disease

- It is important for women to start pregnancy with low ferritin levels in order to avoid a decrease in their systolic function indices

- Women of childbearing age on oral chelators should be counseled to avoid getting pregnant or advised to switch to desferrioxamine if they are planning to get pregnant

Pregnancy in Thalassemia and Sickle Cell Disease, Sorrentino et al. Frontiers in Molecular Biosciences,February 2020
Pregnancy in Thalassemia ,Origa and Comitini, 2019, Mediterr J Hematol Infect Dis 2019

Iron Chelation Therapy
What is the optimum antenatal management of iron chelation therapy?

- In the case of spontaneous pregnancy or suspected pregnancy, the chelation therapy needs to be immediately suspended
- In cases of medically assisted procreation, the iron chelation therapy should be suspended at the time of intrauterine injection of the seminal fluid or the embryonic implant, according to the involved medical procedure
- Iron chelation therapy can be resumed after the first trimester of pregnancy but only with desferrioxamine (DFO), to avoid major increases in serum ferritin

(only in high risk patients- patients with severe heart and liver iron overload, when the potential benefits outweigh the potential risks to the fetus)

- DFO is the iron chelator of choice during pregnancy because its large molecular size prevents the passage through the placenta

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Pregnancy in Thalassemia ,Origa and Comitini, 2019, Mediterr J Hematol Infect Dis 2019

Transfusion (I)

How should the transfusion regimen be managed during pregnancy in women with thalassemia major?

Anemia is common during pregnancy

- **Transfusion dependent patients need transfusion regime adopted on the basis of individual needs in relation to hemoglobin values which should be maintained at hemoglobin level 10 g/dL to optimize fetal growth**

- Women with thalassemia major will already be established on transfusion regimens which generally remain stable during pregnancy
- In cases where lower pre-transfusion thresholds have been used pre-conceptually, the aim is to achieve a pre-transfusion haemoglobin of 10.0 g/dl

Pregnancy in Thalassemia and Sickle Cell Disease, Sorrentino et al. Frontiers in Molecular Biosciences,February 2020
Pregnancy in Thalassemia ,Origa and Comitini, 2019, Mediterr J Hematol Infect Dis 2019
GUIDELINES FOR THE MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIA (TDT)TIF 2021

Transfusion (II)

How should the transfusion regimen be managed during pregnancy in women with thalassaemia intermedia?

- Non-transfusion dependent thalassemia (intermediate thalassemia) patients may need transfusion for the first time in pregnancy due to the dilution of the hemoglobin

  (In accordance with most studies on pregnancy in thalassemia intermedia women, 60–80% of the patients need transfusions during pregnancy, although 30% of them have never had a transfusion before)

- In some cases, it may be appropriate to reduce the transfusion interval and to administer only one unit of red blood cells at a time to support the fetal oxygenation requirements and to reduce the risk of hemolysis and thrombotic complications

Pregnancy in Thalassemia and Sickle Cell Disease, Sorrentino et al. Frontiers in Molecular Biosciences,February 2020

Pregnancy in Thalassemia ,Origa and Comitini, 2019, Mediterr J Hematol Infect Dis 2019

GUIDELINES FOR THE MANAGEMENT OF TRANSFUSION DEPENDENT THALASSAEMIA (TDT)TIF 2021 Pregnancy in thalassemia intermedia Voskaridou et al.2014

Transfusion (III)

How should the transfusion regimen be managed during pregnancy in women with thalassaemia intermedia?

- Transfusion practices in pregnant women with TI, are highly variable, with some centers supporting transfusion in all patients with Hb <10 g/dL and others that reserve transfusion for those patients with severe anemia only or those with evidence of intrauterine growth retardation (IUGR)

- However, no study has evaluated obstetric outcomes based on Hb levels in TI, and therefore the decision to transfuse should be individualized depending on maternal and fetal indications

Pregnancy in Thalassemia and Sickle Cell Disease, Sorrentino et al. Frontiers in Molecular Biosciences,February 2020
Pregnancy in Thalassemia ,Origa and Comitini, 2019, Mediterr J Hematol Infect Dis 2019
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Alloimmunization

- One of the complications of transfusions for TI women who require transfusion for their first time during pregnancy is the possible development of antibodies against erythrocytes and subsequent alloimmune hemolytic anemia, which exacerbates their anemia and leads to increased need for transfusions

- For this reason, a transfusion program in TI pregnant women should take into account the potential alloimmunization and therefore extended genotype and antibody screening should be performed before giving any transfusions and if transfusion becomes necessary phenotypically compatible blood transfusions should be given

Pregnancy in thalassemia intermedia Voskaridou et al.2014,
Pregnancy in Thalassemia and Sickle Cell Disease, Sorrentino et al. Frontiers in Molecular Biosciences,February 2020
Pregnancy in Thalassemia ,Origa and Comitini, 2019, Mediterr J Hematol Infect Dis 2019

Pregnancy and thromboembolic events

Pregnancy increases the risk of thrombosis from three-fold to four-fold

Venous thromboembolism is one of the leading causes of maternal morbidity in pregnancy, and its incidence is estimated to be 0.76 to 1.72 per 1,000 gestations, while maternal death is caused prominently by pulmonary embolism

- Thalassemia, is also a hypercoagulable state with an enhanced risk of thromboembolic complications especially in splenectomised patients
- One of the main factors behind this risk is the procoagulant effect of anionic phospholipids on the surface of altered red cells and erythroblasts, whose number is dramatically increased by splenectomy and in non-transfused or minimally transfused patients
- The presence of further factors, which can increase the risk of thromboembolism such as inherited and acquired thrombophilia, a history of thrombosis and pregnancy outcomes should also be assessed

Pregnancy and thromboembolic events

What antenatal thromboprophylaxis is recommended?

- Although no specific regimen or guidelines have been established, the recommendation is to keep women who are at higher risk on prophylaxis during pregnancy and the postpartum period
- Both acetylsalicylic acid and low molecular weight heparin have been used

- Although there is a predisposition to venous thrombosis no reports of thrombotic episodes have been noted in women receiving low molecular weight heparin

- **For this reason in patients who have undergone splenectomy, and particularly in those with TI, thromboprophylaxis with low molecular weight heparin is required from mid-trimester**

(Eldor & Rachmilewitz, 2002; Nassar et al., 2006) (Origa et al., 2010; Tuck et al., 1998)
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Pregnancy and thromboembolic events

What antenatal thromboprophylaxis is recommended?

- According to recent data, low-dose aspirin, frequently administered to splenectomized β-thalassemia patients, seems to be effective in preventing preeclampsia, preterm birth, and IUGR in high- risk pregnancies without posing a major safety risk to mothers or fetuses
- Splenectomized women or those with a serum platelet count above 600×10^9 /L should begin or continue taking aspirin at a dose of 75 mg/day
- Splenectomized women with a platelet count above 600×10^9 /L should additionally be offered low-molecular-weight heparin (as well as a low-dose of aspirin (75 mg/day))

- Women with thalassemia who are not already using prophylactic low-molecular-weight heparin should be advised to use it during antenatal hospital admissions

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Pregnancy and thromboembolic events

What should be the optimum postpartum care?

- Low-molecular-weight heparin should be administered for 7 days post discharge following vaginal delivery or for 6 weeks following caesarean section

- In case of miscarriage or termination of pregnancy the danger of thromboembolism is still present and low-molecular-weight heparin prophylaxis must be provided during and following the loss for at least 7 days

Pregnancy and thromboembolic events

- Furthermore, apart from antithrombotic and anti-platelets drugs, a regular transfusion regimen aiming to reduce endogenous erythropoiesis and so reducing the circulation of abnormal red cell fragments, especially in splenectomised patients, is also a measure to avoid thrombotic phenomena since these fragments predispose the formation of blood clots

- Interestingly, no reports of thrombotic episodes during pregnancy in thalassemia major patients are reported in the literature

Pregnancy in sickle cell disease
Management of VTE and thromboprophylaxis

- Pregnancy is a well-established risk factor for VTE for women but this risk is magnified in pregnant women with SCD
- In a recent meta- analysis : the risk of VTE ($P < 0.001$) and deep vein thrombosis ($P = 0.02$) were increased when compared to a cohort without SCD
- The prevalence of VTE was 3.5-fold greater in women with complications such as vaso-occlusive crisis, acute chest syndrome and pneumonia when compared to those without these complications, but was less in those with more severe anaemia
- In this study 28.6% and 7.4% of VTE episodes were identified as having occurred in the antenatal and postpartum periods respectively

Management of sickle cell disease in pregnancy. A British Society for Haematology Guideline Eugene Oteng-Ntim et al – British Society for Haematology Guideline,British Journal of Haematology, 2021
Seaman C et al,Venous thromboembolism in pregnant women with sickle cell disease: a retrospective database analysis. Thromb Res. 2014

Pregnancy in sickle cell disease
What thromboprophylaxis is recommended?

- Recommendations:

- All women with SCD should have risk assessments performed in early pregnancy, if admitted to hospital, in the intra-partum and early post-partum period (1C)
- Women with SCD should be considered for prophylactic low-weight heparin (LMWH) from 28 weeks of pregnancy until six weeks postpartum and if women have additional risk factors, prophylaxis should start from the beginning of pregnancy (2B)
- Women admitted to hospital with a vaso-occlusive crisis or for other reasons should be offered LMWH throughout their admission unless there are contraindications (1B)

Management of sickle cell disease in pregnancy. A British Society for Haematology Guideline Eugene Oteng-Ntim et al – British Society for Haematology Guideline,British Journal of Haematology, 2021

Pregnancy in sickle cell disease
What thromboprophylaxis is recommended?

- Women with SCD have an increased risk of pregnancy-induced hypertension and pre-eclampsia
- Aspirin prophylaxis is recommended at 75–150 mg daily from 12 weeks of gestation for women at high risk of pre-eclampsia unless they have aspirin sensitivity
- Although there is no specific evidence that aspirin decreases the risk of pre-eclampsia in women with SCD, in view of their increased risk, it is recommended that women with SCD and no contraindications should be offered aspirin prophylaxis from 12 weeks
- Recent evidence suggests that aspirin may increase the risk of postpartum haemorrhage so it should be stopped at 36 weeks (stopping prior to delivery)

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Conclusion

- Pregnancy in thalassemia/SCD should be considered a high risk for both mother and fetus, and favorable outcomes are the result of continuous preconception, antenatal, and postpartum assessment and management by a team of thalassemia/SCD experts
- Further studies, as well as national and international registries for thalassemic/SCD pregnancies, should be organized and analyzed in order to establish guidelines for this important period of life of a woman with thalassemia/SCD

THANK YOU!