BETA THALASSEMIA IN PREGNANCY UPDATES IN THE MANAGEMENT OF ANAEMIA AND BIRTH (CASE REPORT)

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Abstract: *During the visits and assessments made by the pregnant woman during the antenatal period, there are many occasions when changes in complete blood count can be discovered in the sense of anemia.(1) Often, pregnant women benefit from iron treatment without being investigated haematologically and are often refractory to treatment. That is why we suggest a three-stage full screening by presenting the next case. We mention that this pathology meets all criteria for screening: increased frequency of healthy carriers (haematological defects), low cost screening tests with high specificity, low false positive rate (complete blood count, sideremia, ferritin), and on long term, the complications of the underlying haematological disease (which have an impact on the costs of hospitalization) can be avoided and, last but not least, iatrogenicity avoidance.*

INTRODUCTION

In the case of modified blood count in a pregnant woman, in the sense of a moderate microcytic, hypochromic anemia regarding the normal number of red blood cells, we will assess the iron reserve of the organism - sideremia and ferritin (if the values suggest normosidemia/ ferritinemia or are elevated) we are facing an anemia that has a genetic cause, respectively hemoglobinopathy, e.g. beta thalassemia, which due to iron reserves in normal or even elevated limits, will have a refractory character to the usual iron treatment.(2) Further, hemoglobin electrophoresis will be performed.

We mention that hemoglobinopathies have a pattern of autosomal recessive transmission, and the meeting of two partners carrying the mutated gene (haematological defect) or a minor form of β-Thalassemia can lead to a major form of the disease.

The costs involved in a haematological screening are not significant. It is important to emphasize that a correct blood count and evaluation of iron reserves of the body, carefully read and interpreted (normosideremic hypochromic anemia regarding the normal number of red blood cells), guides our screening through three stages, and also leads us to a correct etiopathogenic diagnosis and treatment (roborating, catalytic factors - folic acid, vitamin B12), interdisciplinary management of the pregnancy and, last but not least, genetic counselling (the need to investigate the partner, the fetus/ new-born). Also, the postpartum of these patients is not to be neglected, loaded by thromboembolic events, secondary to erythrocytes with abnormal structure (and additionally, because of the alpha globin chains in secondary excess, which form Fessas bodies, which tend to precipitate, thus causing a prothrombotic field) where the need for anticoagulation treatment for 7 days for vaginal delivery and 6 weeks in the case of postoperative caesarean.(3)

CASE REPORT

We present the case of the pregnant woman, H.A., 25-year-old, with anamnestic amenorrhea for 15 weeks, correctly managed, diagnosed from 2014 with thalassemia minor form, for which she received roborating treatment (with folic acid 1tb/ day and vitamin B12 1tb/ day, both for 15 days a month), is presented at the Obstetrics Gynecology (OG) Clinic within Sibiu County Clinical Emergency Hospital, complaining about: pelviabdominal pain of increased intensity, slightly increased uterine tonus, pallor, asthenia, moderate fatigability. She is hospitalized for specialized interdisciplinary OG - haematological interventions and treatment.

From personal medical history, we mention: ♂ the father, in 2014, on the occasion of regular occupational health check, was diagnosed with suspicion of β-Thalassemia, anemia refractory to iron treatment. Receiving a medical recommendation, in order to initiate a haematological assessment of descendants, the family members have started the screening. Following the investigations, both daughters were diagnosed with beta thalassemia, mentioning the pregnant woman's sister with an intermediary form (22 years old, para 1, who during pregnancy followed iron chelation therapy in the second trimester of pregnancy and anticoagulant treatment). The screening was also performed in extenso and, ♀ the paternal aunt was diagnosed in turn with a minor form of β-Thalassemia.

We also noted the following: menarha at the age of 10 years, regular menstrual cycles, normal menstrual fluid volume, nulliparous, history of primary infertility (possibly due to a transient iron impregnation at pituitary level, which shows increased iron sensitivity, resulting in a status of hypogonadotropic hypogonadism).

From the personal medical history of the pregnant woman we mention: β-Thalassemia minor diagnosed in August 2014 (for which hemoglobin electrophoresis has been performed, which shows obvious increases in adult Hb type A2).

The objective general exam on all organ systems revealed the following: during the inspection – attention is drawn upon the accentuated pale teguments and mucous (yellowish shade), apparent mild jaundice, facies mongoloid

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like. At palpation: the liver and the spleen were in normal limits (which additionally is suggestive for the "minor" form, respectively the lack of secondary complications of depositing excess iron in the target organs). Obstetrical exam - no cervical changes, uterus increased like a 15-week pregnancy that occupies the adrenal areas and the Douglas' pouch.

Stage diagnosis (clinically suggested, strengthened by paraclinical examinations, confirmed by the haematological episode): Pregnancy - 15 weeks. Abortion imminence. Beta thalassemia minor. In observation, microcytic hypochromic anemia in the context of hemoglobinopathy.

The following paraclinical investigations were performed during hospitalization: laboratory investigations and, in dynamics, ultrasound assessment of the pregnancy (we mention the absence of fetal complications).

We propose the following algorithm of laboratory investigations in the context of an anemia of β-Thalassemia – microcytic hypochromic anemia normosideremic or hypersideremic.

In the first stage, a simple full, a carefully read and interpreted blood count (CBC) will guide our screening. In the case of the present CBC, we have seen the followings: RBC 4,38 x 10 6 /ul, Hb 9, 1g /dl, VEM 63,7 Fl, HEM 20,8 pg, the diagnosis being: moderate microcytic hypochromic anemia of normal erythrocyte count. Differential diagnosis was performed with posthemorrhagic secondary anemia (iron deficiency microcytic hypochromic anemia), in which the number of red blood cells is low.

Within the RBC morphology, the following specific aspects are noted: anisocytosis with microcytosis, moderate towards severe poikilocytosis (ovalocytes, drops, echinocytes, rare schizocytes - hemolysis tendency), mild hypochromia. Target erythrocytes and erythrocytes with basophilic stippling. Modified erythrocyte morphology requires a shorter life span, resulting in increased markers of homolysis.

Reticulocyte counts indicate 0.6% with a reference range (0.5-2.2%) - indicating that the hematogenic marrow still recovers, but still not at a sustained pace, the values approaching the range lower value.

In the second stage of screening, sideremia and ferritin will be assessed. We obtained the following results: sideremia - Fe 131.8 ug /dL, ferritin - normal values, thus pleading for beta thalassemia minor (hypersideremia would have also suggested it). We will make the differential diagnosis with posthemorrhagic secondary anemia, serum iron reserve being low (in practice, in such a situation, the body removes the iron from its reserves to restore the number of red blood cells).

In the third stage, hemoglobin electrophoresis (ELFO Hb) was performed, which highlighted: Hb A2 5.6% (2-3.3%) elevated value, abnormal Hb absent. Adult Hemoglobin Type A2 (Hb A2) elevations are a diagnostic criterion for beta thalassemia minor, a criterion also suggested by the SOGC guidelines, with the reference that in the Hematology Treaty under Paun R, it is also necessary to increase fetal hemoglobin (Hb F). In the differential diagnosis of other increases in adult Hb type A2, the following conditions occur: hyperthyroidism, antiretroviral treatment, deficiency of vitamin B9 /B12, viral hepatitis C /B, trisomy 21. We also mention other causes of Hb F, such as hereditary persistence, myelomonocytic leukemia, Fanconi anemia.(4)

Additionally, the following paraclinical investigations were performed in order to assess any possible complications of the underlying haematological disease and in order to strengthen the elements of the differential diagnosis: BT /BID and LDH as hemolysis marker (in the present case, the values were within normal limits, possibly due to the roborating treatment strictly observed since diagnosis). Then, we evaluated possible iron deposits at certain target organs level (we mention the results in normal limits of the following laboratory tests): TGO, TGP, glycemia (referred to in the NICE guidelines of the possible presence of a chronic insulitis with the secondary destruction of pancreatic endocrine cells). TSH, FT3, FT4 were measured and were within normal limits.

The positive diagnosis (suggested, strengthened and confirmed by the above mentioned, of which the haematological investigation in 2014 is sovereign) is the following: beta thalassemia minor form, moderate hypochromic normosideremic anaemia, 15-week pregnancy, abortion imminence. Etiological diagnosis: chromosomal damage. Pathogenic diagnosis: mechanisms leading to hemoglobin deficiency and defects in these mechanisms cause a hemoglopenia with a seemingly normal number of red blood cells. Histopathological diagnosis: we are dealing with the absence of hypersidemia and impregnation of target tissues with iron (heart, spleen, liver, endocrine glands, placenta). Clinical diagnosis: the previously mentioned diagnoses validate the diagnosis of β-Thalassemia minor form. Evolution without treatment leads to the risk of complications. Possible complications: accumulation of iron in the target organs with their dysfunction, plus the dysfunctions characteristic of anemia. Prognosis in the absence of treatment is relatively reserved.

Evolution under treatment relieves the patient of the above-mentioned complications and is based on roborating therapy, chelation of excess iron, antiaggregants if appropriate (primary and secondary thrombocytosis to splenectomy), anticoagulants if appropriate (due to the tendency to agglomeration of erythrocytes in the capillaries, secondary to morphological changes as well as due to the excess of the alpha globular chains compensatorily in the structure of hemoglobin, forming Fessas bodies with a tendency to precipitate, causing the appearance of a prothrombotic field).(3) It is worth mentioning that these patients can benefit from stem cell transplantation.(4) Establishing and initiating treatment will be implemented in disciplinary partnership with hematology. The rate of monitoring or correctly observed therapy will be more specific to the disease, and more frequently with haematological aim and obstetrical assessment (especially, ultrasound to establish embryonic /fetal viability, fetal morphology /biometry every 4 weeks, from week 24 to exclude any possible complications namely: RCIU, immune hydrops fetalis - mentioned in guidelines especially in maternal transfusion history not observing the principle of isogroup izoRh). NICE guidelines recommend the following rhythm of antenatal evaluation (table no. 1).(3)

Table no. 1. Rate of antenatal evaluation of pregnant women with beta thalassemia and therapeutic conduct

Rate of antenatal evaluation of pregnant women with beta thalassemia and therapeutic conduct	
between 7 - 9 gestational age (GA)	ultrasound in order to establish the presence of the intrauterine gestational sac, respectively the viability of the product of conception
Between 11-14 GA	screening trisomy, +/- prenatal diagnosis - bearing partners, to continue treatment with Folic Acid 5mg
at 16 GA	multidisciplinary re-evaluation (obstetrical, haematological, diabetological, cardiological)
between 18 – 20 GA	fetal biometrics
from 24 GA	every 4 weeks, ultrasound will be performed to capture in time any RCIU, secondary to placental excess iron
at 20 SG	multidisciplinary re-evaluation (obstetrical, haematological, diabetological)

between 20 – 24 GA	cardiac evaluation, possible cardiac damage; requires chelator administration
at 24 GA	multidisciplinary re-assessment (obstetrical, haematological, diabetological), fetal biometrics
at 28 GA	multidisciplinary reevaluation, fetal biometry, birth control in the context of an altered cardiac function
at 32 GA	multidisciplinary re-evaluation, fetal biometry, establishing the modality to delivery in the context of a complication of the underlying disease
at 34 GA	routine exam
at 36 GA	multidisciplinary re-assessment, fetal biometrics, recommendations on birth management, modality of delivery, time (gestational age), analgesia at birth. Special neonatal assistance.
at 38 GA	routine exam. If the pregnant woman has diabetes, labour will be induced, with the exception of the presence of a macrosomic fetus that requires caeserian section
at 39 GA	routine exam
at 40 GA	obstetrical examination and evaluation
at 41 GA	obstetrical examination and evaluation. Induction of labour in a nondiabetic pregnant woman pregnancy, in the absence of any RCIU or other fetal complications

The proposed treatment in β Thalassemia consists of drugs or surgery. Treatment is generally roborating, namely folic acid 3 tablets /day for 10 to 15 days a month or daily and vitamin B12 (cobalamin). The role of vitamin therapy is to be a catalytic factor, interfering with DNA synthesis reactions and in the maturation of cells of the erythrocyte series. It is recommended to initiate preconceptional treatment with 5 mg tablets, 3 months before getting pregnant. We also should mention iron chelators, having the criterion of administering the status of hypersermia and only in the second trimester of pregnancy after 20 GA (having teratogenic effect).(3) The commonly used product is subcutaneous deferoxamine, the proposed regimen being 5 days per week. Preconceptional use is also recommended in assisted reproductive techniques (TRA), before administering gondatrophins in order to induce ovulation. Intrapartum, in case of hypersidemia, 2g /24h subcutaneously will be administered, with the indication that it is secreted in the breast milk but is not absorbed orally. Another substance used is the anti-aggregate platelet, having as a criterion of administration: thrombocytosis> 600,000 /ul or splenectomy post-hypersplenism due to transfusions. Another therapeutic principle is the anticoagulant administration (administration criterion proposed by NICE guidelines(3): splenectomy and thrombocytosis> 600,000 /ul). Anticoagulation will also be given during postpartum period due to the prothrombotic field for 7 days if birth was vaginal and for 6 weeks after cesarean delivery. In case of severe maternal chronic anemia (Hb below 7g /dl), iso-group, iso-Rh blood transfusion, will be performed and by performing an anti-hepatitis B vaccination prophylaxis (if the booster dose in the immunization scheme has not been performed). Post-transfusion HCV antibodies will be also useful to early detect any complications.

Not to be neglected is the treatment by stem cell transplantation or allogeneic bone marrow transplantation.

Surgical treatment, respectively the splenectomy will be imposed in the context of a hypersplensism. Postplenectomy, the patients will enter the pneumococcal (Pneumovax) Haemophilus influenzae type B vaccine programme. We mention that these patients will have an increased risk of infection with encapsulated bacteria (Neisseria meningitidis, Streptococcus pneumoniae, H.Influentzae type B) and will require prophylactic treatment with Penicillin daily (if there is a drug allergy to this substance, it will be replaced with Erythromycin).

The particularity of the reported case is defined by the following three aspects: the infertility episode (with a transient character, possibly due to the underlying condition), the need for specific prophylaxis of the complications, the need for investigating the partner and the fetus /newborn (genetic profile).

DISCUSSIONS

Thalassemia syndromes are hereditary disorders and are based on a defect in the globin chain synthesis, resulting in erythrocytes with inappropriate hemoglobin contents. Hemoglobinopathies are among the most common diseases with a pattern of autosomal recessive transmission.(2) In the following charts we mention the possible transmission patterns (figure no. 1, a.b.c.):

Figure no. 1. a. Possible transmission pattern of thalassemia

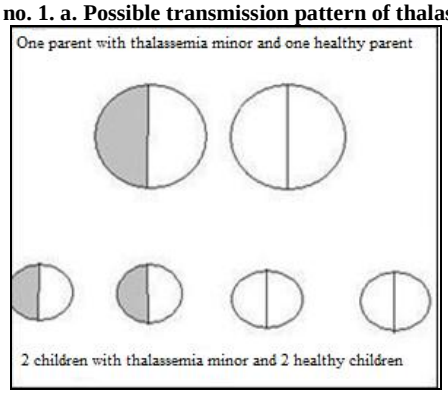

Figure no. 1.b. Possible transmission pattern of thalassemia

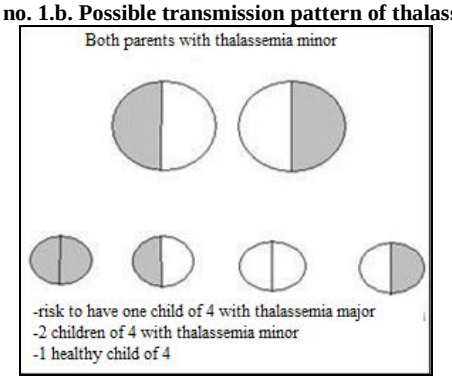

Figure no. 1.c. Possible transmission pattern of thalassemia

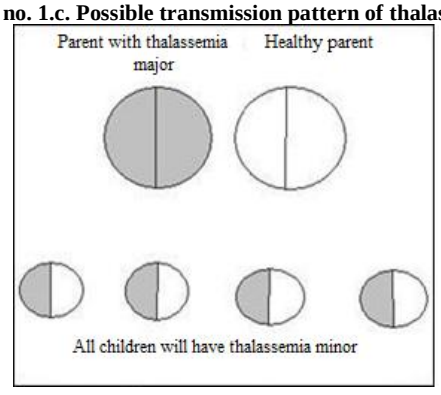

Figure no. 2. Geographical distribution of Thalassemia

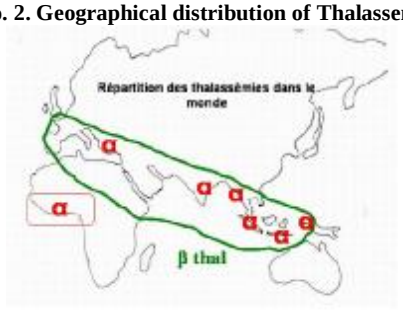

Image taken - http://www.hematocell.fr/Laboratoire d'Hematology du Chu D'Angers)

It can be said that it is the first genetic disorder, due to multiple mutations, representing a natural selection process, developed during the development and diversification of the population groups, with an obstetrical negative impact (due to the possible fetal complications, for example as a result of maternal transfusions or genetic transmission of a major form) and a positive one from the point of view of paludism.(2) It is common in the Mediterranean Basin, the Middle East, Asia Minor, South Africa (figure no. 2 - Geographical distribution of Thalassemia is superimposable over the regions with an increased frequency of Plasmodium falciparum).(5)

Thalassemia results from a genetic defect of the genes encoding a certain type of hemoglobin globin chain, the type of thalassemia being named by the affected chain type (we mention for the beta form of the disease, the presence of some mutations with plus or deletion type at the level of chromosome 11, respectively the short beta-globin gene arm (figure no. 3. Gene mutation in thalassemia at chromosome 11 level in the beta form and at chromosome 16 level in form α).(4)

Figure no. 3. Gene mutation in thalassemia at chromosome 11 level in the beta form and at chromosome 16 level in form α

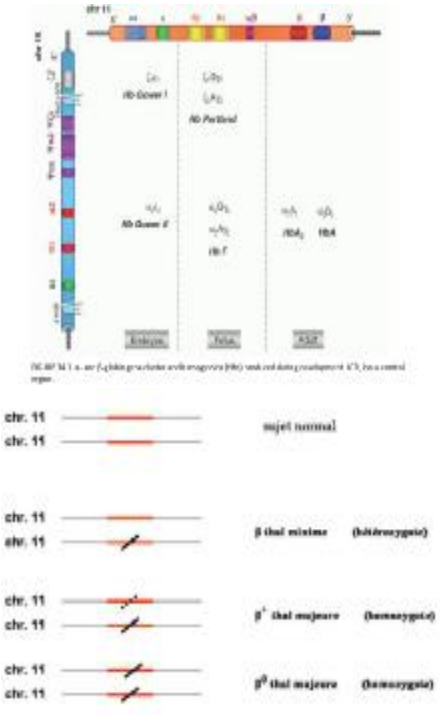

Image taken from Wintrobes Clinical Hematology (13th Edition) (2014)

Thus, the following clinical forms of β-Thalassemia occur: a.) Asymptomatic carriers (haematological defect) show the mutation of a gene, having the genotypic representation - β/β^{o} or β/β^{+}; b.) β-Thalassemia minor; c.) β-Thalassemia intermedia - the transmission of two mutated genes from each parent, genotypic representation of β^{+}/β^{+} or β^{+}/β^{o}. In this form, the β-chains are limited; d.) β-Thalassemia major: genotypic representation of β^{+}/β^{o} or β^{o}/β^{o}, with the indication that β-chains are not synthesized in this form.(4)

Embryology elements, important for understanding ELFO Hb: Hb synthesis begins from the second month of gestation in the erythroblastic islets of the yolk sac. In the adult-embryonic period, several types of Hb succeed: embryonic Hb - Gower 1, 2. Portland that will be replaced at the end of the third month with fetal Hb. Hb F in the fetal period is weighting 70-80% within ELFO, being replaced at its turn after birth, and at the age of 1, the weight will be <1%. Adult A and A2 Hb synthesis begins from the fetal period.

Elements of physiology: Erythrocytes are figurative elements of blood counting approximately 4,700,000 /mm^3 of blood, representing 43-45% of the circulating volume (hematocrit, Ht). An erythrocyte contains about 280 million Hb molecules. Hb shows normal values between 12-14g /100ml, is a chromoprotein, and structurally it is a tetramer containing a Heme group and a polypeptide chain of the globin. The heme is a tetrapirolic nucleus that has a divalent iron atom in the center, which binds an oxygen molecule (figure no. 4. - Structure of Hemoglobin, The normal polypeptide chains are of 6 types: alpha, beta, gamma, delta, epsilon and zeta).

Figure no. 4. Structure of haemoglobin, image taken from https://www.fastbleep.com/biology-notes/40/1172

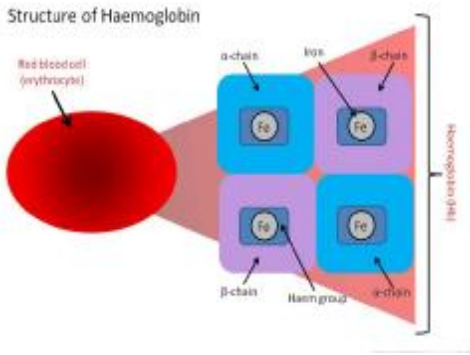

Image taken https://www.fastbleep.com/biology-notes/40/1172).

By combining the genetic, embryological and physiological data, the following are resulting: ELFO-Hb: in an adult: Hb A (2 alpha and 2 beta chains) 95% and Hb A2 (2 alpha chains and 2 delta chains) 2-3% Hb F <1%. And in a fetus ELFO-Hb: Hb F 70% -80% (2 alpha chains and 2 gamma chains), with the Hb F dissociation curve diverted to the left, meaning an increased affinity to oxygen, linking it to partial smaller pressures and yielding it harder to tissues. After birth, it is replaced with Hb A, with the indication that at 1year old, HbF will be <1%.

In the pathophysiology of thalassemia syndromes, the following are reported: βeta-thalassemia anemia is the result of the interaction of two mechanisms (ineffective erythropoiesis and short-lived erythrocytes with their structural changes). Extravascular haemolysis is secondary to peripheral circulation release of some altered erythrocytes and of some erythrocyte precursor cells due to ineffective erythropoiesis.

We conclude this article with some elements of incidence and frequency. All over the world, there are annually diagnosed with Thalassemia over> 700,000 new-borns, and over 100 million individuals are asymptomatic carriers of thalassemia. In Romania, the incidence of beta thalassemia ranges between 0.5% - 1%, most frequently occurring in the south of the country and in Moldova.

A coincidence or not, the pregnant woman's grandparents, in this case, are from Moldova region. An analysis of DNA sequencing or reverse hybridization could have clarified the mutation type of β-Thalassemia, which is specific to a geographic region of an ethnic group and retrospectively, we could have outlined the filiation of the migration of the population groups (e.g. in Human Genetic Diseases, publisher In Tech, 2011, chapter 6 by reverse-hybridization and DNA sequencing techniques of β-Thalassemia globulin mutations concluded that: in Iran, the most common type of mutation and specific to the ethnic group is β^+ IVS 2-2,3 (+ 11, -2), in the Mediterranean are, there are multiple mutations specific for the ethnic groups β^0 CD39 (C to T), β^o IVS 1-1 (G to A); IVS 1-6 (T to C).(6)

In this case, we suggest the inclusion of another three types of diagnosis, namely: preimplantational genetic diagnosis within Assisted Reproductive Techniques (ART) - in IVF (in the case of a partner with the minor form) plus oocytes /sperm donors originating from geographic areas with increased incidence of thalassemia.

Prenatal diagnosis (ideal): genetic counselling focuses on explaining the nature of the disease and the risk of having affected descendants. Prenatal diagnosis and therapeutic abortion target the situation when both partners are carriers, resulting in descendants with the major form. It can be done by direct DNA analysis of fetal cells obtained either by amniocentesis or by samples obtained from cortical villi at 9-12 gestational age. Postnatal diagnosis, performed by high-performance liquid chromatography (HPLC) in the first few weeks of life, can diagnose α and β-Thalassemia, with the reference that the minor form of Thalassemia has its onset in childhood, namely at the age of 7 years.

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