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## Pregnancy outcome in patients with β-thalassemia intermedia at two tertiary care centers, in Beirut and Milan

β-thalassemia intermedia (TI) patients can present with a severe clinical disease at 2-6 years of age or remain asymptomatic until adult life. They suffer from mild anemia (hemoglobin (Hb) between 7-10 g/dL), and are usually transfusion independent.[1] Pregnancy in these women, whether spontaneous or through assisted reproductive technology, represents a challenge for the treating physician. The literature is limited by the scarcity of studies about TI and pregnancy. We report on the pregnancy outcome of TI women in two tertiary care centers, the Chronic Care Center, Hazmieh, Lebanon and the Hereditary Anemia Center, Milan, Italy over a 15-year period.

During pregnancy, patients in both centers have regular antenatal visits where Hb levels are assessed every two weeks, serum ferritin every four weeks, and ultrasonographic evaluation of fetal growth every four weeks starting at 24–26 weeks. In Italy, transfusions are administered for Hb<10 g/dL whereas in Lebanon, transfusion is reserved for symptomatic patients or those with fetal growth restriction (IUGR). Maternal medical records were reviewed for several demographic and clinical variables. Women were contacted by phone for any missing information.

A total of 44 TI women who had 83 pregnancies, all spontaneous, 30 from Lebanon and 53 from Italy, were identified (Table 1). These pregnancies resulted in 17 abortions (20.5%), 64 live-births (77.1%) and 2 intrauterine fetal deaths at 26 and 36 weeks' gestation. The mean gestational age (GA) at delivery was 36.5±3.1 weeks and birthweight was 2551±621 grams. In pregnancies progressing >20 weeks' gestation (n=66), pre-term delivery and IUGR were noted in 31.8% and 24.2% respectively (Table 2). In those complicated by IUGR, cesarean delivery (CS) rate was 87.5% at GA=5.7±3.4 weeks and birthweight = 2067±530 grams. Two women (Italy) developed severe alloimmune hemolytic anemia. One progressed to cardiac failure at 35 weeks' gestation and had CS. The other underwent CS for IUGR and non-reassuring fetal heart monitoring and is scheduled for a splenectomy postpartum. Worsening alloimmune anemia also developed in 2 women in Lebanon who required splenectomy within eight weeks postpartum. Transfusion was required in 35/44 women during pregnancy (79.5%), with 27.3% requiring transfusion during pregnancy for the first time. The lowest mean Hb level was 6.7±2.0 *vs.* 8.3±1.2 g/dL in Lebanon and Italy, $p<0.001$. The average ferritin level before pregnancy was 885.2±658.9 *vs.* 1232.8±902.9 after pregnancy. CS was performed in 48 pregnancies (72.7%), the indications being elective (41.7%), repeat (31.2%) and obstetrical (27.1%). Pregnancy outcome was similar between Lebanon and Italy with the exception of a significantly higher rate of live-births in Italy (Table 2).

To the best of our knowledge, this is the largest study of pregnancy in TI women. Our results show that these pregnancies are associated with a 20.5% incidence of spontaneous abortion, 31.8% pre-term delivery, 24.2% IUGR, and 72.7% CS. This confirms the findings of a previous publication by our team that reported on 9 pregnancies, all of which were included in the current study.[2]

The chronic anemia due to thalassemia in addition to the physiological anemia in pregnancy (secondary to

**Table 1.** Patient demographics.

| | *Lebanon (n=11)* | *Italy (n=33)* | *Total (n=44)* | *p value* |
|---|---|---|---|---|
| Age at diagnosis (years) | 9.5±7.4 | 9.1±10.3 | 9.2±9.7 | 0.906 |
| Age at first transfusion (years) | 14.1±10.3 | 13.8±12.6 | 13.9±11.8 | 0.944 |
| Splenectomized | 10 (90.9) | 24 (72.7) | 34 (77.3) | 0.408 |
| Age at splenectomy (years) | 17.7±10.3 | 16.3±10.9 | 16.7±10.6 | 0.711 |
| Transfusion requirement (irrespective of pregnancy) | | | | |
| Frequently | 2 (18.2) | 12 (36.4) | 14 (31.8) | 0.456 |
| Occasionally | 8 (72.7) | 17 (51.5) | 25 (56.8) | 0.301 |
| Never | 1 (9.1) | 3 (9.1) | 4 (9.1) | 1.000 |
| Received chelation | 3 (27.3) | 25 (75.8) | 28 (63.6) | 0.009 |

*Data presented as n (%) or mean ± standard deviation. Frequently transfused = those requiring at least four transfusions/year. Occasionally transfused = those transfused in a lifetime under certain conditions such as surgery of pregnancy.*

**Table 2.** Pregnancy outcome.

| *Pregnancies* | *Lebanon (n=30)* | *Italy (n=53)* | *Total (n=83)* | *p value* |
|---|---|---|---|---|
| Abortions | 9 (30.0) | 8 (15.1) | 17 (20.5) | 0.182 |
| Live births | 19 (63.3) | 45 (84.9) | 64 (77.1) | 0.048 |
| Intrauterine fetal death[a] | 2 (6.7) | 0 | 2 (2.4) | 0.128 |
| Pre-term delivery[ab] | 8 (38.1) | 13 (28.9) | 21 (31.8) | 0.642 |
| Cesarean delivery[a] | 12 (57.1) | 36 (80.0) | 48 (72.7) | 0.100 |
| Intrauterine growth restriction[ac] | 6 (28.6) | 10 (22.2) | 16 (24.2) | 0.801 |
| Thrombotic events | 2 (6.7) | 4 (7.5) | 6 (7.2) | 1.000 |
| DVT antepartum | 1 (3.3) | 2 (3.8) | 3 (3.6) | |
| DVT in pregnancy and postpartum | 1 (3.3) | 1 (1.9) | 2 (2.4) | |
| Placental thrombosis | 0 | 1 (1.9) | 1 (1.2) | |

*Data presented as n (%). [a]After excluding abortions; DVT= deep vein thrombosis [b]defined as delivery at <37 weeks of gestation. [c]defined as <10[th] percentile for gestational age.*

increased fluid compartment of the body) may partly explain some of the complications of the pregnant TI mothers.[3] Although currently not a routine treatment approach for women with TI, some centers administer transfusion therapy during pregnancy to maintain Hb>10 g/dL to ensure appropriate fetal growth.[4] Despite following this approach in Italy, 22% of the babies had IUGR. This provides evidence that maintaining Hb>10 g/dL alone is not sufficient to prevent IUGR, therefore, other fetoplacental and maternal factors that increase the risk of IUGR in TI women should be considered. The major fear of initiating transfusions during pregnancy is the development of alloantibodies. These can aggravate anemia and progress into severe hemolytic anemia refractory to transfusions and thus increase the complication rate. Compared to Lebanese women, women in Italy were more frequently transfused and consequently more were maintained on chelation therapy. This could partially explain the significantly higher live-birth rate in these women, although our study was not powered to detect differences in these variables. Preterm delivery and IUGR complicated more pregnancies than is to be expected in the general population.[5,6] CS, which was performed in 72.7% of cases, might be required in TI patients due to the associated cephalopelvic disproportion secondary to skeletal deformity and short stature, especially in non-transfused women. Splenectomy is usually performed in TI women for decreased levels of hemoglobin, hyperactivity of the spleen, leukopenia and symptomatic thrombocytopenia.[7,8] However, 77.3% of our patients were splenectomized and at a considerably early age (16.7 years); only 2 had postpartum splenectomy.

TI is associated with a high rate of thromboembolic events reaching 29% in some studies.[9] We previously reported a 3.9% risk of thromboembolism in TI patients.[10] It is believed that the abnormal circulating red blood cells activate endothelial cells creating a procoagulant state. Hence, frequently-transfused patients have lower rates of thromboembolism compared with those who are not.[9] Pregnancy, as a hypercoagulable state,[8] and inherited thrombophilias,[11] further increase the risk of thrombosis. Despite advances in TI management, many questions remain unanswered. Large-scale multicenter controlled trials are, therefore, needed to establish clear guidelines for initiating transfusions balancing between the benefits of frequent transfusion as prevention of IUGR and its potential negative effects such as antibody development. Since iron overload can complicate TI even in non-transfusion-dependent patients,[12] research is needed to evaluate the safety of chelation and to determine whether aggressive pre-conceptional chelation would improve obstetrical outcome. Since thromboembolic events pose a life-threatening condition, and although in our series these were few, further large-scale investigation is needed to establish guidelines for thromboprophylaxis in pregnant TI patients. Although prophylactic heparin seems to be a reasonable approach, what is not clear is whether pregnant TI patients with additional risk factors, such as splenectomy, thrombocytosis, previous deep vein thrombosis, or anemia, would require therapeutic anticoagulation. In conclusion, despite the progress in the management of patients with β-thalassemia intermedia, those patients are at an increased risk of abortion, pre-term delivery, intrauterine growth restriction, CS and thromboembolic events. This requires a multidisciplinary approach for management which should include close maternal and fetal surveillance.

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