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CLINICAL & BASIC RESEARCH

Pregnancy Outcomes in Women with Homozygous Beta Thalassaemia

A single-centre experience from Oman

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نتائج الحمل في النساء المصابات بأنيميا البحر المتوسط بيتا الثلاسيميا

خبرة مركز واحد في عُمان

نهال الريامية، مها الخضورية، شاهينا داعر

ABSTRACT: ***Objectives:*** Pregnancy in women with homozygous beta thalassaemia (HBT) carries a high risk to both the mother and fetus. The aim of this study was to investigate pregnancy outcomes among this group at a single tertiary centre. ***Methods:*** This retrospective descriptive study was conducted between January 2006 and December 2012 on all women with HBT who received prenatal care and subsequently delivered at Sultan Qaboos University Hospital, Muscat, Oman. Women who delivered elsewhere and women with the beta thalassaemia trait were excluded. ***Results:*** Ten women with HBT were studied with a total of 15 pregnancies and 14 live births. The mean maternal age ± standard deviation (SD) was 27.9 ± 3.7 years, with a range of 24–35 years. There were 14 spontaneous pregnancies and one pregnancy following hormone treatment. Eight women had been on chelation therapy before pregnancy, one of whom needed chelation during late pregnancy. Of the pregnancies, 93% had a successful outcome with a mean ± SD gestational age at delivery of 38.6 ± 0.9 weeks, with a range of 37–40 weeks. Eight babies (57%) were delivered by Caesarean section. The mean ± SD birth weight was 2.6 ± 0.2 kg, with a range of 1.9–3.0 kg. Three babies (21%) were born with low birth weights. ***Conclusion:*** Pregnancy is safe and usually has a favourable outcome in patients with HBT, provided that a multidisciplinary team is available. This is the first study of Omani patients with HBT whose pregnancies have resulted in a successful outcome.

Keywords: Thalassemia, beta; Pregnancy; Fetus; Mother; Assessment, Patient Outcomes; Chelation Therapy; Oman.

الملخص: الهدف: ينطوي الحمل في النساء المصابات بمرض بيتا الثلاسيميا على مخاطر عالية على كل من الأم والجنين. هدفت الدراسة إلى رصد نتائج الحمل في هذه المجموعة من المريضات في مركز واحد. **الطريقة:** أجريت هذه الدراسة الإستعادية الوصفية بين يناير 2006 و ديسمبر 2012 على جميع النساء المصابات بالبيتا ثلاسيميا الذين تلقوا الرعاية قبل الولادة و وضعن في مستشفى جامعة السلطان قابوس، مسقط، سلطنة عمان. تم استبعاد النساء اللائي وضعن في أماكن أخرى والنساء حاملات صفة البيتا ثلاسيميا **النتائج:** درست عشر نساء مصابات بالبيتا الثلاسيميا حيث حدث 15 حملا أسفرت عن 14 ولادة حية. بلغ متوسط عمر الأمهات في عينة الدراسة 3.7 ± 27.9 وتراوحت اعمارهن بين 35–24 عاما. كان هناك 14 حالة حمل عفوي وحالة واحدة بعد العلاج الهرموني. تعاطت ثمانية نساء عقاقير إزالة معدن الحديد من الجسم قبل الحمل بينما تعاطت حالة واحدة فقط هذه العقاقير في أواخر الحمل. أسفرت 93% من الولادات عن نتيجة ناجحة وبلغت فترة حمل الجنين من 0.9 ± 38.6 أسابيع في المتوسط، وتراوحت فترة الحمل بين 40–37 أسبوعا. ولد ثمانية أطفال (57%) بعمليات قيصرية.بلغ متوسط وزن الطفل عند الولادة 0.2 ± 2.6 كلغ وتراوحت أوزانهم بين 3.0–1.9 كلغ. كان وزن الولادة منخفضا في ثلاثة أطفال فقط (21%). **الخلاصة:** أظهرت هذه الدراسة نتائج إيجابية للحمل و أمان في المصابات بالبيتا ثلاسيميا، شريطة أن يكونوا تحت رعاية فريق متعدد من المتخصصين. هذه هي الدراسة الأولى في المرضى العمانيين.

مفتاح الكلمات: الثلاسيميا، بيتا؛ الحمل؛ الجنين؛ الأم؛ تقييم، النتائج ؛ عقاقير إزالة معدن الحديد من الجسم؛ عمان.

Advances in Knowledge

- *Thalassaemia is not well-studied during pregnancy, especially in Oman. However, thalassaemia is an important blood disorder in Oman and carries major risks during pregnancy to both the mother and fetus. The results of this study will increase knowledge of this disorder in the region.*
- *Specifically, the findings of this study will increase the awareness of the safe outcomes of pregnancies in women with homozygous beta thalassaemia in Oman, especially for healthcare professionals.*

Application to Patient Care

- *This study highlights certain issues in pregnant women with homozygous thalassaemia, which will help obstetricians in their management of this patient group.*
- *Recent advances in the treatment and management of thalassaemic patients are discussed in this study.*

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Beta thalassaemia is one of the most common genetic blood disorders in Oman, the Mediterranean region, Arabian Peninsula and Far East. The prevalence of the beta thalassaemia gene in Oman is reported to be 2.2–2.6%.[1,2] Patients with homozygous beta thalassaemia (HBT) have high morbidity and mortality rates due to the consequences of blood transfusions and iron overload. Two forms of thalassaemia are distinguished, with different clinical phenotypes: thalassaemia major (TM), which is transfusion-dependent, and thalassaemia intermedia (TI), which varies in clinical severity and has variable transfusion requirements.

In recent years, TM survival rates have improved with patients suffering fewer complications due to the advances in transfusion treatment and the use of chelation therapy.[3–6] As a consequence, pregnancy is feasible in these patients. The main cause of infertility in TM is due to pituitary gland haemosiderosis leading to hypogonadotropic hypogonadism.[7,8] TI has a wide clinical spectrum ranging from patients presenting late, after the age of three years, and then requiring regular blood transfusions, to those who are completely transfusion-independent. The latter group requires occasional transfusions during periods of stress such as pregnancy and infection, as well as pre-operatively.

Patients with HBT require close follow-up throughout the duration of their pregnancy due to the physiological changes and high demands of pregnancy.[9] Chelation therapy should be halted during pregnancy due to the teratogenicity of this treatment and haemoglobin (Hb) levels should be checked regularly to assess the need for transfusions. An increased frequency of blood transfusions is usually noted in these patients. Complications for both the mother and the fetus include gestational hypertension, gestational diabetes, thromboembolism, anaemia, cardiac failure, premature delivery, intrauterine growth restriction and fetal death.[10]

The aim of this study was to review the maternal and fetal outcomes of pregnant women with HBT at Sultan Qaboos University Hospital (SQUH), Muscat, Oman.

Methods

This retrospective descriptive study was conducted between January 2006 and December 2012 on all pregnant women with HBT who received both prenatal and postnatal care and delivered at SQUH. Data were obtained from the SQUH database including the patients' medical and delivery ward records.

Women who delivered elsewhere and women with the beta thalassaemia trait were excluded from the study. A total of 10 women (seven with TI and three with TM) were included giving a total of 15 pregnancies. The patients were followed closely in the SQUH high-risk pregnancy clinic by both an obstetrician and a haematologist. They were screened for infectious diseases upon presentation, including hepatitis B, syphilis and human immunodeficiency virus (HIV). An obstetric ultrasound was performed to confirm gestational age. Maternal weight gain, blood pressure and fetal well-being were assessed at each visit. A fetal anatomy scan was performed at 18–20 gestational weeks and fetal growth scans were performed monthly. Patients received blood transfusions approximately every two to three weeks to maintain Hb levels above 9.0 g/dL. The maternal medical records were reviewed for age, parity, use of fertility-inducing agents, any history of splenectomy, baseline Hb levels at first visit as well as at delivery, frequency of blood transfusions, serum ferritin levels and the use of chelation therapy during pregnancy.

Pregnancy outcomes were defined as follows: an abortion was defined as a pregnancy loss before 20 weeks' gestation;[11] intrauterine fetal death was defined as the death of the fetus *in utero* after 20 weeks' gestation;[11] preterm delivery was defined as a delivery before 37 weeks' gestation;[11] fetal growth restriction was recorded if the estimated fetal weight was less than the 10th percentile;[12] low birth weight (LBW) was defined as a birth weight of less than 2,500 g,[12] and the mode of delivery was recorded as either vaginal delivery or a Caesarean section. Maternal complications were also recorded, including gestational hypertension, gestational diabetes, infections and antepartum and postpartum haemorrhaging.

Descriptive data are presented as means, standard deviations (SD) and percentages. The study was approved by the Medical Research & Ethics Committee of the College of Medicine & Health Sciences at Sultan Qaboos University.

Results

This study evaluated 15 pregnancies in 10 women with HBT. One patient with TM became pregnant twice but miscarried during her first pregnancy. Three patients with TI had subsequent pregnancies during the study period, with one of these patients becoming pregnant three times.

The mean maternal age ± SD was 27.9 ± 3.7 years, with a range of 24–35 years. Nine women were nulliparous at the start of the study. All of the women

Table 1: Maternal characteristics of pregnant women with homozygous beta thalassaemia (N = 10)

Characteristics	Mean	Range
Age in years	27.9	24–35
Gravidity	2.7	1–9
Parity	1.1	0–6
Hb levels during pregnancy in gm/dL	8	6.4–9.8
SF levels before pregnancy in ng/mL (normal range 20–300 ng/mL)	585.6	236–1,258
SF levels at the end of pregnancy in ng/mL	1,357.5	336–3,054

Hb = haemoglobin; SF = serum ferritin.

Table 2: Pregnancy outcomes of women with homozygous beta thalassaemia* (N = 15 pregnancies)

Outcomes	TI patients (n = 7)	TM patients (n = 3)
Miscarriage	0	1
IUGR	3	0
UTI	1	0
GDM	1	0
Mean GA at delivery in weeks	38.6	38.3
Mean birth weight in kg	2.5	2.8
C/S	5	3
Vacuum-assisted delivery	2	0
SVD	4	0
Postpartum fever	3	1

TI = thalassaemia intermedia; TM = thalassaemia major; IUGR = intrauterine growth restriction; UTI = urinary tract infection; GDM = gestational diabetes mellitus; GA = gestational age; C/S = Caesarean section; SVD = spontaneous vaginal delivery.

**Only one patient with TM underwent chelation therapy during her pregnancy.*

conceived spontaneously, apart from one of the three women with TM, who conceived using hormone treatments. In total, four women (40%)—one with TM and three with TI—were splenectomised. All women required blood transfusions every two to three weeks during their pregnancies, including the seven patients with TI who had not received regular blood transfusions before pregnancy. Eight women (80%)—three with TM and five with TI—had been on chelation therapy before their pregnancies [Table 1].

The pregnancy outcomes of all patients with TI and TM are presented in Table 2. In patients with TI, there were 11 live births. The mean ± SD gestational age at delivery was 38.6 ± 1.0 weeks with a range of 37–40 weeks. Three babies were delivered by elective Caesarean section due to a fetal breech presentation in two patients and a previous Caesarean section in one patient. Two further patients underwent emergency Caesarean sections due to fetal distress. The mean ± SD birth weight was 2.5 ± 0.3 kg, with a range of 1.9–3.0 kg.

Three babies were born with LBWs of 1.9, 2.2 and 2.3 kg. The first baby was born to a 28-year-old *gravida* one para zero (G1P0) woman who had no antepartum complications. She had been on regular blood transfusions every two weeks during her pregnancy. Her lowest Hb level was 6.4 g/dL in the first trimester and her highest serum ferritin level was 1,469 ng/mL at the end of the pregnancy. Her baby was born by vacuum-assisted delivery at 38 weeks' gestation due to a non-reassuring fetal heart rate in the second stage of labour. The baby was female with a birth weight of 1.9 kg; she demonstrated good Apgar scores and therefore did not require admission to the Neonatal Intensive Care Unit (NICU). The second baby was born to a 30-year-old *primigravida* woman who had no antepartum complications. Her lowest Hb level during pregnancy was 8.7 g/dL in the second trimester and her highest serum ferritin level was 336 ng/mL at the end of the pregnancy. She delivered by emergency Caesarean section at 40 weeks' gestation due to a non-reassuring fetal heart rate during labour. The baby was male, with good Apgar scores and normal pH levels as determined by the cord blood gas, indicating normal hydrogen ions in the blood. The third baby was born to a 30-year-old G1P0 woman whose lowest Hb level in pregnancy was 7.5 g/dL in the middle of the first trimester and whose highest ferritin level was 1,334 ng/mL at the end of the pregnancy. She delivered at 37 weeks' gestation by elective Caesarean section due to a breech presentation; the boy had a birth weight of 2.3 kg and good Apgar scores.

In patients with beta TM, the mean ± SD gestational age was 38.3 ± 0.6 weeks, with a range of 38–39 weeks. The mean ± SD birth weight was 2.8 ± 0.2 kg, with a range of 2.7–3.0 kg. Two patients had elective Caesarean sections, one because of a fetal breech presentation and one at the patient's request. The third patient had an emergency Caesarean section due to fetal distress.

One patient elected to restart chelation therapy during her pregnancy. The patient was a 26-year-old *primigravida* woman who conceived spontaneously and was progressing well during pregnancy. Her baseline serum ferritin level was 522 ng/mL, however this increased throughout her pregnancy and reached 2,767 ng/mL at 28 weeks' gestation. After extensive counselling, the patient opted for iron chelation with

Table 3: Liver and cardiac iron status in three patients with transfusion-dependent thalassaemia major based on T2* MRI

Values before pregnancy/after delivery	Patient 1	Patient 2	Patient 3
Liver iron in mg/g dry weight	2.9/10.8	2.6/9.6	2.1/3.6
Cardiac T2* MRI in ms	19.7/20.3	34.8/37.4	46.4/46.8

MRI = magnetic resonance imaging; ms = milliseconds.

deferoxamine in the middle of her third trimester. Repeat testing of her serum ferritin levels showed marked improvement, with a level of 1.536 ng/mL by the end of her pregnancy. She had an elective Caesarean section at 38 weeks' gestation and delivered a live male baby with a birth weight of 2.7 kg and Apgar scores of nine and ten at one and five min, respectively.

All TM women underwent T2* magnetic resonance imaging (MRI) before and soon after pregnancy to investigate their iron status. All three patients, and in particular the first two patients, had increased liver iron loads during their pregnancies. The third patient had undergone chelation therapy in her third trimester, as mentioned above. The cardiac iron status of all the three patients remained normal [Table 3].

All women were on prophylactic low-molecular-weight heparin in the postpartum period and were encouraged to breastfeed their infants for the first 12 weeks before restarting chelation therapy.

Discussion

This study found a 93% rate of successful pregnancy outcomes among 10 women with homozygous beta thalassaemia. Only one patient with TM suffered a first trimester abortion. Such excellent results are heartening, particularly considering the difficulties that are usually expected in these high-risk pregnancies. The major contributing factors to this excellent rate were the multidisciplinary approach used in the care of these patients as well as the close patient follow-up. All of the women with TM in this study underwent counselling before pregnancy and had achieved low serum ferritin levels (236–522 ng/mL) with extensive chelation therapy before conception. Patients with TI demonstrated slightly higher serum ferritin levels of 194–1,597 ng/mL (median 625 ng/mL). All of the women's partners had been screened and tested for haemoglobinopathies prior to their marriage. There were no preterm births noted in the current study and only three babies (21%) were born with LBWs. However, none required admission to the NICU or suffered any neonatal complications.

The results of this study are comparable to two large studies reported in the literature.[13,14] An Italian multicentre study by Origa *et al.* of 57 pregnant women reported a 91% rate of successful pregnancy outcomes.[13] They also noted favourable maternal and neonatal outcomes; however, women with TI who were not transfused or were on minimal blood transfusions before their pregnancies required more transfusions due to anaemia during their pregnancies.[13] This finding was also observed in the current study.

As reported in other studies, the increase in blood transfusions, due to the physiological changes and increased demands of pregnancy as well as the cessation of chelation therapy, resulted in an increased iron overload and aggravates haemosiderosis; this caused further iron deposits in major organs such as the heart, leading to cardiac dysfunction and complications.[15,16] Due to intensive patient counselling and chelation therapy prior to pregnancy, none of the patients with TM in the current study developed iron overload in their hearts and all had minimal liver iron loads before pregnancy. However, an increase in liver iron load was apparent in all patients after pregnancy; this was expected as the liver is the primary target of iron loading secondary to blood transfusion. Cardiac iron status measured by T2* MRI showed no significant change before or after pregnancy.

Studies have shown that iron loading of the heart usually lags behind that of the liver, which is the initial site of the transfusional iron uptake.[17] As the present study's patients were well-chelated prior to their pregnancies, with low liver iron loads, this may have ensured that a buffer was present, possibly protecting them from accumulating cardiac iron while they ceased chelation therapy during pregnancy. The use of iron chelation therapy during pregnancy has not been well-studied; the main concern is that of fetal teratogenicity, especially if the therapy is used in the first trimester.[18] However, there have been a few reports of successful outcomes with chelation therapy.[19,20] One case reported the use of chelation therapy during the first trimester with a normal outcome for the child.[21] The pregnancy had not been identified until 22 weeks gestation as the patient was on hormone replacement therapy. Fortunately, the fetus was healthy. Another case reported the use of chelation therapy from 18 weeks gestation until delivery, with a successful outcome and a normal assessment of the child at 10 months of age.[20] However, these are aberrant cases, and chelation therapy should be avoided during the first trimester. In later pregnancy, a multidisciplinary assessment before starting chelation is critical and the potential maternal

benefits should outweigh the risk to the fetus. After a detailed multidisciplinary assessment and intensive counselling, one of the women with TM in the current study was started on chelation therapy during her third trimester, resulting in a positive outcome. However, more studies are required to determine the safety of chelation therapy during pregnancy.[15]

The mean gestational age of delivery in the present study was 38.6 weeks, with Caesarean section as the mode of delivery in 8 out of the 14 term pregnancies (57%). The preferable mode of delivery was usually vaginal, however one of the patients insisted on a Caesarean section despite counselling. Results from Origa *et al.*'s study on 58 pregnancies in 46 women with HBT showed a very high rate of Caesarean sections (90%) and a joint study from Lebanon and Milan also showed a high rate (72.7%).[12,22] Compared to other published studies, the rate of Caesarian section in the current study was relatively low; however, this may be because the total number of pregnancies studied was smaller.

Conclusion

Pregnancy is safe and usually has a favourable outcome in patients with HBT, provided that a multidisciplinary team is available for intensive patient evaluation and follow-up. Advances in fertility treatment and chelation therapy have made it possible for women with TM to become pregnant. Pre-pregnancy counselling and assessment, proper care and close follow-up during the antepartum, intrapartum and postpartum periods are essential for a good outcome. This is the first study of Omani patients with HBT showing a high rate of successful pregnancy outcomes.

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