# Fetal outcomes in pregnant women with sickle cell disease

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## ABSTRACT

**الأهداف:** لتحقق من نتائج الجنين في النساء الحوامل اللاتي يعانين من مرض فقر الدم المنجلي (SCD) وتحليل تأثير هذه المتغيرات الأساسية على تلك النتائج.

**الطريقة:** دراسة استعادية على مدى 5 سنوات خلال الفترة من (يونيو 2006م إلى أغسطس 2011م) في جامعة السلطان قابوس، مستشفى مسقط، سلطة عمان بحثت في النتائج والتأثيرات لدى الجنين عند الحوامل المصابات ب SCD وتحليل أثر المتغيرات الأساسية على تلك النتائج. 68 نساء حوامل مصابات بمرض SCD تم تضمينها في الدراسة. تم استخدام الانحدار اللوجستي متعدد المتغيرات لتقدير وضبط تأثير المتغيرات الأساسية على المضاعفات على الجنين.

**النتائج:** كان متوسط عمر الأم30 سنة±3.8. وكان متوسط عمر الحمل عند الولادة 37 أسبوعا 1.88. في الدراسة 62 من المريضات مصابات بالنوع SS الوراثي. وجد أن متوسط الهيموغلوبين الأولي 9.5 غ / دل (1.1 SD، ومجموعة 7.2 – 11.9). كان متوسط الهيموجلوبين (6.6 SD 10.2 F، ومجموعة 29–0.7). لوحظ أن 11 حالة (16.2%) عانت من تقييد النمو داخل الرحم (95% فاصل الثقة 7.2–25.2 CI)، في حين أن 19 حالة عانت من الضائقة الجنينية (27.9%، 95% CI:38.9–17.0). وجد انخفاض الوزن عند الولادة في 22 حالة (32%، 95% CI: 20.9–43.8) مع وزن بمتوسط 2.6 كلغ (0.47 SD، ومجموعة 3.9–1.2). كان هناك اثنين من وفيات المواليد. على الانحدار اللوجستي متعدد المتغيرات لمزيج مركب من نتائج الجنين، لم يكن أيا من هذه المتغيرات ذات دلالة إحصائية.

**الخاتمة:** إن النتائج السلبية للجنين عند النساء الحوامل مع SCD مرتفعة مقارنة بالحوامل الغير مصابات بالمرض. ليس هناك اختلاف كبير في نتائج الجنين بين SS، SCD الوراثي مقابل الآخرين.

**Objective:** To investigate fetal outcomes in pregnant women with sickle cell disease (SCD), and to analyze the impact of baseline variables on those outcomes.

**Methods:** This is a retrospective cohort study carried out over 5 years (June 2006 to August 2011) investigating fetal outcomes at Sultan Qaboos University Hospital, Muscat, Oman. Sixty-eight consecutive pregnant women with SCD (62 women with hemoglobin sickle cell anemia [SS] genotype) were included and analyzed in the study. Multivariable logistic regression was used to estimate the impact of baseline variables on major fetal complications (intrauterine growth restriction, intrauterine fetal death, and low birth weight babies, perinatal mortality, and admission to the neonatal unit).

**Results:** The mean maternal age was 30 years ±3.8. Mean gestational age at delivery was 37 weeks ±1.8. The initial mean hemoglobin was 9.5 g/dl (standard deviation [SD] 1.1, range 7.2-11.9). The mean baseline hemoglobin F was 10.2 (SD 6.6, range 0.7-29). There were 11 cases (16.2%) of intrauterine growth restriction (95% confidence interval [CI]: 7.2-25.2), and 19 cases of fetal distress (27.9%; 95% CI: 17.0-38.9). Low birth weight was seen in 22 cases (32.4%, 95% CI: 20.9-43.8) with a mean weight of 2.6 Kg (SD: 0.47, range 1.2-3.9). There were 2 neonatal deaths. On multivariate logistic regression for a composite of fetal outcomes, none of those variables were of statistical significance.

**Conclusion:** The adverse fetal outcomes in pregnant women with SCD are high compared with the general population. There is no significant difference in fetal outcome between SCD, SS genotype versus others.

***Saudi Med J 2014; Vol. 35 (5): 472-476***

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*Received 30th January 2014. Accepted 18th March 2014.*

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**Disclosure.** No funding for this work was received from any organization or foundation.

Sickle cell disease (SCD) is an inherited hemoglobinopathy with multiple complications affecting both the mother and the fetus.[1,2] Major complications on the fetus include spontaneous miscarriage, intrauterine growth restriction (IUGR), increased rate of intrauterine fetal death (IUFD), and low birth weight babies (LBW).[3-6] Previous fetal outcome in a previous pregnancy may affect fetal outcome in a current pregnancy in women with SCD. The most important fetal factors include previous miscarriage, and previous IUFD.[7,8] Reviewing the literature, a retrospective study[9] involving 58 women with SCD found that there was a high occurrence of preterm labor (45% and 20%), and cesarean sections (52.6% and 37.1%) in hemoglobin sickle cell anemia (Hb SS) and SCD in general. The mean gestational age at delivery was 35.5±4.3 in the Hb SS group, and 37.0±3.7 weeks in the SCD group, and the mean birth weight was 2443±926 g in the Hb SS group, and 2997±807 g in the SCD group ($p$<0.05). There were 2 intrauterine fetal deaths, and one neonatal death in the Hb SS group, and one neonatal death in the SCD group. The perinatal mortality was 10.5% in the Hb SS group, and 2.9% in the SCD group. Another study[10] included 128 women with SCD (95 with SS phenotype and 33 with SC phenotype), and 128 in women with AA phenotype. The SCD patients compared with those without SCD resulted in 2 perinatal deaths (2.1% versus 0%), preterm delivery (15.8% versus 6.2%), birth weight <10th percentile (13.7% versus 3.9%), and cesarean delivery (73.6% versus 26.4%).

These studies highlighted fetal outcomes in pregnant women with SCD. Reviewing the literature and searching the PubMed database, there is a scarcity of data on fetal outcomes in Omani women with SCD. Therefore, in this study, the main objective is to investigate fetal outcomes in pregnant women with SCD who attended and delivered at Sultan Qaboos University Hospital (SQUH) over a 5-year period. The secondary objective is to analyze the impact of baseline variables on those outcomes.

## Methods.

***Data collection.*** Data were collected retrospectively on 71 consecutive pregnant women with SCD who attended the high-risk clinic and delivered at SQUH, Muscat, Oman between June 2006 and August 2011. Sixty-eight women were included in the study, while 3 women were excluded; one delivered at another hospital, and 2 patients had incomplete information. Ethics approval was obtained from the College of Medicine and Health Sciences Research Ethics Committee. Data were collected on different baseline variables including age, gravidity, parity, gestational age at delivery, baseline hematological parameters, history of splenectomy and cholecystectomy, previous pregnancy outcomes including IUGR, preterm labor, prematurity, IUFD, miscarriage, and LBW babies. Information was gathered on IUGR, fetal distress, operative vaginal deliveries, cesarean sections, LBW babies, stillbirth, admission to neonatal intensive care unit and perinatal mortality.

***Definitions.*** Miscarriage was defined as loss of pregnancy prior to 20 weeks of gestation.[11] Intrauterine fetal death was defined as death of the fetus after 20 weeks gestation.[11] Intrauterine growth restriction was defined as a fetus whose estimated weight was below the 10th percentile for its gestational age, and whose abdominal circumference was below the 5th percentile.[11] Preterm labor was defined as delivery before 37 completed weeks of gestation.[11] Low birth weight was defined as a weight of less than 2500 grams irrespective of gestational age.[11] Stillbirth was defined as a baby born with no signs of life at or after 20 weeks of gestation.[11] Fetal distress was defined as abnormal fetal heart tracing as recorded by a cardiotocography machine.[11] Perinatal mortality was defined as fetal or neonatal death occurring at 20 completed weeks of gestational age and or up to 7 completed days after birth.[11]

***Statistical analysis.*** We presented categorical variables as proportion, discrete variables as median with interquartile ranges (IQR), and continuous variables as means with standard deviation (SD). We presented the complications as proportions with the 95% confidence intervals (CI). Given the small sample size, we used a composite end point of major fetal complications. Major fetal complications outcome was defined as development of any of these fetal complications; IUGR, LBW, perinatal mortality, or admission to the neonatal intensive care unit. Development of any of these complications was counted as an event in major fetal outcome composite endpoint regardless of the occurrence of other outcomes. We used multivariable logistic regression to estimate and adjust the impact of baseline variables on major fetal complications (outcome variable was the composite endpoint of major fetal complications). We attempted to estimate and adjust for the impact of predefined baseline characteristics (age, parity, Hb F level, history of splenectomy, and previous cesarean section) using multivariable logistic regression with alpha error of 0.05. We used Stata Statistical Software, Release 11 (StataCorp LP 2009, College Station, TX, USA) for all descriptive and analytical tests used in this study.

**Results.** *Maternal characteristics.* We analyzed 68 pregnant women. The mean age was 30 years. Sixty-two women had the SS genotype, and 6 had other genotypes. The initial mean hemoglobin was 9.5 g/dl. The mean baseline fetal hemoglobin F was 10.2, while the mean hemoglobin S was 71.0%. None of the women were on hydroxyurea during pregnancy, but 8 were on hydroxyurea prior to pregnancy (**Table 1**).

*Maternal obstetric characteristics.* The median gravidity was 2, with an IQR of 1-3, and a range 1-6. Twelve women had prior cesarean section. Only one had previous preterm labor; none had previous premature babies. Five women had previous IUFD, and no IUGR was reported previously (**Table 2**).

*Fetal and neonatal outcomes.* The mean gestational age was 37 weeks (SD 1.8, range 32-41). Eleven cases of IUGR were noted. Nineteen had fetal distress. Five women required operative vaginal delivery while 29 required delivery by cesarean section out of which 5 cases were elective cesarean sections, and 24 were emergency cesarean sections. A mean birth weight of 2.6 Kg was observed in the study. Low birth weight was seen in 22 cases. There were 2 stillbirths. Sixteen newborn babies required admission to the neonatal intensive unit, and there were 2 perinatal deaths (**Table 3**).

*Baseline variables and fetal and neonatal complications.* Using the multivariable logistic regression for the composite on fetal/neonatal complications (IUGR, low birth weight, perinatal mortality, and admission to neonatal units), the following baseline variables were included: age, parity, phenotype, hemoglobin F level, and splenectomy prior to pregnancy. The odds ratio and the *p*-values were obtained. The odds ratio for age was 0.998, for parity 0.635, for Hb F level 0.961, previous splenectomy 2.014, previous cesarean section 1.218, and number

**Table 1 -** Baseline variables in pregnant patients with sickle cell disease included in a study at Sultan Qaboos University Hospital, Muscat, Oman.

| Baseline characteristics | Estimate |
|---|---|
| *Age (years)* | |
| Mean ± SD | 30 ± 3.8 |
| Range | 22-40 |
| *Phenotype* | |
| SS (sickle cell anemia) | 62 |
| Others | 6 |
| SB thal (sickle cell beta thalassemia) | 3 |
| SC (sickle cell C disease) | 2 |
| SD (sickle cell D disease) | 1 |
| *Initial hemoglobin (g/dl)* | |
| Mean ± SD | 9.5 ± 1.1 |
| Range | 7.2-11.9 |
| *Fetal hemoglobin level (%)* | |
| Mean ± SD | 10.2 ± 6.6 |
| Range | (0.7-29) |
| *Sickle hemoglobin level (%)* | |
| Mean ± SD | 71.0 ± 17.8 |
| Range | 19.1-90.9 |
| Hydroxyurea (prior to pregnancy) | 8 |
| Splenectomy | 5 |
| Cholecystectomy | 8 |

**Table 2 -** Maternal obstetric characteristics in pregnant patients with sickle cell disease included in a study at Sultan Qaboos University Hospital, Muscat, Oman.

| Obstetric characteristics | Estimate |
|---|---|
| *Parity* | |
| Median | 1 |
| Range | 0-5 |
| IQR | 0-1 |
| *Gravidity* | |
| Median | 2 |
| Range | 1-6 |
| IQR | 1-3 |
| *Miscarriage* | |
| Median | 0 |
| Range | 0-3 |
| IQR | 0-0 |
| Previous cesarean section | 12 |
| Previous preterm labor | 1 |
| Previous premature babies | 0 |
| Previous intrauterine fetal death | 5 |
| Previous intrauterine growth restricted fetus | 0 |

IQR - interquartile range

**Table 3 -** Maternal obstetric characteristics in pregnant patients with sickle cell disease included in a study at Sultan Qaboos University Hospital, Muscat, Oman.

| Fetal/neonatal complications | Estimate |
|---|---|
| Intrauterine growth restriction | 11 (16.2%, 95% CI: 7.2-25.2) |
| Fetal distress | 19 (27.9%, 95% CI: 17.0-38.9) |
| Operative vaginal deliveries | 5 (7.4%, 95% CI: 1.0-13.7) |
| *Cesarean section* | 29 |
| Elective | 5 (7.4%, 95% CI: 1.0-13.7) |
| Emergency | 24 (35.3%, 95% CI: 23.6-46.9) |
| Low birth weight | 22 (32.4%, 95% CI: 20.9- 43.8) |
| *Birth weight (Kg)* | |
| Mean ± SD | 2.6 ± 0.47 |
| Range | 1.2-3.9 |
| Stillbirth | 2 (2.9%, 95% CI: 0.0-7.1) |
| Admission to neonatal ICU | 16 (23.5%, 95% CI: 13.2-33.9) |
| Perinatal mortality | 2 (2.9%, 95% CI: 0.0-7.1) |

CI - confidence interval, ICU - intensive care unit

of admissions 0.953. The *p*-values ranged from 0.096-0.985 with 95% CI: 0.76-14.8. On multivariate logistic regression for a composite of fetal outcomes, none of the variables were of statistical significance.

**Discussion.** The study included 68 women with SCD of different genotypes. There were more patients with SCD of the SS genotype (62 patients) compared with other genotypes (only 6 patients) owing to the genetic predisposition of the disease in Oman. The SS genotype usually has a severe disease course and is associated with higher fetal complications compared with the other genotypes, which usually have a better outcome. Therefore, the fetal complications reported in the study are mainly for SCD of the SS genotype.

The results of our study showed high hemoglobin F levels. This is explained by the fact that these levels were prior to pregnancy as reviewed from the patient's laboratory investigations. Also, most patients would have been on hydroxyurea prior to pregnancy, which increases Hb F levels. This is supported by a study conducted in Oman,[12] which found that the mean Hb F level in patients with SCD after hydroxyurea was 17.16%.[12] Lastly, the haplotype in Oman is mild with high Hb F levels.[12] The current study showed a wide range for Hb S levels, the lowest being 19.1%, and the highest being 90.9%. Most of these patients were being transfused during pregnancy, and that might be the reason for the very low level of Hb S.

We noted IUGR in 16% of cases. This was unexpectedly high compared with previous studies. One study in Niger reported 14.3% cases of IUGR (n=42 patients),[13] and another study in Bahrain reported 10% of cases (n=31 patients).[14] The cesarean section rate in the study was 42%, which is comparable to rates reported by earlier studies (14-48%).[8,14-22] However, one study showed cesarean sections were carried out on 73.6% of patients.[9] Low birth weight complicated 32% of delivered babies. Previous reports regarding LBW babies ranged from 13.7-42%.[8,14-22] Twenty-four percent of newborns were admitted to the neonatal intensive care unit. The most common causes of admission were prematurity and LBW. There were 2 perinatal deaths (2.9%) reported in this study, which is similar to previous reports. Most studies reported perinatal deaths from 2.1-4.4% with different sample sizes.[8,14-22] Only 2 reports showed high percentages of 9.5%[9] and 9.8%,[14] but both had a small sample size. Our study had only 2 stillbirths with a rate of 3%. This is comparable to results reported in the literature with a similar sample size.[8,14-22]

The following variables were studied to predict their effects on fetal outcomes: age, parity, phenotype, hemoglobin F level, and splenectomy prior to pregnancy, but none of them showed influence on the fetal outcome. This result is consistent with earlier reports. One report showed that there was no association between maternal hematological state and fetal outcome.[17] Another report showed that there was no relationship between maternal age, parity, hematological features, and LBW.[20]

This study had the following limitations. It was a retrospective study, it involved a small sample size, and was conducted in a single institute. Given the small sample size, the lack of demonstrating an impact for the baseline variables is likely due to the low power of the study to detect this rather than true lack of impact. The strength of this study might be attributed to the scarcity of reports addressing fetal outcomes in Omani women with SCD, and the impact of different variables on that outcome. In the future, more prospective studies are recommended with a larger sample size involving multiple institutions to obtain a proper estimate of fetal and neonatal complications in women with SCD, and to determine different risk factors.

In conclusion, our study showed that the adverse fetal outcomes in pregnant women with SCD are high compared with the general population, despite the fact that they are being followed in a tertiary care center with high-risk obstetric care along with specialized hematologists. We were not able to identify significant differences in fetal outcomes between SCD, SS genotype versus others; most likely owing to the small numbers of other subtypes. Larger sample size studies may help to show if there are any significant differences.

**Acknowledgment.** *We would like to thank the hospital information system for all their support and help in providing the data.*

## References

1. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. ***Am J Obstet Gynecol*** 2008; 199: 125.
2. Sickle Cell Society. In: Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. Pregnancy, contraception and fertility. Chapter 5. London (UK): Sickle Cell Society; 2008: p.59.
3. Rajab KE, Issa AA, Mohammed AM, Ajami AA. Sickle cell disease and pregnancy in Bahrain. ***Int J Gynaecol Obstet*** 2006; 93: 171-175.
4. Koshy M, Burd L. Management of pregnancy in sickle cell syndromes. ***Hematol Oncol Clin North Am*** 1991; 5: 585-596.
5. Rappaport VJ, Velazquez M, Williams K. Hemoglobinopathies in pregnancy. ***Obstet Gynecol Clin North Am*** 2004; 31: 287-317.

6. Rutherford J, Strong J. Anemia and White Blood Cell Disorder. In: James DK, Steer PJ, Weiner CP, Gonik B, editors. High risk pregnancy: management options. Philadelphia (PA): Elsevier; 2006. p. 865-888.
7. Koshy M, Chisum D, Burd L, Orlina A, How H. Management of sickle cell anaemia and pregnancy. ***J Clin Apher*** 1991; 6: 230-233.
8. Serjeant GR, Loy LL, Crowther M, Hambleton IR, Thame M. Outcome of pregnancy in homozygous sickle cell disease. ***Obstet Gynecol*** 2004; 103: 1278-1285.
9. Seoud MA, Cantwell C, Nobles G, Levy DL. Outcome of pregnancies complicated by sickle cell and sickle-C hemoglobinopathies. ***Am J Perinatol*** 1994; 11: 187-191.
10. Ngô C, Kayem G, Habibi A, Benachi A, Goffinet F, Galactéros F, et al. Pregnancy in sickle cell disease: maternal and fetal outcomes in a population receiving prophylactic partial exchange transfusions. ***Eur J Obstet Gynecol Reprod Biol*** 2010; 152: 138-142.
11. Cunningham F, Leveno K, Bloom S, Hauth J, Rouse D, Spong C. Chapter 1. Overview of Obstetrics. Williams Obstetrics 2010. Philadelphia (PA): McGraw Hill Inc: 2010.
12. Wali YA, Moheeb H. Effect of hydroxyurea on physical fitness indices in children with sickle cell anaemia. ***Pediatr Hematol Oncology*** 2011; 28: 43-50.
13. Thame M, Lewis J, Trotman H, Hambleton I, Serjeant G. The mechanism of low birth weight in infants of mothers of homozygous sickle cell disease. ***Pediatrics*** 2007; 120: e686-e693.
14. el-Shafei AM, Sandhu AK, Dhaliwal JK. Maternal mortality in Bahrain with special reference to sickle cell disease. ***Aust N Z J Obstet Gynaecol*** 1988; 28: 41-44.
15. Ogedengbe OK, Akinyanju OO. The hemoglobinopathies and pregnancy in Lagos. ***Int J Gynaecol Obstet*** 1988; 26: 229-233.
16. Omo-Aghoja IO, Okonofua FE. Pregnancy outcome in women with sickle cell - a five year review. ***Niger Postgrad Med J*** 2007; 14: 151-154.
17. Serjeant GR, Hambleton I, Thame M. Fecundity and pregnancy outcome in a cohort with sickle cell-haemoglobin C disease followed from birth. ***BJOG*** 2005; 112: 1308-1314.
18. Leborgne-Samuel Y, Janky E, Venditelli F, Salin J, Daijardin JB, Couchy B, et al. [Sickle cell anemia and pregnancy: review of 68 cases in Guadeloupe]. ***J Gynecol Obstet Biol Reprod (Paris)*** 2000; 29: 86-93. French.
19. Dare FO, Makinde OO, Faasuba OB. The obstetric performance of sickle cell disease patients and homozygous hemoglobin C disease patients in lle-lfe, Nigeria. ***Int J Gynaecol Obstet*** 1992; 37: 163-168.
20. Yu CK, Stasiowska E, Stephens A, Awogbade M, Davies A. Outcome of pregnancy in sickle cell disease patients attending a combined obstetric and haematology clinic. ***J Obstet Gynaecol*** 2009; 29: 512-516.
21. Al Jama FE, Gasem T, Burshaid S, Rahman J, Al Suleiman SA, Rahman MS. Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, Eastern Saudi Arabia. ***Arch Gynecol Obstet*** 2009; 280: 793-797.
22. Nomura RM, Igai AM, Tosta K, da Fonseca GH, Gualandro SF, Zugaib M. [Maternal and perinatal outcomes in pregnancies complicated by sickle cell diseases]. ***Rev Bras Ginecol Obstet*** 2010; 32: 405-411. Portuguese.


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Al Zaman AS. Breast cancer in patients with sickle cell disease can be treated safely with weekly paclitaxel. ***Saudi Med J*** 2013; 34: 199-201.

Hellani AM, Akoum SM, Fadel ES, Yousef HM, Abu-Amero KK. Successful pregnancies after combined human leukocyte antigen direct genotyping and preimplantation genetic diagnosis utilizing multiple displacement amplification. ***Saudi Med J*** 2012; 33: 1059-1064.