Pregnancy outcomes among Palestinian refugee women with sickle cell trait in Damascus, Syria

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ABSTRACT

Objectives: The results on pregnancy outcomes of mothers afflicted with sickle cell trait are still contradictory. This study aimed to examine the fetal and maternal outcomes among a cohort of pregnant women.

Methods: This is a prospective cohort study that examined the fetal and maternal outcomes among 98 women with sickle cell trait (HbAS) and 402 women with normal hemoglobin (HbAA). The study was carried out in 4 health centers serving Palestinian Refugees in Damascus, during the period November 2000 to May 2002. Hemoglobin electrophoresis was carried out for all newly registered pregnancy women. Women were then followed up until 40 days after delivery. Data was collected from antenatal records and interviews with women.

Results: Outcomes of pregnancy were compared between women with HbAS and HbAA hemoglobin. There was no statistical difference in the rate of abortion, distribution of birth weight and perinatal mortality. Women with AS hemoglobin reported higher incidence of complications after delivery, namely, fever (risks ratio=4.05, 95% confidence interval=1.34-12.3).

Conclusion: In this study, pregnancies among women with sickle cell trait demonstrated high risk of complications after delivery. Watchful follow up of pregnancies among women with sickle cell trait is very necessary. Doctors and women must know that although the course of pregnancy among women with HbAS can be benign; it may well carry a high risk on women.

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The sickle cell hemoglobinopathy is a major public health problem in some parts of the world. Hemoglobin S is the most common clinically significant variant Hb. Hemoglobin S is most common in Africa, Kingdom of Saudi Arabia, Bahrain and the Mediterranean Basin.[1] Sickle cell trait (HbAS) results in no detectable abnormality under normal circumstances although it is easily diagnosed by specific investigations including electrophoresis. Affected subjects are not anemic even under the additional stress of pregnancy, unless there are additional complications, and sickling crises occur only in situations of extreme anoxia.[2] Although the hematological and clinical profile of the patients was extensively studied, the results on pregnancy outcomes of women afflicted with sickle cell trait are still contradictory.[3-12] Patients with sickle cell trait usually run a benign course, but they may develop vaso-occlusive crisis, which may lead to hypoxia and subsequently to serious complications.[3] Risks associated with pregnancy for mothers with sickle cell disease and

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their infants have decreased markedly during the last decade. The results are attributed to improvements in the state-of-art medical, obstetric, and perinatal care.[6] Syria, a country in the Mediterranean basin, is known to have some ethnic groups with sickle cell hemoglobinopathy.[13] Those ethnic groups largely include women of Palestinian origin. The pregnancy outcome of Palestinian mothers living in Syria and afflicted with sickle cell trait is still unknown. This study aimed to examine the fetal and maternal outcomes among a cohort of Palestinian pregnant women seen in the Health centers of United Nations Relief and Works Agency (UNRWA) for Palestinian Refugees in the Near East based in Damascus, Syria.

Methods. This is a prospective cohort study of pregnant women registered and followed up in 4 health centers affiliated to UNRWA, Damascus, Syria. Study subjects included 500 Palestinian refugees pregnant women registered in 4 selected health centers namely, Dannoun; Sbena, Set Zenab and Jaramana. Those centers were purposely selected as their target populations have a high proportion of ethnic groups known to have high prevalence of sickle cell trait/disease according to routine statistics. The newly registered women in those health centers seen from November 2000 to August 2001 were included in the study. Inclusion criteria included: a newly diagnosed pregnant woman whose first visit to the antenatal clinic was before 16 gestational weeks, and who accepted to give blood for the study, and of course whose place of residence is within the catchment's area of the center. Assuming a 20% rate of positive sickle cell trait, 600 women were required to demonstrate a doubling in the rate of a bad outcome with 80% power and level of significance of 0.05, with a ratio of 4:1 for unexposed to exposed.

Data collection. On recruitment, a blood sample was taken from all women. Data on obstetric history, risk status during current pregnancy, and follow up information from current pregnancy were collected from women's antenatal records kept at the centers. After the delivery, the first 2 authors interviewed all women within 40 days of delivery. Detailed information on pregnancy outcomes was collected from the interviews. The interviews took place in the health centers after inviting women to come on specific dates. Data on pregnancy outcomes was double-checked from the medical records, if available. The high quality of medical records in the UNRWA health centers has facilitated the work.

Laboratory methods. A 5 ml blood sample was collected and centrifuged in the health centers. Sera were then kept in K3 EDTA Vacutainer, at +8 Celsius in the refrigerators of centers. Sera were then transferred to Al-Assad University hospital laboratory, where the hemoglobin electrophoresis was carried out. The Midigel hemoglobin kit (Biomidi) was used. Analysis was done according to the manufacturer instructions. The results were read on Appraise™ Densitometer (Beckman, California, USA). The laboratory results were kept confidential until the analysis of data was carried out, since all women received the best-proven diagnostic and therapeutic method during pregnancy, and no specific management protocols existed for women with sickle cell trait. Thus, minimal bias was introduced during the follow up. The principles of Helsinki declaration were complied with.

Statistical methods. Three data files were compiled; the first from the laboratory results; the second from antenatal records and the third from interview with mothers. The 3 files were then merged in the analysis period. The unique identification number of the woman was used to merge the files. In this cohort study, exposure was defined as a positive result on electrophoresis; namely, the existence of a characteristic electrophoretic pattern of HbA1SA2, while outcomes were defined as to include abortion; low birth weight; maternal complications of pregnancy and after delivery; and maternal and perinatal mortality. The incidences of different outcomes were calculated among women with sickle cell trait (HbAS) and normal women (HbAA). Relative risk and its 95% confidence intervals were calculated using HbAA pregnancies as the referent group. The statistical analysis was carried out using SPSS for Windows (version 10) and the Epi info 2000 software.

Results. A total of 500 women were studied; those consisted of 98 women with HbAS, and 402 women with HbAA. **Table 1** shows the background characteristics of the study subjects. The age of the study subjects ranged from 15-44 years (mean age = 25.8, SD=5.9). No differences in the background characteristics were noted among women with sickle cell trait and those with normal hemoglobin, except for the consanguinity where a statistically significant difference was noted between women with HbAA and HbAS hemoglobin (16.7% versus 27.6%). As can be seen in table one, clusters of women with HbAS were more dominant in Dannoun area as compared to other areas. **Table 2** demonstrates the results of risk assessment according to the antenatal package provided by UNRWA. According to the risk scoring system utilized in UNRWA health centers, the classification of risk status was as follows in the first antenatal visit during pregnancy: Normal pregnancy (79.8%); alert pregnancy (15.2%) and high-risk pregnancy (5%). As can be seen from **Table 2**, the only risk line where a significant difference was shown between the 2 groups of women was anemia. Anemia defined, as hemoglobin measurement $\leq$9 grams, occurred more frequently in women with sickle cell trait (7.1% among HbAS versus 2.2% among HbAA).

During the follow up period, the number of antenatal visits ranged from 1-14. The mean number of visits did not differ between normal pregnancies and sickle cell trait pregnancies (6.17 $\pm$ 1.75 visits for HbAA, and 6.32

Table 1 - Characteristics of women with normal hemoglobin and those with sickle cell trait.

Items	HbAA n (%)	HbAS n (%)	p-value
Health center			0.005
Sbeina	122 (30.3)	27 (27.6)	
Dannoun	81 (20.1)	36 (36.7)	
Jaramana	149 (37.1)	27 (27.6)	
Set Zeinab	50 (12.4)	8 (8.2)	
First degree relative with husband			0.01
Yes	67 (16.7)	27 (27.6)	
No	335 (83.3)	71 (72.4)	
Woman's occupation			0.96
None (housewife)	367 (91.3)	89 (90.8)	
Work outside	35 (8.7)	9 (9.2)	
Husband's occupation			0.33
Laborer	279 (69.4)	73 (74.5)	
Clerk	60 (14.9)	9 (9.2)	
Others	63 (15.7)	16 (16.3)	
Woman's level of education			0.91
None/primary	237 (59)	60 (61.2)	
Secondary	142 (35.3)	33 (33.7)	
High	23 (5.7)	5 (5.1)	
Husband's level of education			0.98
None/primary	158 (39.3)	38 (38.8)	
Secondary	206 (51.2)	51 (50)	
High	38 (9.5)	9 (9.2)	

HbAA - hemoglobin AA, HbAS - hemoglobin AS, RR - risks ration, CI - confidence interval

Table 2 - Assessment of risk status during pregnancy among normal women and those with sickle cell trait.*

Factors related to past history or present pregnancy	HbAA (N=402) n (%)	HbAS (N=98) n (%)	p-value †
Hemoglobin: 9 grams or less currently	2.2 (9)	7.1 (7)	0.022
Proteinuria in second semester of current pregnancy	0.5 (2)	- -	1.0
Proteinuria in third semester of current pregnancy	0.7 (3)	1 (1)	0.583
Edema in second semester of current pregnancy	0.7 (3)	- -	1.0
Edema in third semester of current pregnancy	2.2 (9)	3.1 (3)	0.711
Diastolic blood pressure above 90 mm Hg	2 (8)	3.1 (3)	0.457
Systolic blood pressure above 140 mm Hg	2.7 (11)	2 (2)	1.0
Bleeding in first semester of current pregnancy	1 (4)	3.1 (3)	0.140
Bleeding in second semester of current pregnancy	2.5 (10)	2 (2)	1.0
Bleeding in third semester of current pregnancy	3 (12)	2 (2)	1.0
Age <18	3.5 (14)	3.1 (3)	1.0
Age >39	2 (8)	3.1 (3)	0.457
Multiparity (6 deliveries or more)	4.7 (19)	5.1 (5)	0.797
Three consecutive abortions or more	1.7 (7)	1 (1)	1.0
Two perinatal deaths or more	0.7 (3)	1 (1)	0.583
History of eclampsia in the previous pregnancy	2 (8)	3.1 (3)	0.457
Previous cesarean section	8.5 (34)	7.1 (7)	0.838
History of bleeding in pregnancy	1 (4)	3.1 (3)	0.140
History of bleeding after delivery	1 (4)	1 (1)	1.0
The existence of diabetes mellitus	0.7 (3)	- -	1.0
The existence of heart disease	1.7 (7)	1 (1)	1.0

*Based on the scoring system used by United Nations Relief and Works Agency. All data were obtained from antenatal records. †Chi square test or Fisher's exact test. HbAA - hemoglobin AA, HbAS - hemoglobin AS

Table 3 - Pregnancy outcomes among study subjects

Outcome	HbAA pregnancies n (%)	HbAS pregnancies n (%)	RR and 95% CI*
High risk pregnancy	4.5 (18/402)	7.1 (7/98)	1.6 (0.7 - 3.7)
Pre-eclampsia	0.7 (3/402)	1 (1/98)	1.4 (0.1 - 13)
Urinary tract infection	3 (12/402)	3.1 (3/98)	1.03 (0.3 - 3.6)
Abortion	2.2 (9/402)	1 (1/98)	0.5 (0.06 - 3.6)
Cesarean section	16.6 (65/392)	13.5 (13/96)	0.6 (0.4 - 1.05)
Low birth weight	12.7 (50/393)	14.4 (14/97)	1.1 (0.7 - 2)
Congenital anomaly	1.3 (5/393)	2.1 (2/97)	1.6 (0.3 - 8.2)
Maternal mortality	0 (0/402)	1 (1/98)	- -
Perinatal mortality	1.5 (6/393)	4.1 (4/97)	2.7 (0.8 - 9.4)
Bleeding after delivery	4.6 (18/393)	9.2 (9/97)	2.03 (0.9 - 4.4)
Fever after delivery	1.5 (6/393)	6.2 (6/97)	4.05 (1.3 - 12.3)

*Referent group: HbAA pregnancies. HbAA - hemoglobin AA, HbAS - hemoglobin AS

± 1.59 visits for HbAS). In addition, the average increase in weight during pregnancy did not differ between the 2 groups of women (7.5 ± 4.1 kg for HbAA, and 7.9 ± 3.9 kg for HbAS). Outcomes of pregnancy were compared between women with HbAS and HbAA hemoglobin (**Table 3**). There was no statistical difference in the rate of abortion, rate of cesarean section, pre-eclampsia, urinary tract infection, distribution of birth weight, incidence of congenital anomalies, and perinatal mortality. Women with HbAS hemoglobin reported higher incidence of fever after delivery (risks ratio [RR] = 4.05, 95% confidence interval [CI] = 1.3-12.3). One maternal death occurred in the group with sickle cell trait. She was primigravida and was complicated by pre-eclampsia at the end of pregnancy. Among study subjects, delivery took place at hospital in 74.6% of the study subjects, and 18.2% delivered in their own homes by dayas or midwives. The rate of delivery in hospital exceeds the rate reported nationally in Syria.[14] The rate of after-delivery complications was reanalyzed after stratifying by the place of delivery. The rate of complications was significantly higher among women with sickle cell trait only if deliveries occurred at home (RR = 2.4 [95% CI = 1.2-4.6]). On the contrary, the rate of complication after delivery in hospital did not significantly differ between normal pregnancies and pregnancies with sickle cell trait.

Discussion. This study compared the pregnancy outcomes between the 2 groups of Palestinian women with sickle cell trait and with normal hemoglobin. The results showed that the only bad outcome, which significantly differed between women with sickle cell trait and those with normal hemoglobin, was the rate of fever after delivery. The rate was significantly higher only if delivery occurred at home, indicating that medical supervision is of paramount importance among women with sickle cell trait. This finding agrees with other studies that reported higher rate of complications of pregnancy.[10,15] Larrabee and Monga[15] reported higher rate of postpartum endometritis among women with sickle cell trait. Fever as reported by women in our study may well indicate puerperal infection or postpartum endometritis. One limitation of this study is that it relied on women's reporting of fever in the absence of a physician-verified diagnosis. However, we do not have a reason to think that there was a bias in reporting fever among women who have HbAS and HbAA hemoglobin. One maternal death was reported in this study. The death complicated a woman with HbAS that had pre-eclampsia. Although not significant due to sample size limitation, this may well indicate the seriousness of sickle cell trait among pregnant women. According to Larrabee and Monga[15] women with sickle cell trait are at increased risk for pre-eclampsia. Vasospasm, which is basic to the pathophysiology of pre-eclampsia, leads to endothelial cell damage. The latter together with hypoxia evoke sickling crisis with massive vaso-occlusion that lead to multiple widespread infarctions causing death. The results did not demonstrate poor fetal outcomes. Other studies did not report a correlation with the baby weight. The type of hemoglobin among newborns was not studied, since it is well known that the sickle cell disease is one of the most

commonly inherited genetic disorders. Hemoglobin S is transmitted through an autosomal recessive inheritance mechanism and with the higher rate of consanguinity among women with sickle cell trait in the study group, serious work needs to be devoted towards health education activities. Families should be aware that the problem will run in their offspring, and that it will be exaggerated with time. It should be noted that this study is prone to many limitations; such as the relative small sample size; the reliance on women's reporting of pregnancy outcomes instead of physician verification; added to the underestimation of some bad outcome such as abortion.

This study focused on women seen in UNRWA health centers. This may mean that women attending antenatal care are being monitored very closely, to ensure best care. In other words, we hypothesize that the risks shown in this study can well increase in other settings where women do not attend antenatal clinics. Marked amelioration of risk can be obtained via comprehensive health care. Cronin et al[16] from United Kingdom reported that antenatal screening is cost-effective even at quite low levels of trait prevalence. Cost-effectiveness studies are recommended in setting similar to the study's setting.

In conclusion, it is very important that women with sickle cell trait are given the correct advice and information on pregnancy and childbirth. They should be aware that most pregnancies can go straightforward to give birth to healthy babies, but some may be problematic and encounter serious complications. Medical monitoring and support should be available during all and critical time.

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