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ORIGINAL ARTICLE

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Does first-trimester serum pregnancy-associated plasma protein A differ in pregnant women with sickle cell disease?

Gergana Peeva[1] | Laura Oakley[4,5] | Inez von Rège[1] | Kypros Nicolaides[3] | Eugene Oteng-Ntim[1,2,4]

[1] Women's Services, Guy's and St Thomas' NHS Foundation Trust, London, UK

[2] Women's Health Academic Centre, King's College London, London, UK

[3] Harris Birthright Research Centre of Fetal Medicine, King's College Hospital, London, UK

[4] Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

[5] Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

Correspondence
Correspodence: Eugene Oteng-Ntim, Women's Health Directorate, Guy's and St Thomas'NHS Foundation Trust, London SE1 7Eh, UK.
Email: eugene.oteng-ntim@gstt.nhs.uk

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Abstract

Objective: To assess whether levels of first-trimester pregnancy-associated plasma protein A (PAPP-A) differ between women with and without sickle cell disease (SCD).

Methods: Retrospective study of 101 singleton pregnancies in women with SCD (including 55 with genotype HbSS, 37 with genotype HbSC, and nine with other genotypes). Measured levels of PAPP-A were converted to multiple of the median (MoM) values corrected for gestational age and maternal characteristics. Median PAPP-A MoM in the SCD group was compared with that of 1010 controls.

Results: In the SCD group median, PAPP-A MoM was lower than in the non-SCD group (0.72, interquartile range [IQR] = 0.54-1.14 versus 1.09, IQR = 0.74-1.49; $P < .001$). Within the SCD group median PAPP-A MoM was lower for those with genotype HbSS than HbSC (0.62, IQR = 0.44-1.14 versus 0.94, IQR = 0.72-1.25; .006). In 7.3% (4/55) of the HbSS group, there was stillbirth, and in these cases, PAPP-A was less than or equal to 0.5 MoM; in the control group, the incidence of stillbirth was lower (1%; $P < .001$). In HbSS disease, the incidence of small for gestational age (SGA) neonates was increased.

Conclusion: Pregnancies with HbSS have lower PAPP-A MoM values and higher incidence of stillbirth and birth of SGA neonates than in non-SCD controls.

1 | INTRODUCTION

Sickle cell disease (SCD) is the commonest single gene defect in the world.[1-3] It is defined as an autosomal recessive hemoglobinopathy that includes sickle cell HbSS disease and various compound heterozygous genotypes, such as sickle cell HbSC disease or sickle cell β-thalassemia (HbSβ-thal) disease, characterized by chronic hemolytic anemia and vaso-occlusive complications. A recent systematic review and meta-analysis has shown a strong association between SCD and adverse perinatal outcomes, including stillbirth and birth of small for gestational age (SGA) neonates.[4] These manifestations could be as a result of abnormal placentation, which may result in reduced levels of first-trimester pregnancy-associated plasma protein A (PAPP-A). However, there are no reported studies that examined the association of SCD and first-trimester PAPP-A levels.

The objective of this study is to investigate whether serum PAPP-A levels differ in pregnancies of women with SCD compared with those in women without SCD and whether it is associated with adverse pregnancy outcome.

2 | METHODS

2.1 | Study population

The data for this study were derived retrospectively and included all pregnant women affected by SCD who attended for combined first-trimester screening for aneuploidies (fetal nuchal translucency, serum free ß-HCG, and PAPP-A) at St Thomas' Hospital, London, UK, between 2009 and 2017. Each SCD pregnancy was matched with

10 non-SCD controls, selected from women of the same racial origin who underwent first-trimester screening within 10 days of the date of screening of each SCD pregnancy. The inclusion criteria were singleton pregnancy with live fetus at 11 to 13 weeks' gestation, delivery greater than 20 weeks' gestation with livebirth or stillbirth and known pregnancy outcome. Pregnancies with fetal abnormalities and those ending in induced abortion were excluded. Gestational age was determined from the fetal crown-rump length (CRL).[5] The following characteristics were extracted from maternal records: maternal age, weight, height, racial origin (Black, White, Asian), method of conception (spontaneous or assisted), cigarette smoking during pregnancy (yes or no), and genotype of SCD (HbSS, HbSC, HbSß-thal, nonspecified SCD).

Serum PAPP-A was measured by an automated devise (Kryptor analytical system, Brahms AG, Berlin, Germany) with results being available within 40 minutes of blood collection. The measured levels were converted into multiple of the median (MoM) for gestational age and corrected for maternal weight, smoking status, racial origin, and mode of conception.[6] Data on PAPP-A levels recorded in MoM were obtained from the fetal medicine unit recording system (Astraia Software GmbH, Version 1.24.10, Munich, Germany, 2016). Data on pregnancy outcome were obtained from hospital records in UK Maternity Patient Data Management, National Maternity Care Record System for the NHS (BadgerNet Version 2.9.1.0).

2.2 | Statistical analysis

Data were not normally distributed and therefore nonparametric tests were used. Characteristics were compared across study groups by the Mann–Whitney U test for continuous variables and by the chi-square test for categorical variables. Data are presented as median and interquartile range (IQR) or n (%). PAPP-A MoM values for SCD pregnancies were compared with the reference group (non-SCD pregnancies), and the process were repeated for the two main SCD genotypes (HbSS and HbSC). Pregnancy outcome (live birth or stillbirth, birthweight and birthweight percentile according to the Fetal Medicine Foundation fetal, and neonatal population weight charts[7]) was presented by SCD group.

Analysis was conducted using Stata 15. All tests were two-tailed and *P* values < .05 were taken to be statistically significant.

3 | RESULTS

The genotype of the 101 women with SCD, included 37 cases of HbSC, 55 of HbSS, three of HbCC, five of HbSß-thal, and one of nonspecified SCD. There were no significant differences in maternal characteristics between the SCD group and controls (Table 1). In patients with SCD, compared with controls, the median birth weight in grams and centiles was significantly lower (2940 versus 3280 g; *P* < .001 and 17.5 versus 34.7 centiles, respectively.) Stratifying by SCD genotype, median birth weight in grams and centiles in pregnancies complicated by HbSC was not significantly different from non-SCD pregnancies (median for HbSC = 3070; .007 and 23.7 centiles; 0.06). Median birth weight in grams and centiles was significantly lower in those with genotype HbSS compared with non-SCD pregnancies (median for HbSS = 2860 g; *P* < .001 and 12 centiles; *P* < .001).

What is already known about this topic?

- Pregnancies in women with SCD are at increased risk of stillbirth and birth of small for gestational age neonates.
- Women with HbSS disease have worse perinatal outcome compared to those with HbSC disease.

What does this study add?

- In women with HbSS disease, serum PAPP-A at 11 to -13 weeks' gestation is significantly reduced, and this may be an early marker of adverse perinatal outcome in these pregnancies.

In the SCD group median PAPP-A MoM was lower than in the non-SCD group (0.72, IQR = 0.54-1.14 versus 1.09, IQR = 0.74-1.49; *P* < .001) (Table 2). Within the SCD group median, PAPP-A MoM was lower for those with genotype HbSS than HbSC (0.62, 0.44-1.14 versus 0.94; 0.72-1.25; .006). The incidence of PAPP-A less than or equal to 0.5 MoM was significantly higher in the HbSS group than the controls, but there was no significant difference between the HbSC group and controls (Table 3). Similarly, the incidence of stillbirth and birth of SGA neonates was significantly higher in the HbSS group than the controls. The four stillbirths in the HbSS group were diagnosed at 20, 23, 25, and 29 weeks' gestation, respectively; the birthweight was less than 3rd percentile in three and serum PAPP-A was less than or equal to 0.5 MoM in all four. In the 10 stillbirths of the control group, the birthweight was less than 3rd percentile in four, and serum PAPP-A was less than or equal to 0.5 MoM in three.

4 | DISCUSSION

4.1 | Main findings of the study

The findings of this study demonstrate the following: first, in pregnant women with SCD, first-trimester levels of PAPP-A are significantly lower than in non-SCD controls; second, in HbSS disease, but not in HbSC disease, median PAPP-A MoM is lower, and incidence of PAPP-A less than or equal to 0.5 MoM is higher than in non-SCD pregnancies; third, in HbSS disease, but not in HbSC disease, the incidence of stillbirth and birth of SGA neonates were higher than in non-SCD pregnancies; and fourth, in HbSS disease, but not in HbSC disease, the incidence of PAPP-A less than or equal to 0.5 MoM in pregnancies with stillbirths and SGA neonates was higher than in non-SCD pregnancies.

TABLE 1 Maternal and pregnancy characteristics in SCD and non-SCD control group

Characteristic	Controls (N = 1010)	SCD		
		All SCD (N = 101)[a]	HbSS (n = 55)	HbSC (n = 37)
Gestation at PAPP-A analysis, weeks	12.6 (12.1-13.0)	12.4 (12.0-12.9)	12.3 (11.7-12.9)	12.4 (12.0-13.3)
Age (years)	31.0 (26.8-35.3)	30.5 (26.0-35.4)	30.5 (26.0-35.5)	31.5 (28.1-35.9)
Body mass index[b]	26 (23-30)	24 (22-27)	23 (21-25)	25 (22-29)
Racial origin				
Black	1000 (99.0)	100 (99.0)	55 (100)	37 (100)
East Asian	10 (1.0)	1 (1.0)	0	0
Spontaneous conception[c]	795 (97.8)	82 (97.6)	44 (100)	30 (93.8)
Cigarette smoking	46 (4.6)	0	0	0
Nulliparous	430 (42.6)	43 (42.6)	26 (47.3)	13 (35.1)
Birthweight percentile	34.7 (8.9-68.5)	17.5 (1.6-45.5)	12.0 (0-41.4)	23.7 (3.3-48.8)
Birthweight, gm	3280 (2950-3580)	2940 (2500-3210)	2860 (2400-3140)	3070 (2720-3460)
Gestation at birth, weeks	39.9 (38.9-40.7)	38.4 (37.9-39.1)	38.3 (37.7-38.9)	38.6 (38.1-39.9)

Note. Values are given as median (interquartile range) or n (%).

Abbreviations: PAPP-A, pregnancy-associated plasma protein A; SCD, sickle cell disease.

[a]Including nine women with other types of SCD.

[b]Available BMI values: all cases in SCD and 821 cases in comparison group.

[c]Available data on conception method: 85 cases in SCD and 813 cases in comparison group.

TABLE 2 PAPP-A MoM levels in SCD group by genotype and non-SCD control group

Study Group	Median (IQR)	*P* value*
Comparison group (N = 1010)	1.09 (0.74-1.49)	-
All SCD (N = 101)[a]	0.72 (0.54-1.14)	<.001
HbSS (n = 55)	0.62 (0.44-1.14)	<.001
HbSC (n = 37)	0.94 (0.72-1.25)	.14

Abbreviations: IQR, interquartile range; MoM, multiple of the median; PAPP-A, pregnancy-associated plasma protein A; SCD, sickle cell disease.

[a]Including nine women with other types of SCD.

*Mann–Whitney U test, using non-SCD group as comparison group.

4.2 | Interpretation and implications of the study

Low first-trimester serum PAPP-A is associated with increased prevalence and severity of placental pathology during pregnancy such as stillbirth and fetal growth restriction.[8,9] A recent systematic review and meta-analysis including greater than 26 000 pregnancies in women with SCD showed strong association between SCD and adverse perinatal outcome, including fourfold increased risk of stillbirth and 2.5-fold increased risk of fetal growth restriction; women with HbSS disease had significantly worse perinatal outcomes compared with those with HbSC disease.[4]

In SCD, there is abnormal placentation and or sickling in the placenta,[4,10] and the low serum PAPP-A may be a reflection of this

TABLE 3 Birth outcomes and proportion of low PAPP-A by study group

Characteristic	Controls (N = 1010) n (%)	SCD					
		All SCD (N = 101)[a]		HbSS (n = 55)		HbSC (n = 37)	
		n (%)	*P* value*	n (%)	*P* value*	n (%)	*P* value*
PAPP-A ≤0.5 MoM	95 (5.0)	24 (23.8)	<.0001	21 (38.2)	<.001	2 (5.4)	.44
Stillbirth	10 (1.0)	4 (3.9)	.01	4 (7.3)	<.001	0 (0)	.54
PAPP-A ≤0.5 MoM	3 (30.0)	4 (100)	<.0001	4 (100)	<.0001	-	-
Small for gestational age[b]	263 (26.0)	43 (42.3)	<.001	24 (43.6)	<.001	14 (37.8)	.12
PAPP-A ≤0.5 MoM	40 (15.2)	14 (32.6)	<.0001	10 (41.7)	<.0001	2 (14.3)	.65

Abbreviations: MoM, multiple of the median; PAPP-A, pregnancy-associated plasma protein A; SCD, sickle cell disease.

**P* values from ×2 test, using non-SCD group as comparison group.

[a]Including nine women with other types of SCD.

[b]Birthweight ≤10th percentile for gestational age.[7] In this section, we include only live births.

placental pathology. Pregnancies with HbSS disease and low levels of PAPP-A less than or equal to 0.5 MoM seem to be at the highest risk of adverse outcome. In this respect, serum PAPP-A could potentially act as a marker of increased risk of complications and stimulate the need for closer surveillance and earlier therapeutic interventions in this specific group of women. Additionally, in the calculation of PAPP-A MoMs in screening for fetal trisomies, it may be necessary to adjust for maternal SCD; otherwise, the associated low PAPP-A would increase the false positive rate for trisomies 21, 18, and 13 and lead to unnecessary invasive testing for fetal karyotyping.

4.3 | Strengths and limitations

This study was conducted at one of the largest referral centers for SCD in the United Kingdom, but the sample of affected pregnancies is small. Despite this small number, we were able to demonstrate significant differences between HbSS disease and non-SCD pregnancies in serum PAPP-A levels and adverse pregnancy outcome. The incidence of stillbirth in the controls (1%) was higher than the national average (04%),[11] but this could be explained by first, inclusion in this study of stillbirths at greater than or equal to 20 weeks' gestation, rather than greater than or equal to 24 weeks in national statistics and second, inclusion of a highly vulnerable inner city Black population. A similar reason may also be true for the observed incidence of SGA in the control group (26%), which was higher than the rate of 17% reported in the reference range for Black women.[7]

5 | CONCLUSION

In HbSS disease, first-trimester serum PAPP-A is decreased, and these pregnancies are at high risk of stillbirth and birth of SGA neonates.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Eugene Oteng-Ntim https://orcid.org/0000-0001-8867-2909

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