Mildly raised tricuspid regurgitant velocity 2.5–3.0 m/s in pregnant women with sickle cell disease is not associated with poor obstetric outcome – An observational cross-sectional study

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Abstract

Pulmonary hypertension is associated with 36% mortality in pregnancy, and 6–10% of patients with sickle cell disease have pulmonary hypertension. Tricuspid regurgitant velocity ≥ 2.5 m/s on echocardiography is a well validated means of screening for pulmonary hypertension in the non-pregnant population. This is a pilot study to determine if this is a useful non-invasive screening test for pulmonary hypertension in pregnancy, and whether raised tricuspid regurgitant velocity ≥ 2.5 m/s was associated with poor outcomes. This is a cross-sectional study over a five-year period in a tertiary referral centre with a specialised multidisciplinary clinic for pregnant women with sickle cell disease. Women with sickle cell disease, no prior pulmonary hypertension and singleton pregnancies who had echocardiography with a measurable tricuspid regurgitant velocity in pregnancy were included. There were 34 pregnancies, of which eight had tricuspid regurgitant velocity ≥ 2.5 m/s. There were no significant differences in their characteristics, sickle cell-related complications or medical co-morbidities. The women with tricuspid regurgitant velocity ≥ 2.5 m/s had similar obstetric and perinatal outcomes as those with a tricuspid regurgitant velocity < 2.5 m/s.

Keywords

Sickle cell disease, pregnancy, obstetric outcomes, pulmonary hypertension, tricuspid regurgitant velocity

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Background

Sickle cell disease (SCD) is one of the most common and the fastest growing inherited disorders in the UK with an estimated prevalence of 12–15,000 affected individuals.^{1,2} With improved care, more women are reaching childbearing ages and becoming pregnant.³ Pregnancy in women with SCD is associated with increased risks of maternal and fetal complications including maternal pain, acute chest syndrome (ACS), hypertension, premature delivery and reduced birth weight.⁴

In a non-pregnant population, pulmonary hypertension (PH) is a resting mean pulmonary arterial pressure ≥ 25 mmHg on right heart catheterisation, seen in 6–10% of patients with SCD.⁵ In a non-pregnant population, a raised tricuspid regurgitant velocity (TRV) ≥ 2.5 m/s on echocardiography, in the absence of pulmonary valve pathology, is associated with PH. TRV ≥ 2.5 m/s is found in 30–40% of patients with SCD and is associated with increased mortality, despite cardiac catheterisation confirming PH in only 25–32% of patients with a raised TRV.^{5,6} In UK patients with SCD, a TRV ≥ 2.5 m/s was associated with a >4 -fold increased risk of death.⁷ Although it has a high false-positive rate, TRV remains an effective and non-invasive screening test for PH. American Thoracic Society Clinical Practice Guidelines now endorse the use of TRV ≥ 2.5 m/s as a marker of increased risk of mortality in SCD.⁸

Morphological and functional changes occur in the maternal heart and pulmonary arteries as part of normal adaptation in pregnancy. These changes could potentially be dynamic as the gestation progresses.^{9,10} TRV as a screening tool for PH remains unvalidated in pregnancy.

In pregnancy, PH is associated with up to a 36% risk of mortality and significant morbidity in both the mother and offspring.^{11,12} In 2011, the Royal College of Obstetricians and Gynaecologists (RCOG) included TRV > 2.5 m/s as part of screening for PH in all women who have not had an echo performed in the last year.

At present, there are no published data on the effect of TRV ≥ 2.5 m/s during pregnancy on obstetric outcomes in SCD. The objective of this study was to determine the prevalence of TRV ≥ 2.5 m/s on Doppler echocardiography during pregnancy in women with SCD, and whether this was associated with poor obstetric and perinatal outcomes.

Methods

This was a cross-sectional study from 1 January 2008 to 31 December 2012 of all women attending the specialised SCD Pregnancy Clinic at Guy's and St Thomas' NHS Foundation Trust. There is a high prevalence of SCD in our population and a specialised multi-disciplinary clinic has been involved in the care of these women in pregnancy. Routine echocardiography in pregnancy has been offered in this centre prior to the publication of the RCOG guidelines.¹³

Our inclusion criteria were of all women with SCD and singleton pregnancies who had echocardiograms performed during pregnancy.

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Due to the unacceptable risk of PH in pregnancy, the women who already had an established diagnosis of PH were advised to terminate their pregnancies. Women were excluded if lost to follow up, had early terminations due to maternal comorbidities or did not have measurable tricuspid regurgitation on echocardiography.

Echocardiograms were performed in accordance with British Society Guidelines. The TRV measured from the best Doppler trace of tricuspid regurgitation obtained.

Maternal data collected included sickle genotype, demographic data, smoking status, sickle cell complications prior to pregnancy, maternal functional capacity at baseline and booking bloods. Maternal morbidity recorded included pre-eclampsia, ACS during pregnancy, days admitted in hospital and maternal mortality. Perinatal outcomes recorded were length of gestation, birth outcome, birth weight, and customised birth-weight centiles, Apgar scores and neonatal intensive care admissions. ACS was defined according to British Thoracic Society Guidelines as an acute illness characterised by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray.

Data analysis

Continuous variables were expressed using medians and interquartile ranges and the Mann–Whitney U test was used for comparisons between groups. Due to the small numbers, the Fisher's exact test was used for univariate comparisons of dichotomous data.

The main outcome of interest was preterm delivery defined as delivery <37 weeks' gestation. Other outcomes of interest included birth-weight, prevalence of small-for-gestational-age (SGA) and admission to special care for the neonate. SGA was defined as <10th centile on customised birth weight centile chart.¹⁴

The risk of an event was modelled with exact logistic regression on a complete dataset. Univariate analysis was performed on the outcome of interest. Multivariate analysis was performed adjusting for maternal age, ACS in pregnancy and medical comorbidities (stroke, renal disease, chronic transfusions, asthma, ACS and other respiratory disease).

A $p < 0.05$ was deemed to be significant for all hypotheses tested. Data were analysed using Stata IC 13.1.

Results

Over the study interval, there were 100 pregnancies, but only 34 pregnancies in 30 women who met the inclusion criteria (Figure 1).

The median age of the study population was 31 (20–41) years; 24/34 (71%) of pregnancies were in women with HbSS. The median gestation at time of echocardiography was 21 weeks (full range of 13–275 days gestation). All the women were of African or Afro-Caribbean descent.

The median TRV was 2.2 (full range 1.4–3.0 m/s). All women had normal left and right ventricular systolic function. At the time of pregnancy, all women except one had good exercise tolerance.

The prevalence of TRV ≥ 2.5 m/s is 23.5% in our total population, and 33% in HbSS women in pregnancy.

Baseline characteristics were compared in women with a TRV <2.5 m/s and women with a TRV ≥ 2.5 m/s (Table 1). Eight women (23.5%) had TRV ≥ 2.5 m/s on echocardiography with a range of 2.5–3.0. None of the women had a TRV of >3.0 m/s.

The only significant difference was a higher systolic blood pressure at booking in the group with TRV <2.5 m/s (100 vs. 107 mmHg $p = 0.04$). (Table 1) Baseline bloods at booking (haemoglobin, platelets, ferritin, lactate dehydrogenase, creatinine, reticulocyte count) were the same in both groups. ACS during pregnancy was more common in women with TRV ≥ 2.5 m/s with 50% experiencing this complication compared to only three (11.5%) of the women with TRV <2.5 m/s ($p = 0.04$). (Table 1)

There were no significant differences in maternal and perinatal outcomes between the two groups (Table 2). There were no maternal deaths. There were no significant differences in total days admitted during pregnancy, need for induction of labour or mode of delivery between groups.

Six women had preterm delivery <37 weeks' gestation. A quarter (25%) of the women in TRV ≥ 2.5 m/s had a preterm delivery compared with 16.7% in the other group ($p = 0.63$). The odds ratio for preterm delivery was 1.63 (95% CI 0.12–15.24); this non-significant finding persisted after full adjustment in the multivariate analysis.

In the whole cohort, the live birth rate was 94% and 28% of babies were admitted to the special care baby unit. The babies were born in good condition with their median Apgars 9–10 at 1 and 5 min. The median customised birth weight for the cohort was 24.1 centile (IQR 3.15–48.4) of the UK population.¹⁴ The prevalence of SGA was 35.29%. There were no significant differences in fetal outcomes between the groups with similar rates of admission to special care units. (Table 2)

Two pregnancies did not result in live births. One was a termination for maternal medical co-morbidities including PH treated with sildenafil. The second was an unexplained intrauterine death at 22⁺6 weeks' gestation of a male infant who was <3rd centile of his customised birth weight centile, in a woman with chronic sickle lung disease and TRV 2.1 m/s.

Figure 1. Study cohort.

Table 1. Characteristics of the cohort and echocardiographic differences.

Variable	TRV <2.5 m/s (n = 26)	TRV ≥2.5 m/s (n = 8)	p
Maternal age, years (IQR)	31 (26–35)	28 (25–33)	0.53
HbSS genotype, n (%)	16 (61.5)	8 (100.0)	0.07
Maternal BMI, kg/m ² (IQR)	23.4 (21.2–28.6)	22.5 (21.8–23.1)	0.42
Maternal smoking, n (%)	3 (11.5)	1 (12.5)	1.00
Systolic BP at booking, mmHg (IQR)	107 (102–120)	100 (90–107)	0.04
Medical comorbidities			
Asthma, n (%)	4 (15.3)	2 (25.0)	0.61
Other chronic respiratory problems, n (%)	6 (23.1)	1 (12.5)	0.47
Past history of acute chest syndrome, n (%)	11 (42.3)	4 (50.0)	1.0
Renal disease, n (%)	5 (19.2)	0	0.24
Previous stroke, n (%)	2 (7.7)	2 (25.0)	0.23
Laboratory results six months prior or at the time of booking			
Hb, g/L (IQR)	8.9 (7.9–9.5)	9.6 (7.9–10.1)	0.58
Reticulocyte count, 10 – 100 × 10 ⁹ /l (IQR)	193 (148–237)	144 (138–197)	0.29
LDH, U/L (IQR)	510 (429–686)	712 (558–902)	0.13
Creatinine, μmol/L (IQR)	54 (41–66)	47 (41–57)	0.26
Bilirubin, mg/dL (IQR)	26 (15–48)	26 (21–52)	0.75
Echocardiographic data performed in pregnancy			
TAPSE ^a , mm (IQR)	24.0 (22.5–28.0)	24.5 (18.5–30.5)	0.87
TRV, m/s (IQR)	2.1 (2.0–2.3)	2.6 (2.6–2.8)	

^aAn indicator of right ventricular systolic function.

Table 2. Maternal and perinatal outcomes of singleton SCD pregnancies.

Variable	TRV <2.5 m/s (n = 26)	TRV ≥2.5 m/s (n = 8)	p
Live birth, n (%)	24 (92.3)	8 (100.0)	1.0
Pre-eclampsia ^a , n (%)	6 (24.0)	0	0.16
Acute chest syndrome during pregnancy, n (%)	3 (11.5)	4 (50.0)	<0.05
Total days admitted during pregnancy (excluding delivery), median (IQR)	6 (0–19)	8 (6–14)	0.58
Length of gestation, days (IQR) ^b	268 (264–272)	269 (257–274)	0.93
Preterm <37 weeks' gestation, n (%)	4 (16.7)	2 (25.0)	0.63
Birthweight, g (IQR) ^c	2920 (2420–3240)	3015 (2375–3190)	0.93
Customised birthweight centile, centile (range) ^b	24.1 (0–84.0)	23.2 (0.1–51.2)	0.62
Admission to special care, n (%)	5 (20.8)	4 (50.0)	0.18

^aOnly if gestation ≥20 weeks.

^bOnly for live births.

^cIQR = Inter-quartile ranges.

Of the four women who had more than one pregnancy, there was no evidence of increasing TRV measurements in the subsequent pregnancies ($p = 0.70$).

Conclusion

This is the first study to assess the prevalence of a raised TRV ≥2.5 m/s in pregnant women with SCD and to determine if it is associated with poor obstetric and perinatal outcomes. The prevalence of TRV ≥2.5 m/s of 33% in our cohort and its preponderance in HbSS is in accordance with other studies in the non-pregnant adult sickle population.^{5,15}

The rate of ACS was higher in the group with TRV ≥2.5 m/s, but could be linked to the effect of genotype. While the birth weight

distribution of our cohort was in the lower end of the curve for UK population, which is in keeping with published literature. SGA is higher in women with SCD due to its effect on the placental function.^{4,16}

A limitation of this study is its small numbers. We applied stringent selection criteria to ensure a well-defined cohort in whom echocardiography was deemed comparable. Ideally, echocardiography should have been performed at fixed gestation ranges, as the gestation affects maternal cardiovascular physiology and therefore cause variations in echocardiography parameters.¹⁰

The exclusion of the women who did not have measurable TR jets may have introduced ascertainment bias and an overestimation of raised TRV as other papers have included these cases, where the TR jet was not quantifiable in their TRV <2.5 m/s group so long as there are no other signs of PH.^{5,17} Although all echocardiograms in our

study were performed in accordance with the British Society of Echocardiography standards, variations in the amount of time spent looking for and interrogating tricuspid regurgitation may have affected the number of exclusions due to the absence of tricuspid regurgitation or an adequate Doppler signal to quantify TRV.

Further work still needs to be done to validate the use of echocardiography in pregnancy and to define gestation specific parameters. With the changes in cardiovascular haemodynamics in pregnancy, TRV values that are acceptable in the non-pregnant population may not be applicable to pregnant women. Furthermore, studies will need to determine whether echocardiographic parameters prior to or during pregnancy are able to predict obstetric and perinatal outcomes or sickle complications in pregnancy.

Some studies have demonstrated that placental growth factor (PlGF) is an angiogenic factor produced by erythroid cells induces hypoxia-independent expression of the pulmonary vasoconstrictor endothelin-1 in pulmonary endothelial cells.¹⁸ Therefore, it is possible that repeated pregnancies could theoretically increase the risk of developing PH in women with SCD esp. when complicated by anaemia. In the four women who have had more than one pregnancy and the TRVs re-quantified in the subsequent pregnancy, did not demonstrate a significant increase in TRV values in their subsequent pregnancy. The numbers in this subgroup analysis are far too small to generate results of clinical significance, but this remains an area in which future research should explore further.

Future work should also focus on women with HbSS, as none of the women with HbSC had a TRV ≥ 2.5 and the low rates of raised TRV in HbSC outside pregnancy indicate that the group at greatest risk of significant PH will be those who are HbSS.

In conclusion, our data suggest that women with SCD with a TRV ≥ 2.5 m/s have similar obstetric outcomes to those with a normal TRV. This study raises several interesting points, and provides pilot data upon which to base a larger observational study.

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Ethical approval

The study was approved by the research and ethics committee at St Thomas' (reference number: 04/Q0707/65).

Guarantor

MCS.

Contributorship

MCS was responsible for data collection, analyses and interpretation of data, study design and writing the manuscript.

SS – preliminary data collection, study design, obstetric input, revision of the manuscript.

NAYC – Study design, cardiology input and revision of the manuscript.

SR – Sickle database, haematology input and revision of the manuscript.

EON – Study design, obstetric input, revision of the manuscript.

CNP – Revision of the manuscript.

JH – Sickle database, haematology input, revision of manuscript.

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