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**Maternal and perinatal outcomes among
haemoglobinopathy carriers:
A systematic review**

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Specialty area:	



Maternal and perinatal outcomes among haemoglobinopathy carriers:

A systematic review

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Abstract

Background: With the introduction of screening programs for haemoglobinopathies, more women will be aware of their HbP status. Midwives and obstetricians need to know whether pregnant HbP carriers have any special needs besides the genetic risk.

The objective was to investigate the hypothesis that being a carrier of HbP has no consequences for the health of pregnant women and the outcome of their pregnancies.

Methods: A systematic search was carried out until august 2008 in the Cochrane Library; Medline; EMBASE and CINAHL databases. All references were inspected to identify further studies. The authors of key-publications were contacted for any unpublished research.

Selection criteria: Cohort and case control studies, pregnant women with a singleton pregnancy. Exposure: HbAS or thalassaemia minor. Outcomes: urinary tract infection, anaemia, (pre-)eclampsia, gestational diabetes, premature labour, low birth weight, intra-uterine growth retardation, miscarriage, neonatal death, low apgar score, neural tube defects.

Quality assessment and data extraction were carried out by two researchers.

Results: 780 Studies were identified of which nine were included in the study. A protective effect of sickle cell trait was found for premature birth, low apgar score and perinatal mortality rate. No significant effect was found for low birth weight, growth retardation,

1
2 urinary tract infection or high blood pressure. The risk of anaemia and bacteriuria was
3
4 increased.

5
6 *Conclusions:* The risks among pregnant HbP carriers are low. Midwives and obstetricians
7
8 need to be aware of the risk of anaemia and urinary tract infection.
9

10
11
12 *Keywords:* Haemoglobinopathy, sickle cell trait, thalassaemia minor, pregnancy
13
14

15 16 **Introduction**

17
18 It is generally accepted that the pregnancy of a woman with homozygotic
19
20 haemoglobinopathy (HbP) disease and some double heterozygous conditions, such as
21
22 HbSC and HbS- β -thalassaemia, carries a higher risk. While the genetic implications of HbP
23
24 carrier status are clear, the effect if any, on the outcome of pregnancy remains subject to
25
26 debate.

27
28 Thalassaemia minor (carriers) constitutes of alpha and beta defects and some rare
29
30 exceptions(1). The most well known of the structural defects is HbS, like beta thalassaemia
31
32 this is a beta gene defect that is non-active in the fetus until birth.

33
34 Over the years, several studies on the effect on pregnancy have been published but provide
35
36 inconsistent conclusions. Some studies suggest an increased risk for adverse perinatal
37
38 outcomes(2-4) while others cannot confirm this risk (5-9). Pregnant women with
39
40 homozygotic HbP disease need to be referred to a tertiary care centre. Pregnant women
41
42 who are (known) HbP carriers are usually considered low risk as no risks for their health or
43
44 the outcome of their pregnancies are assumed. However it is unclear whether these women
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46 have special needs during pregnancy. As far as we are aware, no systematic review has
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48 been conducted on this subject.
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2 Screening for sickle cell disease has been added to the existing neonatal screening program
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4 in several countries, such as the Netherlands and England. If a baby has been diagnosed
5
6 with sickle cell disease or thalassaemia major or is a carrier, the parents will be offered
7
8 genetic screening tests to confirm their carrier status which will then enable them to make
9
10 appropriate reproductive choices concerning any subsequent pregnancies. Midwives and
11
12 obstetricians will therefore increasingly encounter women who are aware of their HbP
13
14 carrier status. The prevalence of an HbP carrier status is currently estimated to be 4-14 %
15
16 amongst people with non-Northern European background in the Netherlands (10) and
17
18 according to the World Health Organisation approximately 5 % of the world population is a
19
20 carrier of a significant variant of haemoglobin disorders such as sickle cell disorders or
21
22 thalassaemias with as many as 40% carriers in some regions (11). It is therefore important
23
24 that midwives and obstetricians are aware of any potential risks among HbP carriers during
25
26 pregnancy.

27
28 In this systematic review we will address the possible risks for pregnant HbP carriers and
29
30 investigate the hypothesis that being an HbP carrier has no consequences for the health of
31
32 pregnant women and the outcome of their pregnancies.

33 34 35 **Methods**

36
37 With the aid of a librarian, we searched the Cochrane Library; Medline; EMBASE and
38
39 CINAHL databases for publications in English, French, German, Spanish and Dutch,
40
41 examining the effect of sickle cell trait and/or thalassaemia minor on maternal morbidity or
42
43 perinatal morbidity and mortality.

44
45 The search was not restricted by publication date and was carried out until August 2008. We
46
47 only searched for (prospective and retrospective) cohort studies and case control studies.
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1
2 Keywords used were: Pregnant women, sickle cell, sickle cell trait, sickle cell anaemia,
3
4 sickle cell disease, thalassaemia, heterozygote thalassaemia, haemoglobinopathy, abnormal
5
6 haemoglobines, pregnancy outcome, complications of pregnancy, urinary tract infections,
7
8 iron deficiency anaemia, folic acid deficiency anaemia, (pre-)eclampsia, gestational
9
10 diabetes, premature labour, low birth weight, miscarriage, fetal / neonatal death, low Apgar
11
12 score and neural tube defects.

13
14 We inspected the references of all studies found to identify any further studies. The authors
15
16 of key-publications were contacted for any unpublished research.

17
18 The initial selection of studies by title and abstract was carried out by one reviewer (SJ)
19
20 based on its relevance to the research question and, if possible, by the inclusion criteria
21
22 (table 1). The studies found were assessed and scored by two independent reviewers (SJ
23
24 and AdJ). Details of authors, affiliated institutions, journal name, and year of publication
25
26 were removed for the second reviewer.

27
28 Selection for inclusion into the review was made on the basis of in- and exclusion criteria
29
30 and quality assessment. The use of checklists is disputed by some (12). Sanderson
31
32 highlighted the lack of existence of an adequate tool, but he nevertheless advised to use a
33
34 simple checklist rather than a scale and concluded that it is important to use a small number
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36 of key domains for quality assessment (13). We decided to use the guidelines for assessing
37
38 the quality of observational and case control studies as defined by the Dutch Institute for
39
40 Healthcare Improvement to support our quality assessment (14). These include all the
41
42 elements mentioned by Sanderson(13), and have been carefully developed by the institute
43
44 in collaboration with the Dutch Cochrane Centre and are generally accepted as adequate in
45
46 the Netherlands (table 2). We awarded a maximum of two points for each item on the list,
47
48 meaning that each study could score a maximum of 16 points. We excluded any study
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50 which obtained a score of less than 12 points. This high cut-off point was chosen because
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1
2 almost all studies automatically scored high on “adequate follow-up” and “selective loss-
3 to-follow-up”. Some authors were contacted for clarification of the study methods.

4
5 Data were extracted independently from the included studies by two investigators (SJ and
6 AdJ) on study design, population and setting, screening method, exposition, outcome
7 variables, confounders and point estimates. Differences were resolved by discussion.
8
9

10 11 12 13 14 **(Statistical) analysis**

15 We used population (ethnicity), exposition, screening method and (definition of) outcome
16 variables to assess clinical heterogeneity. Study design, confounders and point estimates
17 were used to assess methodological heterogeneity. Confounders were assessed for all
18 separate outcomes.
19

20 Both clinical and methodological homogeneity could not be established; therefore after
21 consultation with a statistician, we decided not to pool the results.
22
23

24 25 26 27 28 29 **Results**

30 We initially identified 780 studies from which we selected 91 titles (fig.1). After screening
31 the abstracts, we read 36 papers. By inspecting the references of these papers, we identified
32 a further 30 studies of which nine studies were read and assessed. Contact with the authors
33 provided one additional study which was only available as a (PhD-) thesis (15). In total 46
34 studies were assessed for methodological quality. The two reviewers disagreed on six out
35 of 46 studies (13 %). Consensus was reached by discussion.
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38 Nine studies on HbAS met the inclusion criteria and scored 12 points or more and therefore
39 were of sufficient methodological quality to be included in the review. Only one of these
40 studies investigated the effect of thalassaemia minor on pregnancy (15).
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2 *Premature birth/ (Low)Birth weight (LBW)/ Intra Uterine Growth retardation (IUGR)*

3
4 None of the studies into premature birth stated whether the expected date of delivery was
5 confirmed by ultrasound scan (table 3). Bryant (16) showed a significant protective effect
6 for delivery before 32 weeks in women with sickle cell trait (SCT), whereas Tita (8)
7 showed a protective effect for deliveries at less than 37 weeks gestation. Stamilio (7)
8 showed no difference between the two groups. The prospective cohort study of Landman
9 (15) found that HbP carriers had a smaller but non-significant risk of a premature delivery.
10 The prospective cohort study by Larrabee (17) only looked at the mean gestational age and
11 showed a significant reduction in the length of gestation by one week in women with SCT.
12 None of the four studies examining the risk of low birth weight in infants of women with
13 SCT showed a significant effect (2;5;7;8) (table 3).

14 Four studies (5;8;15;18) looked at intra uterine growth retardation (IUGR) (table 3). Two
15 studies stated that dates were confirmed by ultrasound scan and only Tan (18) and
16 Landman (15) gave a clear definition of IUGR. Tita (8) supplied the definition of IUGR
17 and Landman (15) confirmed dating by ultrasound scan when contacted. None of the
18 studies found any effect of HbP carrier status on the risk of IUGR.

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35 *Risk of urinary tract infection (UTI) and pyelonephritis:*

36 None of the three studies into the risk of UTI in pregnant women with SCT showed an
37 increased risk (2;5;15) (table 4). In only one study, a definition of UTI was given (15).
38 Two studies showed a small but statistically significant increased risk for bacteriuria in
39 pregnant women with SCT (8;19) and in one of them the risk of pyelonephritis was also
40 increased (19).

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49 *Iron Deficiency Anaemia (IDA) and folate deficiency*

1
2 Only three included studies looked at anaemia in pregnant HbP carriers (2;5;15) (table 4).
3
4 None of them took physiological haemodilution into account. Adeyemi (5) did not give a
5
6 definition of IDA and found no statistically significant difference between groups.
7
8 Abdulsalaam (2) found significantly more anaemia in the HbAS group. Landman (15)
9
10 found a difference between groups when IDA was found in combination with folate
11
12 deficiency. A significantly higher percentage of anaemia with a Hb \leq 90 g/l was found in
13
14 the HbAS group (5.5% vs 3.6%, $p < 0.05$). Looking at the specific causes of anaemia, IDA
15
16 occurred more often in the control group but this difference was not statistically significant.
17
18 A combined iron and folate deficiency occurred significantly more frequently in the HbAS
19
20 group. The group with thalassaemia trait had less IDA but this was not statistically
21
22 significant. Folate deficiency and combined iron and folate deficiency, occurred more in
23
24 the thalassaemia group but this was not statistically significant.
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26
27

28 *High blood pressure: Pregnancy Induced Hypertension (PIH) and Preeclampsia (PE)*

29
30 Three studies (5;8;15) investigated the relationship between being a HbP carrier and PIH of
31
32 which two (8;15) gave a definition of PIH (table 5). None of the three studies was able to
33
34 demonstrate a significant effect.

35
36 Four studies (2;7;8;17) looked at pre-eclampsia of which only one (17) found a
37
38 significantly increased risk for PE in women with SCT.
39
40

41 *Miscarriage, fetal and neonatal death*

42
43 Three studies into the risk of fetal and neonatal death found opposite effects but none of
44
45 these were significant (2;5;8) (table 5). Another study (15) found only one case in the
46
47 control group (results not in table).
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1
2 Two studies investigated the effect of SCT on stillbirths alone (5;8). These studies showed
3
4 a protective effect but in one this was not significant(5).

5
6 Tita (8) found a very small non-significant reduction in fetal death. No studies examined
7
8 the risk of miscarriage.
9

10 11 *Low Apgar score*

12
13 Two studies looked at the Apgar score (table 5) (5;15). One study showed a decreased
14
15 incidence of low Apgar scores among women with HbAS (5) and another study showed an
16
17 insignificantly increased risk (15).
18

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21
22 None of the included studies examined the effect of HbP carrier status on gestational
23
24 diabetes or neural tube defects.
25

26 27 **Discussion**

28
29 As far as we know, this is the first systematic review that examines possible risks of
30
31 pregnant women who are HbP carriers. Besides the obvious need for genetic counselling, it
32
33 is important for midwives and obstetricians to be aware of any risk factors if these do exist.

34
35 Some studies showed a protective effect of sickle cell trait for premature birth, low Apgar
36
37 score and stillbirth: there was some evidence of an increased risk of anaemia and
38
39 bacteriuria. No significant effect of HbP carrier status was found on low birth weight,
40
41 growth retardation, urinary tract infection or high blood pressure.
42

43
44 These results should be interpreted with caution because of several methodological
45
46 problems. All studies gave adequate definitions of the exposure factor and of the
47
48 population under investigation; however, many authors failed to give adequate definitions
49
50 of the outcomes assessed in their studies and they often did not control for confounders
51

1
2 such as SES. In some studies (7;8;16;20) it was not clear how the expected date of delivery
3
4 was calculated and if this was confirmed by ultrasound scan. Nevertheless, considering the
5
6 time frame and the setting in which the studies took place (academic hospitals) it could be
7
8 assumed that women had an ultrasound scan to assess the expected date of delivery.

9
10 However, in view of the fact that only one author (8) was able to confirm this when
11
12 contacted, we need to be cautious with the overall conclusion.

13
14 In some studies (7;17) ethnicity was poorly defined and SCT may therefore have been
15
16 underreported resulting in considerable bias.

17
18 The testing method to confirm carrier status was a problem in most studies. Only two
19
20 studies used adequate methods that identified the presence of thalassaemia (15;18). The
21
22 other studies used a sickle cell test and / or electrophoresis to establish HbP status of
23
24 pregnant women. Two studies tested all women with a sickle test and confirmed only the
25
26 positive women with electrophoresis (7;17). According to The British Committee for
27
28 Standards in Haematology (BCHS) a sickle test may not detect low levels of HbS and
29
30 should only be used in an emergency (www.bcsghguidelines.com). Carriers may have been
31
32 missed in these studies giving rise to further bias. According to the BCHS, electrophoresis
33
34 is not recommended for the quantification of HbA2 necessary to establish carrier status of
35
36 thalassaemia: HPLC or micro column chromatography should be used (21). Most studies
37
38 did not specifically state whether other fractions such as HbAC, HbAE or any of the
39
40 thalassaemias were found and whether or not they were excluded. With the exception of
41
42 two studies (18;15) none of the studies gave any information on the co-existence of HbS
43
44 and thalassaemia. Many people of Afro-Caribbean descent with HbAS have a combination
45
46 of HbAS and α -thalassaemia. [High HbA2 \$\beta\$ -thalassaemia or any other trait found in early](#)

47
48 [pregnancy and suspected to be associated with thalassaemia major, sickle cell disease or](#)

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with other severe pathologies, should be confirmed at DNA level in particular when a couple at risk is suspected (22).

Deleted: Confirmation of traits other than those associated with sickle cell disease should be done at DNA level

Protective effect

A protective effect was found for preterm labour in carriers of HbP. However in view of the many methodological pitfalls, the conclusion of a protective effect is only tentative.

Besides, the patho-physiological pathways underlying these results are unclear.

In order to find a significant effect on stillbirth or perinatal mortality, a large population needs to be studied. Only Tita investigated a large group of women and found a small reduction in perinatal mortality and stillbirth which was borderline significant (8). Apart from chance playing a role in this study, the antenatal policy of serial urine culture and the reduction in premature labour may also have had an effect on the rate of perinatal mortality.

Two studies found opposite effects on stillbirth (2;5). Consanguinity may have played a role in the study which found an increased risk (2). Bittles (23) showed that consanguinity is responsible for 4,4% of deaths between 6 months of pregnancy and 10 years of age. The other studies did not take consanguinity into account. The effect may be particularly important in studies carried out in the Middle East where the incidence of consanguine marriages is relatively high (24).

HbP carrier status appears to offer a small protective effect on perinatal mortality. However the patho-physiological mechanism behind this remains unclear and in view of the methodological flaws, the results remain questionable.

No effect

1
2 No statistically significant difference was found for the risk of low birth weight (due to
3 prematurity or growth retardation). Two of the studies were carried out in developing
4 countries where both the health care standards can differ considerably and the population
5 may have different needs than those in developed countries (25). As both a poor nutritional
6 status and anaemia increase the risk of low birth weight (26), a difference based on HbP
7 status may not have been detected. On the basis of these studies, it cannot be concluded
8 that HbAS has any effect on the risk of low birth weight.
9

10 We found no increased risk of intra uterine growth retardation among women with a
11 positive carrier status for HbP.
12

13 Only Larrabee (17) found a significantly higher risk of both (pre-) eclampsia and
14 pregnancy induced hypertension in women who are a carrier of SCT. Other studies found
15 no significant differences (2;5;7;8;15). This could be due to methodological problems as
16 discussed earlier. None of the authors corrected for maternal weight in their study. We
17 conclude that the relation between HbP carrier status and the risk of (pre-) eclampsia or
18 pregnancy induced hypertension is inconclusive. Further studies are urgently needed to
19 shed light on this issue. Especially since hypertensive disorders in pregnancy are the
20 leading cause of maternal death in the Netherlands (27), rank fourth place in the United
21 Kingdom (28) and are the second direct cause of maternal death in the United States of
22 America (www.mchb.hrsa.gov). Moreover, a recent study carried out in the Netherlands
23 showed that non-Western immigrant women had a 1.3-fold increased risk of severe
24 maternal morbidity, including PIH, when compared with Western women (29).
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45 *Increased risk*
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2 The generally accepted claim that pregnant sickle cell carriers have a higher risk of UTI in
3 pregnancy (30;31) could not be substantiated in this review. Two of the three included
4 studies (2;5;15) failed to give a definition of UTI which may have led to classification bias.
5
6

7 Although we could not confirm an increased risk for UTI in the pregnancies of HbP
8 carriers, we did find an association between sickle cell trait and an increased risk of
9 bacteriuria in two studies (8;19). Treatment of asymptomatic bacteriuria reduces the risk of
10 pyelonephritis in pregnancy (32).
11
12

13 Surprisingly, only three studies were included which investigated the risk of anaemia
14 amongst pregnant women with an HbP-trait. It is generally accepted that a positive carrier
15 status for HbP can give rise to anaemia in pregnancy (32); however this has not been very
16 well investigated. Although the overall consensus seems to be that sickle cell trait is
17 asymptomatic and thalassaemia minor may cause mild microcytic or hypochromic anaemia
18 in the general population at risk (33) (www.thalassaemia.org.cy), this systematic review
19 shows that few investigators have adequately studied the effect of HbP carrier status on
20 anaemia in pregnancy. Small numbers in all three studies may be the reason that little or no
21 effect was found.
22
23

24 Despite the limited power, Landman (15) found that women with HbAS or β -thalassaemia
25 trait have a higher chance of having a combined iron and folate deficiency anaemia. This
26 study did not take confounders for anaemia into account, such as twin-pregnancy, poor
27 dietary habits or a low socio-economic status (SES) and the study was carried out amongst
28 a high risk population which may have included women that were already referred because
29 of an increased risk of anaemia.
30
31

32 Abdulsalaam (2) did not use anaemia as an outcome measure but instead used it as a risk
33 factor for the outcomes to be studied and subsequently found a significantly increased
34 percentage of women with HbAS that were anaemic. Whether this is due to iron and/or
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1
2 folate deficiency was not clarified in this study. It is possible that women who were sickle
3
4 cell carriers had in fact a combination of sickle cell trait and α -thalassaemia which was not
5
6 investigated. It is very likely that a higher risk of anaemia amongst HbP carriers is caused
7
8 by the (combined) effect of thalassaemias as these are known for ineffective erythropoiesis
9
10 which in pregnancy because of the increase in blood volume, could result in more
11
12 pronounced anaemia especially in the second trimester. Because of the disturbed Hb
13
14 synthesis in HbP carriers, it is very likely that extra folic acid is needed. This may very well
15
16 be the reason that most textbooks (30;31;34) recommend supplementing these pregnant
17
18 women with folic acid. However we found no study that investigated and confirmed this
19
20 theory.

21
22 Besides this, a recent study found that women of Non-Northern European descent had a
23
24 significantly increased risk of becoming anaemic in pregnancy (35). The researchers were
25
26 not able to identify the cause of this increased risk. In view of the evidence found in this
27
28 systematic review the increased risk could partly be explained by women who are a carrier
29
30 of HbP.

31 32 33 **Conclusion**

34
35 In conclusion, the findings of this study show that pregnant women who are HbP carriers
36
37 have a low risk of adverse outcomes of pregnancy. In expectation of further research on
38
39 this subject, midwives and obstetricians should be aware of the possibility of anaemia,
40
41 asymptomatic bacteriuria and the subsequent risk of pyelonephritis and investigate
42
43 pregnant women who are known HbP carriers more frequently for these conditions.

44
45 If carrier status of these women is known and anaemia is present, the cause of it should be
46
47 investigated further before any treatment is started. Each woman should be correctly
48
49 diagnosed and be offered partner testing if necessary so that she can make a well informed
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1
2 reproductive choice in order to avoid unexpected outcomes. It also remains important that
3
4 women with SCT or thalassaemia minor are given correct advice on how this will affect
5
6 their pregnancy and be reassured that it will not increase their risk of developing
7
8 complications during pregnancy or shortly thereafter. We found no reason at present to
9
10 refer pregnant women who are a carrier of HbP to a high risk setting.

11 This study highlights the lack of evidence of the effect of a positive HbP status on the
12
13 outcome of pregnancy and the need for large, well controlled prospective studies. With
14
15 routine investigations into HbP becoming more standard in many countries, it will become
16
17 easier to conduct further research to thoroughly investigate any possible effect that this may
18
19 have on pregnancy.
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23
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32
33

34 35 **Reference List**

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10. Table/Figure caption list:

Table 1: Inclusion criteria

Table 2: Quality assessment criteria

Table 3: Premature birth, Low birth weight, Small for gestational age / Intra uterine growth retardation

Table 4: Urinary tract infection, Anaemia in pregnancy

Table 5: Pregnancy induced hypertension / pre-eclampsia, Post natal mortality rate / still birth, Low apgar score

Fig.1: Flowchart of search

Table 1. Inclusion criteria

Inclusion criteria*Types of studies*

All observational (prospective and retrospective) cohort studies and case control studies examining the effect of sickle cell trait and/or thalassaemia minor on maternal morbidity and neonatal morbidity and mortality.

Types of participants

Pregnant women with singleton pregnancy.

Types of exposure

Sickle cell trait or heterozygous α - β -thalassaemia or homozygous α + thalassaemia versus no trait or no thalassaemia.

Sickle cell trait is defined as the presence of HbAS. Carrier ship of thalassaemia is defined as α + thalassaemia heterozygote; α 0-thalassaemia heterozygote; α + thalassaemia homozygote or β -thalassaemia heterozygote.

Types of outcome measures

Urinary tract infections

Iron deficiency anaemia

Folic acid deficiency anaemia

(Pre-) eclampsia

Gestational diabetes

Premature labour

Low birth weight

Intra uterine growth retardation

Spontaneous abortion

Fetal / neonatal death

Low Apgar score

Neural tube defects

Table 2. Quality assessment criteria

Quality assessment criteria
(The Dutch Institute for Healthcare Improvement (CBO) www.cbo.nl)
Each item scores 0 to 2 points:
- Were the groups that were compared clearly identified?
- Could selection bias be sufficiently excluded?
- Was the exposure factor clearly identified and was the method for assessing the exposure factor adequate?
- Was the outcome clearly identified and was the method for assessing the outcome adequate?
- Was the outcome assessed blinded for the exposure factor?
- Was the follow-up adequate?
- Could selective loss-to-follow-up be excluded?
- Were the most important confounders identified and was correction for the confounders carried out?

Table 3. Premature birth / Low Birth weight / IUGR

First Author Country Study design Publication year	N Population Setting	Definition of outcome	Exposure	Premature birth Point estimate (CI/P-value)	LBW Point Estimate (CI / P- value)	IUGR Point Estimate (CI / P- value)
Bryant (16) USA Retrospective cohort study 2007	5028 African American, non- Hispanic > 24 wks pregnant University hosp	< 37 weeks gestation EDD confirmed by US: unclear	SCT (326) vs none-SCT (4702)	AOR 0.76 (CI: 0.52 – 1.12)		
		< 37 wks Singleton gestations		AOR 0.85 (CI: 0.57 – 1.26)		
		< 32 wks		AOR 0.15 (CI: 0.05 – 0.49)		
		< 32 wks Singleton gestations		AOR 0.26 (CI: 0.08 – 0.84)		
Tita (8) USA Retrospective cohort study 2007	35743 African American >22 wks gestation University hospital	< 37 wks EDD confirmed by US: unclear	HbAS (3019) vs HbAA (32724)	AOR 0.8 (CI: 0.7 – 0.9)	AOR = 0.9 CI:0.8 – 1.1	AOR = 1.1 CI:0.9 – 1.2
Stamilio (7) USA Retrospective cohort study 2003	1996 Ethnicity mixed University hospital *Sub analysis on afro-American women: requested from author: no reply	< 37 wks EDD confirmed by US: unclear	SCT (87) vs none-SCT (1909)	(11% vs 11%) (p=0.89)	AOR = 0.5 CI:0.1 – 2.1	
Adeyemi (5) Nigeria Prospective cohort study 2006	420 African University hospital	< 2500 grm EDD confirmed by US: yes	HbAS (210) vs HbAA(210)		15.9% vs 17.8% p:0.5	HbAS 2.4% vs HbAA 1.9% p:0.99
Abdulsalaam (2) Syria Prospective cohort study 2003	500 Palestinian refugees Health clinics (primary care setting)	No definition given (author contacted; no reply)	HbAS (98) vs HbAA (402)		RR 1.1 CI:0.7 - 2	
Bail (19) USA Retrospective cohort study 1990	1828 No information on ethnicity given University hospital	Mean birth weight EDD confirmed by US: unclear	HbAS (914) vs HbAA (914)		3113 g (SD 640g) vs 3062 (SD 638g) n.s	
Tan (18) Uk Retrospective cohort study 2008	16825 All ethnicities University hospital African / Afro- Caribbean	< 10 th birth centile (Gardosi) EDD confirmed by US: yes	SCT (505) vs Control (no HbP) (16320)			OR = 1.0 (CI: 0.81 – 1.24) OR = 1.06 (CI: 0.84 – 1.33)
Landman (15) Netherlands Prospective	1662 Black Asians Mediterraneans	< 5 th birth centile: corrected for	HbAS (73) vs HbAA (83)			11.1% vs 2.4% (n.s)

cohort study 1988	2 University hospitals 2 Peripheral hospitals	sex, parity and gestational age EDD confirmed by US (author contact)	β-thal heterozygote (40) vs controls (160) α-thal trait (8)vs Asian controls (77) Homozygote α- thal.2 (8) vs Black controls (83)			10.0% vs 7.5% (n.s.) 12.5% vs 13.0% (n.s.) 12.5% vs 2.4% (n.s.)
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Table 4. Urinary Tract Infection / anaemia

First author Country Study design Year of publication	N Population Setting	Definition of outcome	Exposure	UTI Point Estimate (CI / P-value)	Anaemia Point Estimate (CI / P-value)
Adeyemi (5) Nigeria Prospective cohort study 2006	420 African University hospital	No definition given	HbAS (210) vs HbAA(210)	9(4.3) vs 9(4.3) p: 1.00	6(2.9%) vs 9(4.3%) (p: 0.61)
Abdulsalaam (2) Syria Prospective cohort study 2003	500 Palestinian refugees Health clinics (primary care setting)	No definition given	HbAS (98)vs HbAA(402)	RR = 1.03 (CI: 0.3 – 3.6)	7(7.1) vs 9(2.2) p: 0.022
Tita (8) USA Retrospective cohort study 2007	35743 African American Univ hosp	Bacteriuria: Positive urine culture at booking	HbAS (3019) vs HbAA (32724)	AOR = 1.4 (CI: 1.2 – 1.5)	
Bail (19) USA Retrospective cohort study 1990	1828 No information on ethnicity given University hospital	Bacteriuria: >100.000 / ml MSU	HbAS (914) vs HbAA (914)	OR 1.4 (p: 0.011)	
Landman (15) Netherlands Prospective cohort study 1988	1662 Blacks Asians Mediterraneans 2 University hospitals 2 Peripheral hospitals	Iron Deficiency Anaemia Hb < 110 g/l and Serum ferritine <15µg/l Or Hb<110g/l and low serum iron level and responsive to iron therapy Or Hb< 110g/l and reduction in MCV and responsive to iron therapy Combined folate and IDA	HbAS (73) vs HbAA (83) β-thal heterozygote (40) vs controls (160) α-thal trait (8) vs Asian controls (77) Homozygote α- thal.2 (8) vs Black controls (83) HbAS (73) vs HbAA (83) β-thal heterozygote (40) vs controls (160) α-thal trait (8) vs Asian	9,6% vs 7.2% (ns) 7,5% vs 9,4% (ns) - vs 11.7% 12,5% vs 7,2% (ns)	30,2% vs 54,2% (ns) 15% vs 53,8% (ns) 25,0% vs 53,2% (ns) 37,5% vs 54,2% (ns) 20,6 % vs 4,8 % (ns) 12,5 % vs 5,0% (p: <0.05) - vs 5,2% (ns)

			controls (77)		
			Homozygote α -thal.2 (8) vs Black controls (83)		25.0% vs 2.4% (ns)

Table 5. PIH (PE) / PNMR / Low apgar score

First author Country Study design Publication year	N Population Setting	Definition of outcome	Exposure	PIH (PE) Point estimate (CI / P-value)	PNMR Point Estimate (CI / P-value)	Low Apgar Score Point Estimate (CI / P-value)
Adeyemi (5) Nigeria Prospective cohort study 2006	420 African University hospital	PIH: No definition given Stillbirth: no definition given Low apgar: Apgar 1 min \leq 6 Apgar 5 min \leq 6	HbAS (210) vs HbAA (210)	8(3.8%) vs 6(2.9%) P: 0.81	2 (1.0%) vs 7 (3.3%) (p= 0.20)	Apgar 1: 11.7% vs 12.9% (p=0.04) Apgar 5: 0.9% vs 4.9% (p=0.04)
Tita (8) USA Retrospective cohort study 2007	35743 African American University hospital	PIH: According to NHBWP Working Group (systolic \geq 140 mmHg and /or diastolic \geq 90 mmHg on 2 occasions) PE: PIH and proteinuria \geq 300 mg/24 hrs	HbAS (3019) vs HbAA (32724)	AOR: 1.1 (CI: 0.9 – 1.2) AOR: 1.0 (CI: 0.8-1.2)	Stillbirths and neonatal deaths < 28 days post partum: AOR = 0.7 (CI 0.5 – 1.0) Stillbirths: AOR 0.6 (CI:0.3-0.9)	
Landman (15) Netherlands Prospective cohort study 1988	1662 Blacks Asians Mediterraneans 2 University hospitals 2 Peripheral hospitals	PIH: Increase in diastolic blood pressure of 20 mmHg or more as compared to the 1 st trimester values	HbAS (73) vs HbAA (83) β -thal heterozygote (40) vs controls (160) α -thal trait (8)vs Asian controls (77) Homozygote α - thal.2 (8)vs Black controls (83)	8.6% vs 9.6% (ns) 7.5% vs 10% (ns) 12.5% vs 10.4% (ns) 25.0% vs 9.6% (ns)		4.2% vs 2.4% (ns) 5.0% vs 0.6% (ns) - 12.5% vs 2.4% (ns)
Larrabee (17) USA Prospective cohort study 1997	1584 African American University hospital	PE: Hypertension (bloodpressure >140/90 mm Hg, or an increase of > 30/15 mm Hg from baseline) and proteinuria (>300 mg/24hrs. or > 100 mg/dl in 2 random specimens)	SCT (162) vs non-SCT (1422) Nullipara	RR 3.0 (CI 2.0 - 4.6) 33.3% vs 13.3% (p: 0.002)		
Abdulsalaam (2) Syria Prospective cohort	500 Palestinian refugees	PE: No definition given	HbAS (210) vs HbAA (210)	RR 1.4 (CI: 0.1 – 13)	RR 2.7 (CI:0.8 – 9.4)	

study 2003	Health clinics (Primary care setting)	PNMR: no definition given				
Stamilio (7) USA Retrospective cohort study 2003	1996 Ethnicity mixed University hospital *Subanalysis on afro-american women: author contacted but no reply	PE: Blood pressure of >140/90 mm Hg on 2 separate occasions, at least 6 hrs apart and proteinuria >300mg/24 hrs or 1+ to 2+ on serial quali exam.	SCT (87) vs none-SCT (1909)	AOR = 0,5 (CI: 0.2 – 1.6)		

For all tables:

SCT: Sickle cell trait

EDD: Expected date of delivery

US: Ultra sound

OR: Odds ratio

AOR: Adjusted odds ratio

RR: Relative risk

CI: Confidence interval

P: P-value significant if < 0.05

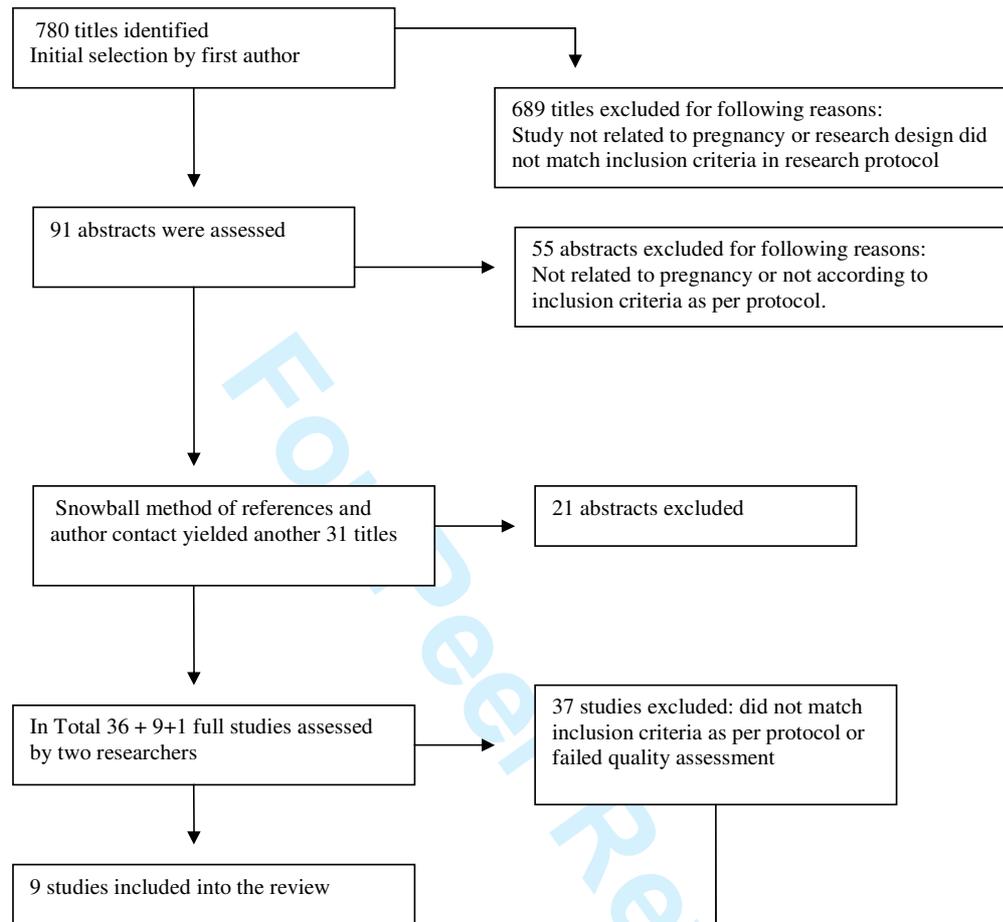
NS: not significant

PNM: Post natal mortality rate

PE: Pre-eclampsia

PIH: Pregnancy Induced Hypertension

MSU: Mid stream specimen of urine

Fig. 1 Flowchart of search

Taylor 2006 (4), Switzer (36), Whalley 1963 (9), Roopnarinesingh 1986 (3), Hoff 1983 (37), Lam 1999(38), Landman 1985 (39), Miller 1983 (40), Okunofua 1990 (41), Thurman 2006 (42), White 1985 (43), Lao 2001 (44), Abrahams 1959 (45), Balgir 1997 (46), Tuck 1983 (47), Whalley 1964 (48), Ssebabi 1977 (49), Roopnarinesingh 1986 (50), Rimer 1975 (51), Ibba 2003 (52), Hamdi 2002 (53), Cooley 1984 (54), Brown 1972 (55), Blattner 1977(56), Pearson 1969 (57), Pritchard 1973 (58), McCurdy 1964 (59), Morrison 1979(60), Pakes 1970 (61), Pastore 1999 (62), Whiteside 1973 (63), Pastore 1999(64), Hoff 2001 (65), Sheiner 2004 (66), Lewis 1982 (67), White 1986(68).