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EFFECT OF TREATMENT OF ANAEMIA IN PREGNANCY WITH ORAL HAEMATINICS ON PREGNANCY OUTCOMES AT KENYATTA NATIONAL HOSPITAL
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ABSTRACT

Objective: **To assess the effect of treatment of anaemia in pregnancy with oral haematinics on pregnancy outcome.**
Design: **Prospective cohort study.**
Setting: **Kenyatta National Hospital.**
Participants: **The exposed were pregnant women with haemoglobin (Hb) concentration of 6-10g/dl at 28-34 weeks of gestation recruited sequentially and the unexposed were pregnant women with Hb ≥11g/dl individually matched by age, parity and gestational age to the exposed.**
Interventions: **The exposed received Ranferon one capsule twice daily and the unexposed received one capsule once daily.**
Main outcome measures: **Haematological response, weight gain and body mass index (BMI) over the pregnancy period, estimated blood loss at delivery, participants' temperature 24 hours post-delivery and foetal outcome (birth weight and Apgar score).**
Results: **There were 69 exposed and 69 unexposed women available for analysis. After four weeks of treatment, 78.3% of the exposed had Hb ≥11g/dl. In addition, statistically significant differences in the mean increase in Hb concentration, mean corpuscular volume and mean corpuscular haemoglobin between the exposed and unexposed were observed (P <0.001, P = 0.005 and P = 0.005, respectively). Differences in weight gain, change in BMI, estimated blood loss at delivery, temperature 24 hours post-delivery and infants birth weight between the exposed and unexposed were not statistically significant. There was no difference in the Apgar score between the two arms.**

Conclusion: **Treatment of mild to moderate anaemia in the third trimester of pregnancy with oral haematinics results in outcomes similar to those in women without anaemia but on routine supplementation.**

INTRODUCTION

According to world health organisation (WHO), anaemia in pregnancy is present if the haemoglobin (Hb) concentration is less than 11g/dl or the haematocrit (Hct) equivalent of less than 33% in the peripheral blood (1). In developing countries, anaemia in pregnancy is an important public health problem. The WHO estimates that anaemia affects about two fifths of the non-pregnant and over half of pregnant women in developing countries (2). Iron deficiency, has been shown to be the main underlying cause of anaemia in pregnancy (2).

The choice of mode of treatment of anaemia in pregnancy depends on severity of anaemia, gestational age, and presence or absence of complicating factors. Treatment options include oral haematinics, parenteral iron or blood transfusion (3). The principle is to raise Hb level to as near normal as possible, especially before delivery.

Oral haematinics have for a long time been used for correction of iron deficiency anaemia in pregnancy. Whereas many studies have demonstrated untoward outcomes of anaemia on pregnancy (2, 4, 5) it is not well understood what impact the corrective measures have on maternal and foetal outcomes especially in cases of late diagnosis and intervention. This study sought to assess the effect of treatment of mild to moderate anaemia in the third trimester of pregnancy with oral haematinics on pregnancy outcomes.

MATERIALS AND METHODS

This was a prospective cohort study. The study was conducted at Kenyatta National Hospital (KNH). This is the national referral hospital and the main teaching hospital for the College of Health Sciences, University of Nairobi. The hospital caters for walk-in patients from Nairobi and its environs, as well as referrals from other hospitals in the country and East Africa. Women were recruited into the study on their first visit to the antenatal clinic (ANC). The exposed were pregnant women at 28 to 34 weeks of gestation (by dates and/or ultrasound), with mild to moderate anaemia as indicated by Hb level of 6g/dl to 10g/dl. The unexposed were women who were not anaemic (Hb >11g/dl), individually matched to the exposed by age (within five years), gestation (within two weeks) and parity (primigravida, multiparous and grand multiparous). The gestation 28 to 34 weeks was chosen because iron requirements increase notably during the second half of pregnancy, particularly after 28 weeks of gestation (6). Transfusion is not recommended unless anaemia is severe (7); at 34 weeks there is enough time to increase Hb level by 2g/dl to 4g/dl. All participants were walk-in pregnant women, booked at KNH ANC who planned to deliver at KNH, with singleton pregnancy, and with no medical, surgical or obstetric complications. Women with history of previous still birth or neonatal loss, birth weight of last baby less than 2,500 grams or more than 4,500 grams, diagnosed or suspected multiple pregnancy or history of vaginal bleeding in current pregnancy were excluded from the study.

The study was conducted from November 2009 to June 2010. One of the researchers and trained research assistants (two ANC nurses) were responsible for data collection. The nurse in charge of the ANC was requested to introduce the researcher or research assistants to women with anaemia diagnosed by measurement of Hb level. All

those with Hb of 6g/dl to 10g/dl, and qualify for the study were selected. A non-anaemic pregnant woman was then selected for each anaemic pregnant woman. Participants were recruited sequentially, this continued until a sample size of 162 was achieved. Potential participants were informed about the study, procedures and purpose of the study explained, and requested to fill a consent form. A questionnaire was then filled and two millilitres of venous blood was collected in an ethylenediaminetetra-acetic acid (EDTA) bottle for full haemogram (FHG) and peripheral blood film (PBF). Full haemogram was done using the cell-dyn machine and PBF stained with May Grunward Giemsa (MGG) stain. The blood sample taken was used solely for the purpose of an FHG and PBF and no other test was done. Haematological tests were done in the same laboratory. A haematologist reviewed the FHG and PBF to exclude obvious specific haematological conditions.

In order to ensure uniform treatment, all participants were given Ranferon. The exposed received one capsule of Ranferon twice daily (for treatment), whereas the unexposed received one capsule once daily (as routine supplementation). Ranferon is an oral haematinic containing: folate 0.75mg, ferrous fumarate 305mg (equivalent to elemental iron 100mg), cyanocobalamin 5mcg, ascorbic acid 75mg and zinc sulphate 5mg. The ideal would have been to have a reference group constituting of patients with anaemia and offer no treatment and compare with the restorative action of treatment, but this is ethically binding. Participants were weighed and their height measured at entry into the study and weighed every four weeks thereafter. An FHG and PBF were done four weeks to assess haematological changes. Participants were followed up during routine antenatal care. Stickers were placed on the files of study participants for easy identification. Results of FHG and PBF were availed in the participants' files for use in routine patient management. Follow up was done until 24 hours after delivery to assess outcome.

Data was collected using a structured interviewer-administered questionnaire. This covered: sociodemographic characteristics of study participants, obstetric history, haematological response, weight gain and body mass index (BMI) over the pregnancy period, gestation at delivery, estimated blood loss at delivery, participants' temperature 24 hours post-delivery and foetal outcome (birth weight and Apgar score at one and five minutes). All questionnaires were checked for errors or omissions; where possible, these were corrected. All identifiers were removed before analysis. Data processing and analysis were done using Epi info and IBM Statistical Package for the Social Sciences. Descriptive statistics were used to compute frequencies and percentages. Mean differences between the exposed and unexposed groups were used to determine the effect of treatment. Findings were considered statistically significant at a P-value <0.05 or a 95% confidence interval not including unity. Approval to conduct the study was obtained from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH-ERC/A/341).

RESULTS

A total of 162 women were enrolled into the study (81 exposed and 81 unexposed). Among the exposed, seven participants dropped out of the study when they declined the second venepuncture and medication, four were lost to follow up and one participant was diagnosed with sickle cell disease and was referred to the haematologist. An equal number of the exposed and unexposed were dropped out of the study. A total of 138 women, 69

exposed and 69 unexposed, were available for analysis. The sociodemographic and obstetric characteristics of participants in the two arms were comparable (Table 1)

Table 1

Socio-demographic and obstetric characteristics of study participants

	Exposed ***(n = 69)***		**Unexposed** ***(n = 69)***		**P-value**
	No.	*(%)*	*No.*	*(%)*	
Socio-demographic characteristics					
Age in years					
≤20	4	(5.8)	5	(7.2)	
21-25	20	(29.0)	21	(30.4)	
26-30	32	(46.4)	25	(36.2)	0.624
31-35	11	(15.9)	17	(24.6)	
>35	2	(2.9)	1	(1.4)	
Marital status					
Married	54	(78.3)	59	(85.5)	0.269
Single	15	(21.7)	10	(14.5)	
Education					
None	-	-	1	(1.4)	
Primary	14	(20.3)	5	(7.2)	0.120
Secondary	20	(29.0)	22	(31.9)	
Post-secondary	35	(50.7)	41	(59.4)	
Occupation					
Unemployed	21	(30.4)	22	(31.9)	
Self employed	24	(34.8)	21	(30.4)	0.889
Gainful employment	24	(34.8)	25	(36.2)	
Obstetric characteristics					
Parity					
0	29	(42.0)	30	(43.5)	0.863
1-4	40	(58.0)	39	(56.5)	
Gestation in weeks					
<32	43	(62.3)	35	(50.7)	0.170
≥32	26	(37.7)	34	(49.3)	

Haematological Response: Among the exposed, 54 had mild anaemia and 15 had moderate anaemia at recruitment (26 out of 35 and 28 out of 34 for gestation at recruitment <32 weeks and ≥32 weeks, respectively). A majority of anaemic mothers (78.3%) had achieved a normal Hb level (Hb ≥11g/dl) by end of four weeks of treatment. This consisted of 83% of participants with mild anaemia, and 63% of those with moderate anaemia at enrolment. Only two patients in the exposed arm had a repeat FHG and PBF at eight weeks from admission to the study, therefore, this was not included in data analysis.

Table 2

Mean increase in haematological parameters in four weeks from admission to the study and mean rate of change of haematological parameters per week

Parameter	Exposed		Unexposed		Difference			
	Mean	*(SD)*	*Mean*	*(SD)*	*Mean*	*95% CI*		*P-value*
						Lower	*Upper*	
Mean increase in 4 weeks								
Hb (g/dl)	3.3	(1.7)	1.2	(1.4)	-2.18	-2.85	-1.57	<0.001
Hct (%)	4.6	(15.3)	1.5	(19.6)	-3.0	-4.5	10.5	0.425
MCV (fl)	6.6	(12.5)	0.08	(6.8)	-6.5	-11.1	-2.0	0.005
MCH (pg)	3.1	(4.9)	1.9	(10.9)	-5.0	-8.5	-1.5	0.005
MCHC (g/dl)	0.61	(4.7)	0.005	(2.8)	-0.6	-2.3	1.2	0.522
Mean rate of change per week								
Hb (g/dl)	0.84	(0.32)	0.29	(0.31)	-0.6	-0.7	-4.2	<0.001
Hct (%)	1.3	(3.6)	0.6	(4.0)	-0.7	-2.1	0.7	0.325
MCV (fl)	2.2	(3.4)	0.2	(1.8)	-2.0	-3.0	-1.0	<0.001
MCH (pg)	1.0	(1.4)	-0.3	(2.3)	-1.2	-2.0	-0.6	<0.001
MCHC (g/dl)	0.2	(1.1)	0.07	(0.7)	-0.16	0.5	0.2	0.352

SD: standard deviation; CI: confidence interval; Hb: haemoglobin; Hct: haematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration.

As presented in Table 2, the mean increase in Hb concentration was 3.3g/dl for the exposed and 1.2g/dl for the unexposed, a difference that was statistically significant (P <0.001). Increases in mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were also statistically significantly higher among the exposed than the unexposed (P <0.05 in both instances). Although the mean increases in mean corpuscular haemoglobin concentration (MCHC) and Hct were higher among the unexposed, these differences were not statistically significant.

Similarly, there were statistically significant differences in the mean rate of change per week of Hb concentration, MCV and MCH between the exposed and unexposed (P <0.001 in all instances), whereas non-statistically significant higher increase in the exposed compared to the unexposed were observed for Hct and MCHC.

Maternal Response: Among women enrolled at a gestation <32 weeks, statistically significant differences in mean weight gain and BMI change between the exposed and unexposed were observed (1.5kg compared to 1.96kg; P = 0.023 and 0.59kg/m^2 compared to 0.79kg/m^2; P = 0.015). Although there were differences in the weight gain and BMI change between the exposed and unexposed among those enrolled at a gestation ≥32 weeks, the differences were not statistically significant. These findings are presented in Table 3.

Table 3

Mean maternal weight gain and BMI change in four weeks from admission to the study in relation to gestation at admission to the study

Parameter	Gestation at recruitment	Exposed		Unexposed		Difference			
		Mean	*(SD)*	*Mean*	*(SD)*	*Mean difference*	*95% CI Lower*	*Upper*	*P-value*
Weight gain (in Kg)	<32 weeks	1.50	(0.88)	1.96	(1.04)	0.45	0.06	0.84	0.023
	≥32 weeks	1.95	(0.73)	1.50	(0.27)	-0.45	-0.97	0.06	0.115
BMI change(in Kg/m^2)	<32 weeks	0.59	(0.35)	0.79	(0.45)	0.2	0.04	0.4	0.015
	≥32 weeks	0.76	(0.26)	0.58	(0.12)	-0.18	-0.4	0.03	0.085

SD: standard deviation; CI: confidence interval.

Overall, the mean differences in weight gain and BMI change between the exposed and unexposed at four weeks from recruitment were not statistically significant (1.6kg compared to 1.7kg; P = 0.319 and 0.63kg/m^2 compared to 0.77kg/m^2; P = 0.052, respectively). Non-statistically significant mean differences in estimated blood loss and temperature 24 hours after delivery between the exposed and unexposed were also observed (235.9mls compared to 216.4mls; P = 0.131 and 36.6^{0}C compared to 36.5^{0}C; P = 0.461, respectively).

In analyses restricted to the exposed, the mean weight and BMI increase at four weeks from admission to the study by degree of anaemia at recruitment was assessed. Non-statistically significant differences were observed; the mean weight gain was 1.4kg among those with moderate anaemia compared to 1.6kg among those with mild anaemia (P = 0.753), whereas the BMI change was 0.55kg/m^2 and 0.65kg/m^2 respectively (P = 0.488).

Foetal Response: There was a mean birthweight difference of 48 grams between babies born by mothers in the exposed and unexposed arms, which was not statistically significant (3,188 grams compared to 3,236 grams; P = 0.525). The average gestation at delivery was 39.2 weeks in both arms (P= 0.302).

The Apgar scores at one and five minutes were similar in both arms of the study. Four participants in each arm had babies with poor Apgar scores (≤6) at one minute, whereas the remaining 64 in the exposed arm and 65 in the unexposed arm had good Apgar scores (≥7) at one minute (Table 4). Only one baby in the exposed arm had poor Apgar score at five minutes.

Table 4

Apgar score at one minute by gestation at admission to the study

Apgar score	Gestation at admission	Exposed (n = 69)		Unexposed (n = 69)		P-value
Poor (≤6)	<32 weeks *(n = 3)*	3	(100%)	-	-	0.143
	≥32 weeks *(n = 5)*	1	(20.0%)	4	(80.0%)	
Good (≥7)	<32 weeks *(n = 75)*	32	(42.7%)	43	(57.3%)	0.075
	≥32 weeks *(n = 55)*	32	(59.3%)	22	(40.7%)	

The gestation at recruitment into the study did not have any association with the one (Table 4) and five minutes Apgar scores. Similarly, no relationship was observed between Apgar score and degree of anaemia at recruitment (data not shown). Differences in the one- and five-minutes Apgar scores between babies born to mothers who had mild anaemia and those who had moderate anaemia at enrolment were not statistically significant: only three babies born to mothers with mild anaemia had a poor Apgar score at one minute. All participants had good Apgar scores at five minutes.

Relationship between maternal response and foetal outcomes:

Among the exposed, after four weeks of treatment, mothers who had an Hb ≥11g/dl delivered babies with non-statistically significant higher birth weight compared to those who were still anaemic (Table 5). All the babies weighed had a birth weight of ≥2.5kg irrespective of the amount of maternal weight gain (data not shown).

Table 5

Birth weight in relation to degree of anaemia at enrolment and haemoglobin level at four weeks from admission to the study

Degree of anaemia at admission to the study	**Hb level after four weeks**	**Birth Weight**		
		Mean	*(SD)*	*P-value*
Mild anaemia (8-10g/dl)	≥11g/dl *(n =38)*	3442	(423.7)	0.2694
	<11g/dl *(n = 7)*	3264.5	(381.5)	
Moderate anaemia (6-7.9g/dl)	≥11g/dl *(n =8)*	3087.5	(215.1)	0.162
	<11g/dl *(n = 4)*	2575	(960.5)	

DISCUSSION

In this prospective cohort study, treatment of anaemia with oral haematinics effectively raised the Hb level; a majority of anaemic mothers (78.3%) had achieved a normal Hb level by end of four weeks of treatment. This supports the use of oral haematinics in the treatment of mild to moderate anaemia in the third trimester of pregnancy. The mean increase in Hb of 0.84g/dl per week, for anaemic pregnant women on treatment, falls within the rate of increase in a patient responsive to treatment (8). An increase in haematological indices of pregnant women with normal Hb levels and on routine supplementation shows that prophylactic iron supplementation not only prevents a fall, but also improves Hb levels during pregnancy.

Overall, the unexposed had statistically non-significant higher increase in weight and BMI. Low weight before and after pregnancy has been reported in anaemic women (9). The impact of anaemia is to decrease oxygen delivery (10), hence substrate utilisation, which would be expected to have negative impact on both the mother and the foetus. In this study, with correction of anaemia, the anaemic pregnant women were able to gain weight but not as much as the unexposed. This can be attributed to adjustment from a relatively hypoxic state, such that there is haemoglobin increase which improves oxygen delivery to tissues but no reflection in weight change. Whereas the follow up period was short, with a longer follow up period, a significant weight gain might have been demonstrated.

There were no statistically significant differences in estimated blood loss at delivery and temperature 24 hours post-delivery between the exposed and

unexposed. Anaemic pregnant women are at a higher risk of postpartum haemorrhage and puerperal sepsis (11). With correction of anaemia, there is increased oxygen supply to the tissues (10), including the uterus, therefore preventing uterine atony, and an overall improvement in the immune status (11). Correction of anaemia appears therefore to reduce the risk of infection which is prevalent in women delivering with uncorrected anaemia. Majority of mothers had normal Hb level after four weeks of treatment therefore they were not anaemic at the time of delivery.

The foetal outcomes were comparable. Neonates born to anaemic mothers have a higher incidence of low birth weight (2, 11). In this study, however, the timing of correction of anaemia seems to have allowed adequate time for growth of the foetus. Apgar score may not have had much difference because multiple factors in the antepartum and intrapartum period affect the Apgar score (12).

The strengths of this study are that study participants received uniform treatment or prophylaxis of anaemia, haematological tests were done in the same laboratory, and all FHGs and PBFs were reviewed by the same haematologist. In addition, this is one of a few studies assessing pregnancy outcomes following treatment of anaemia in pregnancy. However, potential limitations need to be considered. First, the study was done in KNH, which is a referral hospital; therefore, this might have introduced selection bias. To mitigate this, the study participants were walk-in patients (not referrals) with no medical, surgical or obstetric complications. Second, estimation of blood loss at delivery was subjective rather than objective; however, this was not differential between the exposed and unexposed and may, therefore, not have had much impact on the findings. Third, participants were at an advanced gestation therefore we cannot rule out use of haematinics prior to enrolment to correct anaemia; this might have contributed to the null findings particularly if the unexposed had been anaemic in early pregnancy. In addition, due to logistical constraints, there was no way of verifying that participants took the oral haematinics as prescribed.

CONCLUSION

From the findings of this study, it can be said that oral haematinics are effective in the treatment of mild to moderate anaemia in the third trimester of pregnancy. In addition, correction of mild to moderate anaemia in pregnancy with oral haematinics results in maternal and foetal outcomes similar to those in women without anaemia in pregnancy. There is need for further research to establish the effects of treatment of anaemia on early pregnancy (first and second trimester), post-delivery and the neonatal period.

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