DISSERTATION

TITLE: EFFECT OF TREATMENT OF ANAEMIA IN PREGNANCY WITH ORAL HAEMATINICS ON PREGNANCY OUTCOMES AT KENYATTA NATIONAL HOSPITAL.

PURPOSE: DISSERTATION FOR PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY, UNIVERSITY OF NAIROBI.

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DEDICATION

This dissertation is dedicated to my parents, Isaac and Aloysia Chesang.

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LIST OF ABBREVIATIONS

ANC – Antenatal clinic

BMI- Body mass index

EDTA- Ethylenediaminetetra-acetic acid

FHG- Full haemogram

HB – Haemoglobin

HCT- Haematocrit

IDA-Iron deficiency anaemia

IUGR-Intrauterine growth restriction

KNH- Kenyatta National Hospital

LBW- Low birth weight

LMP- Last menstrual period

MCV-Mean corpuscular volume

MCH-Mean corpuscular haemoglobin

MCHC-Mean corpuscular haemoglobin concentration

MGG-May Grunward Giemsa

PBF-Peripheral blood film

PET- Pre-eclamptic toxaemia

PPH-Post partum haemorrhage

RBC-Red blood cells

RCT-Randomized control trial

SPSS-Statistical package for social sciences

WBC-White blood cells

WHO-World Health Organisation

ABSTRACT

Background: Anaemia in pregnancy continues to be a major health problem in most developing countries, with significant adverse effects for both mother and infant. Iron deficiency is the main underlying cause for anaemia in pregnancy followed by folate deficiency. Anaemia has previously been shown to be associated with adverse pregnancy outcomes. What has not been clearly demonstrated is the effect of treatment of anaemia in pregnancy with haematinics on pregnancy outcome.

Objective: To determine the effect of treatment of anaemia in pregnancy with oral haematinics on pregnancy outcome.

Setting: Antenatal clinic, labour ward and antenatal/ postnatal wards at the Kenyatta National Hospital.

Study design: Prospective cohort study.

Methods: Patients were recruited sequentially until the desired sample size was reached. The exposed were pregnant women with anaemia and the unexposed were non-anaemic pregnant women matched for age, parity and gestational age with the exposed. The anaemic pregnant women received Ranferon one capsule twice daily (for treatment) and the non-anaemic pregnant women received Ranferon one capsule once daily in the third trimester (as routine supplementation). A full haemogram and peripheral blood film was done once every four weeks. Both groups were followed until delivery to assess outcome.

Results: Of the 138 participants, 69 were the exposed and 69 unexposed. Among the exposed, 54 had mild anaemia while 15 had moderate anaemia at recruitment. The mean increase in haemoglobin (Hb) concentration in 4 weeks was 3.3g/dl for the exposed and 1.2g/dl for the unexposed, the difference was highly significant ($P<0.001$). There was also significant change in the MCV ($P=0.005$) and MCH ($P=0.005$), but no significant change in MCHC ($P=0.522$) and Hct ($P=0.425$).The BMI change was minimally less among the exposed than among the unexposed (0.63Kg/m^2 and 0.77 Kg/m^2 respectively). No significant statistical difference in weight gain, BMI change, estimated blood loss at delivery and temperature at 24 hours post delivery was noted between the exposed and unexposed. There was a birth weight difference of 48 grams between the exposed and unexposed, which was not statistically significant ($P=0.525$). No difference in the 1 and 5

minutes Apgar score was noted between the exposed and unexposed. A positive weak correlation between the birth weight and maternal BMI change was noted in the exposed and the unexposed arms. Similarly mothers who had a Hb level of ≥11g/dl after 4 weeks of treatment delivered babies with a higher birth weight compared to mothers who were still anaemic. However, a negative weak correlation was found between Hb change and birthweight, and Hb change and the Apgar score in the exposed and unexposed arms.

Conclusion: Treatment of mild to moderate anaemia in pregnancy in the third trimester with oral haematinics results in outcomes similar to those in women without anaemia but on routine supplementation in terms of haematological, maternal and foetal outcomes.

Recommendation: Anaemia should be aggressively treated with high dose haematinics. Routine supplementation with oral haematinics of all pregnant women should be encouraged.

INTRODUCTION

Anaemia is characterized by a blood haemoglobin concentration lower than the expected reference range for a particular age, gender and physiological state. According to the standard laid down by the WHO, anaemia in pregnancy is present when the haemoglobin concentration is less than11g/100mls or the haematocrit equivalent of less than 33% in the peripheral blood[1]. Anaemia is by far the most common pregnancy complication worldwide. According to WHO estimates, it affects 2/5 of the non-pregnant and over half of all pregnant women in developing countries.

During pregnancy there is disproportionate increase in plasma and red blood cells volume. The red cell mass increases by about 33% and there is 50% elevation in the plasma volume both of which begin early in the first trimester. The greater increase in plasma volume is responsible for the physiological anaemia of pregnancy[2]. In addition, there is marked demand of extra iron, as well as folate, especially in the second half of pregnancy due to overall expansion of red cell mass and rapid growth of fetus. Negative iron balance throughout pregnancy, particularly in the later half, may lead to iron deficiency anaemia during the third trimester. Routine iron and folate supplementation is necessary to cover for the increased demand. [3]

Almost all iron needs occur during the second half of pregnancy,[2] when foetal organ formation occurs. Iron requirements are not as great in the first trimester because of the lack of menstruation and limited foetal needs. During the second trimester, iron requirements begin to increase and continue to do so throughout the remainder of pregnancy. The increase in oxygen consumption by both mother and foetus is related with major haematological changes. As pregnancy progresses, iron requirements for foetal growth rises steadily in proportion to the weight of the foetus, with most of the iron accumulating during the third trimester. Among pregnant women who do not take iron supplementation, haemoglobin concentration and haematocrit remain low in the third trimester and among pregnant women who have adequate iron intake, Hb concentration and Hct steadily rise during the third trimester toward the pre-pregnancy level.[3]

Maternal iron depletion is associated with reduced fetal iron stores but no change in free iron availability.[4] Fetal demand for iron results in a unidirectional flow of iron to the fetus against a concentration gradient regulated by fetal requirements for iron; this iron transfers occur almost entirely irrespective of maternal iron status. Therefore, the fetus is not anaemic even when the mother is severely iron deficient. However, as there is little or no reserve iron, anaemia develops in neonatal periods.

Anaemia is the commonest hematological disorder that occurs during pregnancy. Anaemia in pregnancy most commonly results from a nutritional deficiency in either iron or folate. On the other hand, pernicious anaemia due vitamin B12 deficiency almost never occurs during pregnancy.[3] Iron deficiency is the most common cause of anaemia in pregnancy, reflecting the increased demands of iron. The development of anaemia during pregnancy may be detected by monitoring the haemoglobin concentration frequently.

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

Previous studies have indicated anaemia has adverse effects on pregnancy outcomes. Information is lacking on the impact of correcting anaemia in pregnancy with haematinics on pregnancy outcomes. This study seeks to determine the effect of correcting anaemia with haematinics, on different pregnancy outcomes in relation to degree of anaemia, gestation at diagnosis, duration of treatment and response to treatment. Delivery of anaemic women is precarious as anaemic women may not tolerate even very little blood loss, hence, a need to manage anaemia early.

LITERATURE REVIEW

In developing countries, anaemia in pregnancy is an important public health problem. According to WHO anaemia in pregnancy is present if Hb is below 11g/dl.[1] WHO further grades anaemia as mild of Hb 8-11g/dl, moderate of Hb 6-8g/dl and severe anaemia of Hb less than 6g/dl. Anaemia is responsible for 20% of maternal deaths in third world countries. Micronutrients deficiency and especially iron deficiency has been shown to be the main underlying cause of anaemia in pregnancy.

The mechanism by which anaemia develops in pregnancy is well understood. Haemodilution causes a fall in the haemoglobin concentration during the first and second trimesters of normal pregnancies and is responsible for the physiological anaemia of pregnancy.[2] In addition, there is marked demand of extra iron especially in the second half of pregnancy. Iron requirements may not be increased significantly during the first half of pregnancy and iron that is absorbed from food (approximately 1mg per day) is sufficient to cover the basal loss of 1mg/day. However, in the second half of pregnancy, iron requirements increase due to overall expansion of red cell mass and rapid growth of the fetus. Iron requirements can reach 6 to 7mg per day in the third trimester of pregnancy. The increase in the absolute number of red blood cells and the resultant greater haemoglobin mass require 500mg of iron. Total iron needs of the fetus average 300mg.

Iron and folate supplementation is necessary to cover for the increased demand. During the second half of pregnancy and the puerperium, at least 60mg of elemental iron and 40micrograms of folate should be given daily to prevent anaemia.[3] Routine iron supplementation to all women in the second half of pregnancy should be advocated in order to reach all women without the difficulties associated with assessment of iron status. The Ministry of Health, Kenya recommends routine supplementation with ferrous sulphate or ferrous fumarate 200mg and Folic acid 5mg by mouth once daily for six months during pregnancy.[5]

Compared with placebo, iron supplementation from enrollment to 28 weeks of gestation does not significantly affect the overall prevalence of anaemia or the incidence of preterm births but leads to a significantly higher birth weight, a significantly lower incidence of LBW infants and preterm LBW infants.[6] Prophylactic iron supplementation not only prevents a fall but also improves Hb levels during pregnancy.[7] This is supported by a study in which iron and folate supplementation resulted in a substantial reduction of women with a Hb level below 10.5g/dl in late pregnancy but, had no detectable effect on any substantive measures of either maternal or fetal outcome.[8]

In another study, 60mg/day of elemental iron was found to help prevent IDA in both adolescent and adult pregnancies. However, there was no evidence of maternal or neonatal health benefits from correction of these deficits.[9]

The frequency and severity of complications resulting from anaemia have been reported, in many studies, to be proportional to the severity of anaemia. These includes: abortion, prematurity, IUGR, LBW, intrauterine death and possible inferior neonatal health for the fetus. The anaemic mother is at increased risk of PET, intercurrent infection, preterm labour, abruptio placentae, PPH, puerperal venous thrombosis and in severe cases shock and heart failure.[10 11 12]

In a 2 year retrospective survey of maternal and fetal prognosis in anaemia of pregnancy at KNH, maternal complications including: urinary tract infection, congestive cardiac failure, obstetric haemorrhage, bronchopneumonia, pyrexia of unknown origin, puerperal infection, post partum haemorrhage and deep venous thrombosis, occurred more frequently in the anaemic than in the control cases. Maternal and perinatal mortality rates, abortion rate and incidence of LBW delivery were significantly greater in the anaemic than in the control group.[13]

Anaemic mothers have a significantly low pre- and post-pregnancy weight, a significantly decreased maternal fundal height and abdominal circumference; while,

neonates born to severely anaemic mothers show a significant reduction in ponderal index, birth weight and placental weight.[14]

In a retrospective study of anaemia in pregnancy and its outcome, the birth weight, low Apgar score at the time of birth, prevalence of preterm delivery and IUFD were more common in anaemic group than in non anaemic group.[15] Maternal iron depletion is associated with reduced fetal iron stores but no change in free iron availability [16]

In some cases, anaemic mothers do not recover adequate iron status at six months postpartum, with implications for future iron demands. In addition, infants born of mothers with anaemia in pregnancy appear to be at increased risk of developing iron deficiency anaemia, undetected at birth.[16]

Treatment of anaemia in pregnancy can be achieved by use of oral haematinics, parenteral iron or blood transfusion. For oral treatment, 60mg of elemental iron three times daily and 4mg of folic acid once daily is administered till the Hb level is normal. A change in Hb should be evident within 3 weeks of onset of treatment. In instances where there is intolerance to oral iron therapy or severe anaemia in advanced pregnancy, parenteral iron is preferred. Blood transfusion may be necessary in those seen in later months of pregnancy (beyond 36 weeks).[3]

In a study done in India, parenteral iron did not alleviate moderate gestational anaemia any better than did enteral administration. Given the former's higher cost and more toxic risk, enteral iron is better in the treatment of moderate anaemia.[17]

Treatment of anaemia in pregnancy is best achieved by use of both folate and iron. In a randomized double blind clinical trial, combined iron and folate produced a better therapeutic response than iron alone; there was a significant difference in the increase in haemoglobin levels from baseline between women treated with both compounds and those given iron only.[18]

The prevalence of anaemia varies widely from country to country and from region to region and sometimes in the same country. This has been shown to be the case in Kenya with a study done in Kakamega Provincial General Hospital finding a prevalence of 18.1% amongst women attending the ANC and one done in a Health centre in Nairobi finding a prevalence of 10%.[19] [20] The higher prevalence of anaemia in Kakamega Provincial General Hospital as compared to Nairobi can be attributed to the prevalence of sickle cell disease and malaria in the region. In KNH, the incidence of anaemia among women was found to be 4.3% and 5.3% in two studies done in 1981.[13] [21] The average number of patients seen at the KNH ANC (first visit) in the last two years (2007, 2008) is 6,353 per year, as obtained from the KNH ANC records office.

Anaemia in pregnancy can be mild, moderate or severe and women are offered treatments according to their level of anaemia and the possible cause. The most common cause of anaemia in pregnancy is due to iron shortage. Severe anaemia can have very serious consequences for mothers and babies. The increased iron requirement in pregnancy and the puerperium carry with it an increased susceptibility to iron deficiency and iron deficiency anaemia and perioperative or peripartal blood transfusion. It is with this kind of a background that this study was designed in order to determine the outcomes of remedial actions in terms of haematological response and overall pregnancy outcome.

RATIONALE

Anaemia is a major cause of maternal morbidity and mortality in Kenya and indeed globally. The impact of anaemia is to decrease oxygen delivery, hence substrate utilization, which would be expected to have negative impact on both the mother and the fetus. Many women enter pregnancy in an anaemic state.

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, it is not well understood what impact the corrective measures have on maternal and fetal outcomes especially in cases of late diagnosis and intervention.

There are not many studies which have focused on the impact of treatment in relation to haematological and clinical outcomes. It is therefore necessary to conduct such a study that would examine the impact of treatment in terms of outcomes both haematological and clinical and how they relate to one another. This study seeks to assess the different outcomes in relation to degree of anaemia, gestation at diagnosis and duration of treatment. Of essence is the foetal outcome. Positive outcome will further add credence to a need to correct anaemia during pregnancy and may reveal further gaps in our knowledge of the correlation between correction of anaemia and pregnancy outcomes.

RESEARCH QUESTION

Does treatment of mild to moderate anaemia in pregnancy with oral haematinics result in similar pregnancy outcomes as in women on routine supplementation?

HYPOTHESIS

Null hypothesis

Treatment of mild to moderate anaemia in pregnancy with oral haematinics does not improve pregnancy outcomes.

Alternative hypothesis

Treatment outcomes of mild to moderate anaemia in pregnancy with oral haematinics results in outcomes similar to those in women without anaemia during pregnancy but on routine supplementation.

OBJECTIVES

Broad objectives

To determine the effect of treatment of mild to moderate anaemia in pregnancy with oral haematinics on pregnancy outcomes.

Specific objectives

1) To determine the level of haematological response.
2) To determine maternal response.
3) To determine fetal outcomes.
4) To determine the relationship between maternal response to haematinics and fetal outcomes.

METHODOLOGY

Study site

The study was conducted at Kenyatta National Hospital. This is the national referral hospital and the main teaching hospital for the College of Health Sciences, University of Nairobi. It is situated in Nairobi, Kenya, 4 kilometers west of the central business district. The hospital caters for patients from Nairobi and its environs as well as referrals from other hospitals in the country and Eastern Africa.

The study was carried out in the antenatal clinic (clinic 18), the 3 antenatal/postnatal wards (GF A, GF B and 1A) and the labour ward. The antenatal clinic caters for walk-in patients as well as referrals from other hospitals. Enrollment into the clinic mainly takes place on Mondays, but some clients are also enrolled on Tuesdays, Wednesdays and Thursdays. On the first visit to the clinic, the patient pays a deposit which caters for antenatal profiles (which includes haemoglobin level) and part of delivery costs. As patients wait to be seen by the doctor, counseling is done on diet, danger signs in pregnancy and birth preparedness. Subsequent visits are scheduled according to individual needs of the patients. In case of need for admission, patients in pregnancy above 20 weeks gestation and those who are in immediate puerperium are admitted in the antenatal/postnatal wards. Patients in labour or with a condition requiring close monitoring are admitted in labour ward.

The study area was appropriate for the study due to the presence of a well organized antenatal clinic making the recruitment and follow up of study subjects easy. The hospital has a well equipped laboratory able to carry out haematological studies necessary in diagnosis and follow up of patients. In addition, the labour ward is run by qualified midwives, paediatrics and obstetrics registrars who ensure that deliveries are well supervised and there is proper and complete record keeping.

Study population

The study population consisted of women with mild to moderate anaemia as indicated by Hb of between 6g/dl and 10g/dl inclusive, on their first visit to the clinic. At entry of study the patients were at gestation between 28 and 34 weeks inclusive. These limits of gestation provided ample time for measurable effect of corrective intervention of anaemia.

The unexposed arm consisted of women who were not anaemic and who were at the same gestation at entry into the study. The haemoglobin at entry among the unexposed was more than 11g/dl. The unexposed group formed the baseline of outcomes as expected in women who are not anaemic and on supplementation (as opposed to those on treatment for anaemia). The unexposed were matched for gestation (+/- 2 weeks), age (within 5 years) and parity (primigravida, multiparous and grand multiparous).

Pregnant women have increased risk of developing iron deficiency because of the extra iron required by the growing fetus, the placenta and the increased red blood cell mass. Iron requirements increase notably during the second half of pregnancy and particularly after 28 weeks of gestation when the fetal growth is exponential. Therefore, supplementation ensures normal haemoglobin level throughout pregnancy and at delivery, which presumably provides an environment for optimal pregnancy outcome.

28 weeks corresponds to the beginning of exponential growth of the fetus, a period when the demand on oxidative process is high, which tapers at 36 weeks. Transfusion is not recommended unless anemia is severe; at 34 weeks there is enough time to increase Hb level by 2g/dl to 4g/dl.

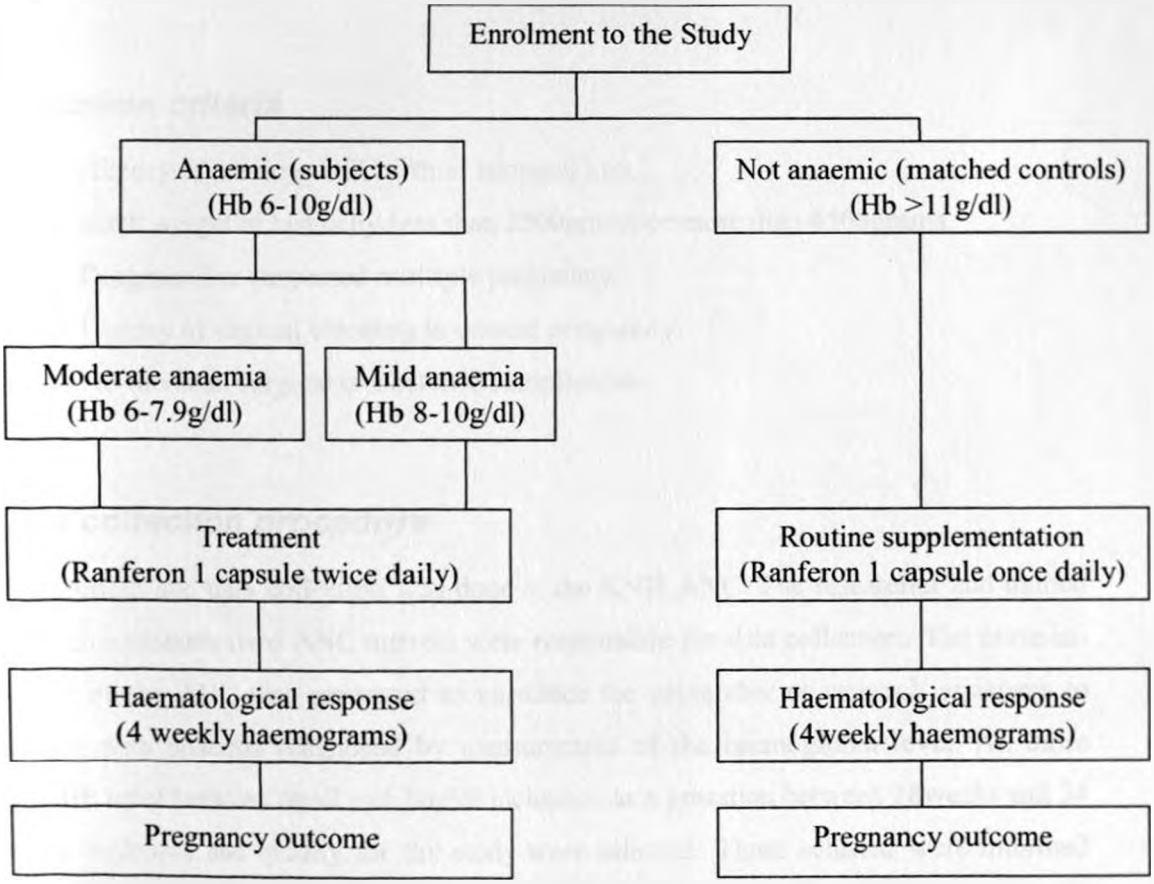
Study design

This was a prospective cohort study consisting of two groups of patients, the unexposed being non-anaemic patients on routine supplementation as a prophylaxis for anaemia and study population consisting of anaemic patients on corrective therapeutic measures. The

two groups were matched for age (within 5 years), parity (primigravida, multiparous and grand multiparous) and gestational age (+/- 2 weeks). Both groups were followed up until delivery to assess outcomes.

This study design was suitable for this particular study because the unexposed constitute the baseline of what can be assumed to be the expected outcome in normal circumstances. The ideal would have been to have controls constituting of patients with anaemia and offer no treatment and compare with the restorative action of treatment, but this is ethically binding.

Diagrammatic representation of the overall study design.



Study duration

The study was carried out from November 2009 to June 2010.

Inclusion criteria

1) Pregnant women booked at KNH ANC.
2) The exposed had anaemia, with an Hb between 6g/dl and 10g/dl; unexposed with a normal Hb level defined as more than 11g/dl.
3) Were at gestation of 28 to 34 weeks by LMP and /or ultrasound.
4) Singleton pregnancy.
5) Planned to deliver in KNH.
6) Those who consented to the study.

Exclusion criteria

1) History of previous still birth or neonatal loss.
2) Birth weight of last baby less than 2500grams or more than 4500grams.
3) Diagnosed or suspected multiple pregnancy.
4) History of vaginal bleeding in current pregnancy.
5) No medical, surgical or obstetric complication.

Data collection procedure

Recruitment and data collection was done at the KNH ANC. The researcher 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 the haemoglobin level. All those with Hb level between 6g/dl and 10g/dl inclusive, at a gestation between 28weeks and 34 weeks inclusive and qualify for the study were selected. Those selected were informed about the study, procedures and purpose of the study explained, and requested to fill consent form. A questionnaire was then filled and a blood sample taken for full haemogram and peripheral blood film.

A non-anaemic pregnant woman (unexposed) was then selected for each anaemic pregnant woman (exposed) from patients in the antenatal clinic with Hb more than 11g/dl and qualify for the study. The unexposed was matched for gestation (+/- 2 weeks), age (within 5 years) and parity (primigravida, multiparous and grand multiparous). The gestation was determined from the LMP and/or ultrasound. The patients who constitute the unexposed were also informed about the study and requested to fill consent form for participation in the study. A baseline full haemogram and PBF was done and questionnaire filled.

Two milliliters of venous blood was collected in an EDTA bottle for FHG and PBF. Full haemogram was done using the cell-dyn machine and PBF stained with MGG stain. The haematologist reviewed the haemogram and blood film to exclude obvious specific haematological conditions.

Stickers were placed on the files of patients involved in the study to identify the cases and controls. The study was publicized in the departments concerned for easier follow up.

The recruitment was over after a sample size of 162 was achieved.
The exposed received Ranferon*, one capsule twice daily, a haematinic containing: folate 0.75mg, ferrous fumarate 305mg (equivalent to elemental iron 100mg), cyanocobalamin 5mcg, ascorbic acid75mg and zinc sulphate 5mg, while the unexposed received Ranferon one capsule once daily. A FHG and PBF were done four weekly to assess haematological changes.

Both groups were followed until 24 hours after delivery to assess outcome.
The data collection instrument was a structured questionnaire (appendix 2) that was administered confidentially (appendix 2).

Sampling

Patients were recruited sequentially, this continued until the desired sample size was reached.

**Declaration: There are no commercial interests in this product.*

Sample size

A total sample size of 162was obtained as shown below.

$$n = \frac{N \times Z^2 \times P(1-P)}{d^2 \times (N-1) + Z^2 \times P(1-P)}$$

Where:

n= the sample size

N= average number of patients seen at the KNH ANC per year in the last two years (2007, 2008) =6,353 As obtained from the ANC records office.

$Z_{(1-\alpha)}$= the 95% confidence interval =1.96

d=absolute precision

p= expected proportion of patients with anaemia in pregnancy seen at KNH= 10% =0.1

Design effect = 1

At p=0.10

$$n = \frac{6{,}353 \times 1.96^2 \times 0.10 \times (1-0.10)}{0.05^2 \times (6{,}353-1) + 1.96^2 \times 0.10 \times (1-0.10)}$$

$$n = \frac{6353 \times 0.345744}{0.05^2 \times 6{,}352 + 0.345744}$$

$$n = \frac{2{,}196.51}{16.23}$$

$$n = 135.34$$

To account for attrition 20% was added to the sample size.

Sample size= 135x1.20 =162

Control Arm=81 patients, Intervention arm=81 patients.

Outcome measures

The following are the variables that were measured:

1. Weight gain and body mass index (BMI) over the pregnancy period.
2. Gestation at delivery.
3. Haematological response as measured by four weekly haemograms.

4. Foetal outcomes: Apgar score and birth weight.
5. Maternal complications: gestation at delivery, estimated blood loss at delivery and fever 24 hours post delivery.

Data collection instrument

The data collection instrument was a structured questionnaire covering the following areas:

1. Sociodemographic data- This was covered in questions 1 to 7.Describes the characteristics of study population and enables comparison with matched controls.
2. Haematological response- This was covered in question 9. This consists of baseline parameters and follow-up monitoring of impact of treatment as compared to matched controls.
3. Maternal outcomes:
    - Weight gain- This was covered in questions 8 and 9. In order to monitor impact of treatment on maternal tissue response due to improved oxidative process.
    - Complications- These were covered in questions 10 to 13. These are any complications that could be attributed to anaemia.
4. Foetal outcomes- These were covered in questions 14 and 15. These includes weight as most important measure but, also other indicators of quality of the newborn infant like Apgar score rating indicative of level of oxygenation or asphyxiation.

Data management, analysis and presentation

The raw data from the questionnaires was verified to check for errors or omissions while completing the questionnaires. Data was then entered into a Microsoft Access database. An attempt to get missing data and to correct the discrepancies was made before closure of the data set.

Data processing and analysis was done using Epi info and SPSS computer packages for descriptive statistics and measures of associations and correlations. All patient identifiers were removed from all patient records before analysis.

The data was presented in tables and scatter grams. Mean differences were used to determine the effect of treatment between the exposed and the unexposed groups. Level of statistical significance was determined using P-values and confidence intervals.

Quality control

The research assistants were trained in history taking, physical examination and phlebotomy. They were trained on filling the questionnaire in a standard way. Haematological tests were done in the same laboratory. The laboratory internal and external quality control measures were adhered to. A haematologist reviewed the haemograms and peripheral blood films to exclude cases of anaemia due to other causes other than deficiency anaemia. There was meticulous recording of laboratory investigation results. The same haematinic was used for all the patients. Cases and controls were matched for gestational age, parity and age.

Limitations of the study

1. The ideal would have been to have controls constituting of patients with anaemia and offer no treatment, but this would be ethically binding. Instead, patients with normal Hb levels and on routine supplementation constitute the controls, to provide a baseline of what can be assumed to be the expected outcome in normal circumstances.

2. The ideal would have been to carry out the study in a public hospital in order to avoid selection bias, as KNH is a referral hospital. But due to logistics, time and budgetary limitation, KNH is preferable. To avoid bias the study population will be walk-in patients and not referrals. Though KNH is a referral hospital, reasonable generalizations can still be drawn from the study.

ETHICAL CONSIDERATIONS

No serious ethical issues arose from this study as there were no major invasive procedures except venepuncture, in which case consent was sought before performing the procedure. Patients were followed up during routine antenatal care. Confidentiality was maintained at all levels. The data did not include specifics of identification of individual mothers during data collection, analysis and report writing. The blood sample taken was used solely for the purpose of a full haemogram and PBF and no other test was done. Patients who were unresponsive to treatment were referred to a haematologist for further investigations.

Patients were informed of the study purpose and informed consent was obtained before recruitment. Results of FHG and PBF were availed in the file for use in routine patient management. Standard care was given to all patients regardless of whether they consented or declined.

Consent to conduct the study was granted by the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (appendix 3).

RESULTS

A total of 162 patients were enrolled into the study. Seven patients among the exposed dropped out of the study when they declined the second venepuncture and medication, while four were lost to follow up. One patient 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 patients, 69 exposed and 69 unexposed, constituted the population studied, which was within the calculated sample size. This forms the basis of these results.

Table 1: Socio-demographic characteristics of the study participants

Characteristic	Exposed (N=69)	Unexposed (N=69)	P value
Age in years			
<20	4 (5.8%)	5 (7.2%)	
21-25	20 (29%)	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%)	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%)	

Table 1 shows the age distribution, marital status, level of education and occupation of the participants in the two arms. Most study participants were aged 26 to 30 years, with the median age being 27.5 years. The youngest participant was 18 years while the oldest was 41 years.. A majority of the study participants were married (78.3% and 85.5% of the exposed and the unexposed respectively). Those who had post-secondary education, were 50.7% for the exposed and 59.4% for the unexposed, with 80% and 81% having secondary education or above for the exposed and unexposed respectively. Participants in

the exposed and unexposed arm had similar age distribution, level of education, marital status and occupation.

Table 2: Obstetric characteristics of the study participants.

Characteristic	Exposed (N=69)	Unexposed (N=69)	P value
Parity			
0	29 (42.0%)	30 (43.5%)	0.863
1-4	40 (58.0%)	39 (56.5%)	
Gestation			
<32 weeks	43 (55.1%)	35 (44.9%)	0.170
≥32 weeks	26 (43.3%)	34 (56.7%)	

Table 2 shows parity and gestation at admission to the study of the study participants. As can be seen, 58% and 56.5% were parous for the exposed and unexposed respectively (P>0.05). As for gestation at admission, 55.4% of the exposed and 44.9% of the unexposed were admitted into the study before 32 weeks (P>0.05). The gestation and parity distribution was similar in both study arms.

Table 3: Haemoglobin concentration of the exposed by gestation at recruitment.

Hb concentration	Gestation at admission	
	<32 Weeks	≥32Weeks
8-10g/dl	26 (74.3%)	28 (82.4%)
6-7.9g/dl	9 (25.7%)	6 (17.6%)
Total	35 (100%)	34 (100%)

Table 3 illustrates the distribution of the exposed in relation to Hb level and gestation at admission to the study. A majority of the participants in the exposed arm had mild anaemia (74.3% and 82.4% for gestation at admission <32 weeks and ≥32 weeks respectively).

Haematological response

Table 4: Mean increase in haematological parameters in 4 weeks from admission to the study.

Parameter	Mean increase		Difference mean 95 % CI	P value
	Exposed x□ (SD)	Unexposed x□ (SD)		
Hb (g/dl)	3.3 (1.7)	1.2 (1.4)	-2.18 (-2.85 to - 1.57)	<0.001
Hct (%)	4.6 (15.3)	1.5 (19.6)	-3.0 (- 4.5 to 10.5)	0.425
MCV (fl)	6.6 (12.5)	0.08 (6.8)	-6.5 (-11.1 to -2.0)	0.005
MCH (pg)	3.1 (4.9)	1.9 (10.9)	-5.0 (-8.5 to -1.5)	0.005
MCHC(g/dl)	0.61 (4.7)	0.005 (2.8)	-0.6 (-2.3 to 1.2)	0.522

Table 4 shows the mean changes in haematological parameters in 4 weeks from admission to the study. The mean increase in haemoglobin concentration was 3.3g/dl for the exposed and 1.2g/dl for the unexposed, the difference was highly significant (P <0.001). Increases in mean corpuscular volume and mean corpuscular haemoglobin were also much more among the exposed as compared to the unexposed ($P < 0.05$ in both instances). Although the mean increases in mean corpuscular haemoglobin concentration and haematocrit were higher among the exposed than among the unexposed, these differences were not statistically significant.

Table 5: Mean rate of change of haematological parameters per week by the exposed and the unexposed in 4 weeks from admission to the study

Parameter	Mean rate of change		Difference mean 95 % CI	P value
	Exposed x□ (SD)	Unexposed x□ (SD)		
Hb (g/dl)	0.84 (0.32)	0.29 (0.310)	-0.6 (-0.7 to -4.2)	<0.001
Hct (%)	1.3 (3.6)	0.6 (4.0)	-0.7 (-2.1 to 0.7)	0.325
MCV (fl)	2.2 (3.4)	0.2 (1.8)	-2.0 (-3.0 to – 1.0)	<0.001
MCH (pg)	1.0 (1.4)	-0.3 (2.3)	-1.2 (-2.0 to -0.6)	<0.001
MCHC(g/dl)	0.2 (1.1)	0.07 (0.7)	-0.16 (0.5 to 0.2)	0.352

Table 5 shows the mean rate of change of haematological parameters per week for the exposed and the unexposed. As can be seen in table 5, mean rate of change of haemoglobin concentration per week was 0.84g/dl for the exposed and 0.29g/dl for the

unexposed, the difference was highly significant (P<0.001). The mean rate of change per week of the mean corpuscular volume and mean corpuscular haemoglobin were also much more among the exposed as compared to the unexposed (P <0.001 in both instances).Although the mean rate of change per week of the haematocrit and mean corpuscular haemaoglobin concentration were higher among the exposed than among the unexposed, these differences were not statistically significant.

Table 6: Proportion of subjects with normal Hb after 4 weeks of treatment by degree of anaemia and gestation at admission to the study.

Gestation at admission	Hb level at admission to the study	Proportion with normal Hb (≥11g/dl) after 4 weeks of treatment.
<32 weeks	Mild anaemia [N =26] (8 - 10g/dl)	23(88.5%)
	Moderate anaemia[N =9] (6 – 7.9g/dl)	5(55.6%)
≥32 weeks	Mild anaemia [N =28] (8 - 10g/dl)	22(78.6%)
	Moderate anaemia[N =6] (6 – 7.9g/dl)	4(66.7%)
All combined	Mild anaemia [N =54] (8 - 10g/dl)	45 (83.3%)
	Moderate anaemia[N =15] (6 – 7.9g/dl)	9 (60.0%)

As can be seen in table 6, treatment of anaemia effectively raised the Hb level. A preponderance of anaemic mothers had achieved a normal haemoglobin level by end of 4 weeks of treatment in all categories. Eighty three percent of the participants with mild anaemia, and sixty percent of those with moderate anaemia at admission to the study had normal Hb at the end of 4 weeks of treatment.

Maternal response

Table 7: Mean maternal weight gain and BMI change in 4 weeks by the exposed and unexposed.

Parameter	Exposed(N=60) x□ (SD)	Unexposed(N=57) x□ (SD)	Difference mean 95% CI	P value
Weight gain (Kg)	1.6 (1.2)	1.7 (0.97)	0.19 (-0.12 to 0.56)	0.319
BMI change (Kg/m^2)	0.63 (0.34)	0.77 (0.56)	0.14 (0.0 to 0.28)	0.052

Table 7 shows that the mean weight gain was minimally less among the exposed than among the unexposed (1.6Kg compared to 1.7Kg). Similarly BMI change was minimally less among the eposed than among the unexposed ($0.63Kg/m^2$ and $0.77Kg/m^2$ respectively). The differences in these changes were not statistically significant.

Table 8: Mean weight gain and BMI change in 4 weeks from admission to study by degree of anaemia.

Weight gain (Kg) and BMI change(Kg/m^2)	Degree of anaemia		P value
	Moderate anaemia (6 – 7.9g/dl) N=13	*Mild anaemia (8 -10g/dl) N=47*	
Mean weight gain (SD)	1.4 (0.82)	1.6 (0.89)	0.753
Mean BMI change (SD)	0.55(0.30)	0.65 (0.36)	0.488

Table 8 shows the mean weight and BMI increase by degree of anaemia within 4 weeks of admission to the study. The mean weight gain was 1.4Kg among the mothers with moderate anaemia compared to1.6Kg among those with mild anaemia, while the BMI change was $0.55Kg/m^2$ and $0.65Kg/m^2$ respectively. The differences in these changes were not statistically significant.

Table 9: Estimated blood loss at delivery and temperature at 24 hours after delivery by the exposed and unexposed

Parameter	Exposed x□ (SD)	Unexposed x□ (SD)	Difference 95% CI	P value
Estimated blood loss (mls) (N =67)	235.9(74.6)	216.4 (74.1)	-19.5(-44.8 to 5.8)	0.131
Temperature(°C) (N=54)	36.6 (0.4)	36.5 (0.3)	-0.06(-0.21 to 0.09)	0.461

Table 9 shows the mean estimated blood loss at delivery and temperature at 24 hours after delivery by the exposed and the unexposed. The mean blood loss at delivery was slightly more among the exposed as compared to the unexposed (235.9mls and 216.4mls respectively). Similarly the average temperature at 24hours after delivery was slightly higher among the exposed than among the unexposed (36.6°C and 36.5°C respectively). However, the differences in these parameters were not statistically significant.

Table 10: Mean maternal weight gain (Kg) and BMI change (Kg/m^2) in 4 weeks by gestation at admission to the study.

Parameter	Gestation at admission	Exposed x (SD)	Unexposed x (SD	Difference mean 95 % CI	P value
Weight gain					
	<32 weeks	1.5(0.88)	1.96 (1.04)	0.45(0.06 to 0.84)	0.023
	≥32 weeks	1.95(0.73)	1.5 (0.27)	-0.45(-0.97 to 0.06)	0.115
BMI change					
	<32 weeks	0.59(0.35)	0.79 (0.45)	0.2(0.04 to 0.4)	0.015
	≥32 weeks	0.76(0.26)	0.58 (0.12)	-0.18(-0.4 to 0.03)	0.084

Table 10 illustrates the mean maternal weight gain and BMI change in 4 weeks from admission to the study in relation to gestation at admission to the study by the exposed and the unexposed The mean weight gain in 4 weeks among the participants enrolled at gestation <32 weeks was 1.5Kg for the exposed and 1.96Kg for the unexposed, while the BMI change was $0.59Kg/m^2$ for the exposed and $0.79Kg/m^2$ for the unexposed. The difference was statistically significant ($P<0.05$ in both instances). Although there was a

difference in the weight gain and BMI change among those admitted at a gestation ≥32weeks, this was not statistically significant.

Table 11: Mean maternal weight gain (Kg) and BMI change (Kg/m^2) after 4 weeks of treatment by Hb level at admission to the study.

Parameter	Hb level at admission to the study		Difference Mean 95% CI	P value
	Mild anaemia (8 – 10g/dl)	*Moderate anaemia (6 – 7.9g/dl)*		
Weight gain	1.63(0.89)	1.50(1.00)	-0.13(-1.1 to 0.8)	0.7782
BMI change	0.65(0.40)	0.60(0.40)	-0.05 (-0.43 to 0.3)	0.8072

Table 11 shows the mean maternal weight gain and BMI change in 4 weeks from admission to the study in relation to the Hb level at admission to the study. The mean weight gain was slightly higher among the exposed with mild anaemia as compared to those with moderate anaemia (1.63Kg and 1.5Kg respectively). Similarly, the BMI change was slightly higher among the exposed with mild anaemia as compared to those with moderate anaemia (0.65kg/m^2 and 0.60kg/m^2 respectively). However, these differences were not statistically significant.

Foetal outcomes

Table 12: Mean birth weight and gestation at delivery by the exposed and the unexposed.

Parameter	Exposed(N=67) X□(95% CI)	Unexposed(N=68) X□(95% CI)	Mean Difference 95% CI	P value
Birth weight (grams)	3188.8 (451.5)	3236.8 (421.7)	48(-100.7 to 196.7)	0.525
Gestation at delivery (weeks)	39.2 (1.5)	39.2 (1.2)	-0.24(-0.7 to 0.22)	0.302

As can be seen in table 12, the average birth weight in the exposed and unexposed arms was 3188 grams and 3236 grams respectively. There was a birth weight difference of 48 grams between babies born by mothers in the exposed and unexposed arms. This

difference was however not statistically significant. The average gestation at delivery was 39.2 weeks in both the case and control arms.

Table 13: Apgar score at 1 minute and at 5 minutes by the exposed and the unexposed

Time	Apgar score	Exposed	Unexposed	P value
1 minute	Poor (≤ 6)	4 (50.0%)	4 (50.0%)	>0.999
	Good (≥ 7)	64 (49.6%)	65 (50.4%)	
5 minutes	Poor (≤ 6)	1 (100%)	0 (0%)	0.493
	Good (≥ 7)	66 (48.9%)	69 (51.1%)	

Table 13 shows the 1 minute and 5 minutes Apgar scores by the exposed and unexposed. The Apgar score at 1 and 5 minutes was similar in both arms of the study. Four participants in each arm had poor Apgar scores (□6) in 1 minute while the remaining, 64 in the exposed arm and 65 in the unexposed arm had good Apgar scores (≥ 7) at 1 minute. Only one baby in the exposed arm had poor Apgar score at 5 minutes.

Table 14: Apgar score at 1 minute by gestation at admission to the study by the exposed and the unexposed.

Apgar Score	Gestation at admission	Exposed (N=69)	Unexposed (N=69)	P value
Poor (≤ 6)	<32 weeks	3 (100%)	0 (0%)	0.143
	≥32 weeks	1 (20.0%)	4 (80.0%)	
Good (≥ 7)	<32 weeks	32 (42.7%)	43 (57.3%)	0.075
	≥32 weeks	32 (59.3%)	22 (40.7%)	

Table 14 illustrates the Apgar Scores at 1 minute in relation to gestation at admission to the study by the exposed and the unexposed. The time of admission into the study did not have any association with the 1 and 5minute APGAR score. In the exposed arm, 32 of the participants in the early and 32 participants in the late admission categories had good Apgar scores.

Table 15: Apgar score at 1 minute and at 5 minutes by Hb level at admission to the study.

Time	Apgar score	Mild anaemia (8-10g/dl)	Moderate anaemia (6-7.9g/dl)	P value
1 minute	Poor (≤ 6)	3 (100%)	-	>0.999
	Good (≥ 7)	50 (92.6%)	4 (7.4%)	
5 minutes	Poor (≤ 6)	-	-	-
	Good (≥ 7)	52 (92.9%)	4 (7.1%)	

Table 15 illustrates the Apgar score at 1 minute and at 5 minutes in relation to the Hb level at admission to the study. Only 3 of the exposed with mild anaemia had a poor Apgar score at 1 minute. All participants had good Apgar scores at 5 minutes. There was no statistical difference in the 1 and 5 minutes Apgar score between the patients with mild and moderate anaemia.

Relationship between maternal response and foetal outcomes

Table 16: Birth weight by maternal weight gain in 4 weeks from admission to the study.

Weight gain in four weeks from admission to the study	Birth weight (N=58)	
	<2.5kg	*≥2.5kg*
<1.6Kg	-	39 (67.3%)
≥1.6Kg	-	19 (32.7%)

Table 16 shows the relationship between birth weight and maternal weight gain in four weeks from admission to the study. All the babies weighed had a birth weight of ≥2.5Kg irrespective of the amount of maternal weight gain.

Table 17: Birth weight in relation to the Hb level at 4 weeks from admission to the study.

Degree of anaemia at admission to the study	Hb level 4 weeks from admission to the study	Mean Birth weight (SD)	P value
Mild anaemia (N-45) [8-10g/dl]	≥11g/dl(N= 38)	3442(423.7)	0.2694
	<11g/dl (N =7)	3264.5(381.5)	
Moderate anaemia(N=12) [6-7.9g/dl]	≥11g/dl(N= 8)	3087.5(215.1)	0.162
	<11g/dl (N =4)	2575(960.5)	

As can be seen in table 17,mothers who had a Hb level of ≥11g/dl after 4 weeks of treatment delivered babies with higher birth weight compared to mothers who were still anaemic (Hb level of < 11g/dl) after 4 weeks of treatment. These differences were however not statistically significant.

Figure 1: Correlation between birth weight and BMI change in the unexposed and the exposed arms.

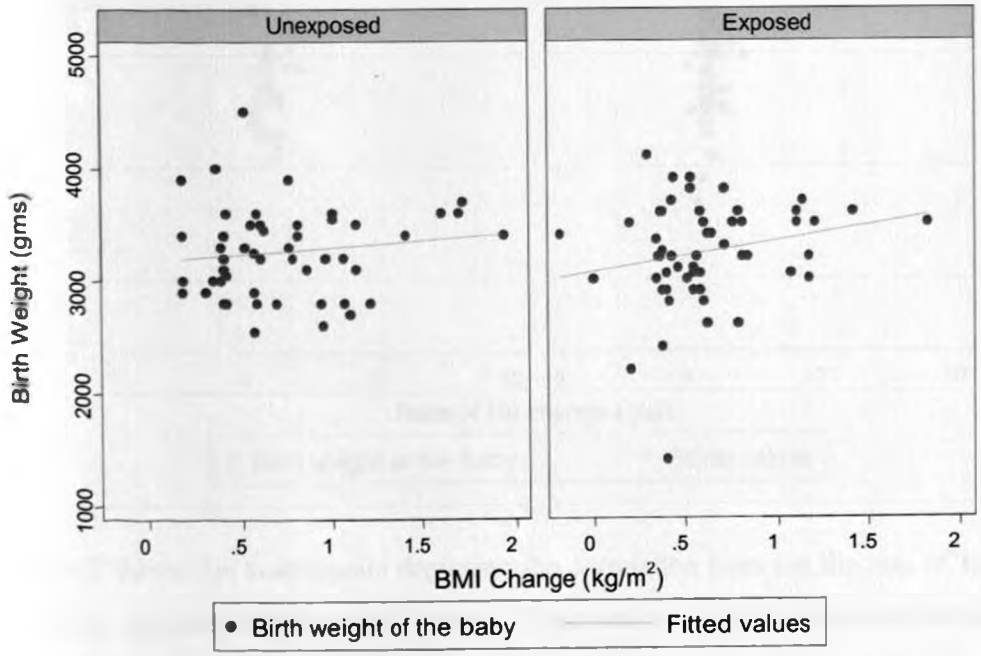


Figure 1 shows the scattergram depicting the correlation between birth weight and BMI change in the unexposed and the exposed arms. There was a positive weak correlation between the birth weights and maternal BMI changes in the exposed and unexposed arms. The correlation coefficients are 0.2068 and 0.1350 in the exposed and unexposed arms, respectively.

None of the relationships between birth weight and change in BMI was statistically significant. The regression co-efficient in the exposed arm 270 gm /unit BMI change (95% CI: 78.5 to 618.8), P=0.126). The regression co-efficient in the unexposed arm was 121.2 gm /unit BMI change (95% CI: -123.9 to 366.3), P=0.326.

Figure 2: Correlation between the rate of Hb change per week and birth weight.

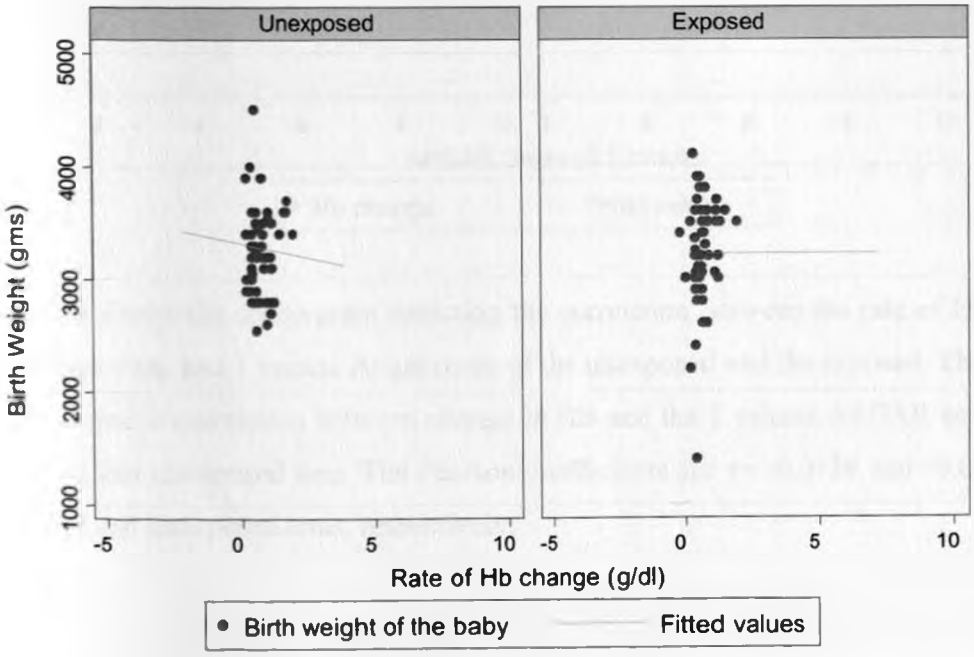


Figure 2 shows the scattergram depicting the correlation between the rate of Hb change (g/dl) per week and Birth weight (grams). There was a negative weak correlation between Hb change and birthweight in both the exposed and unexposed arms. The Pearson

correlation coefficients were – 0.1685 and -0.0943 in the exposed and unexposed arm, respectively.

Figure 3: Correlation between the rate of Hb change per week and 1 minute Apgar score of unexposed and the exposed.

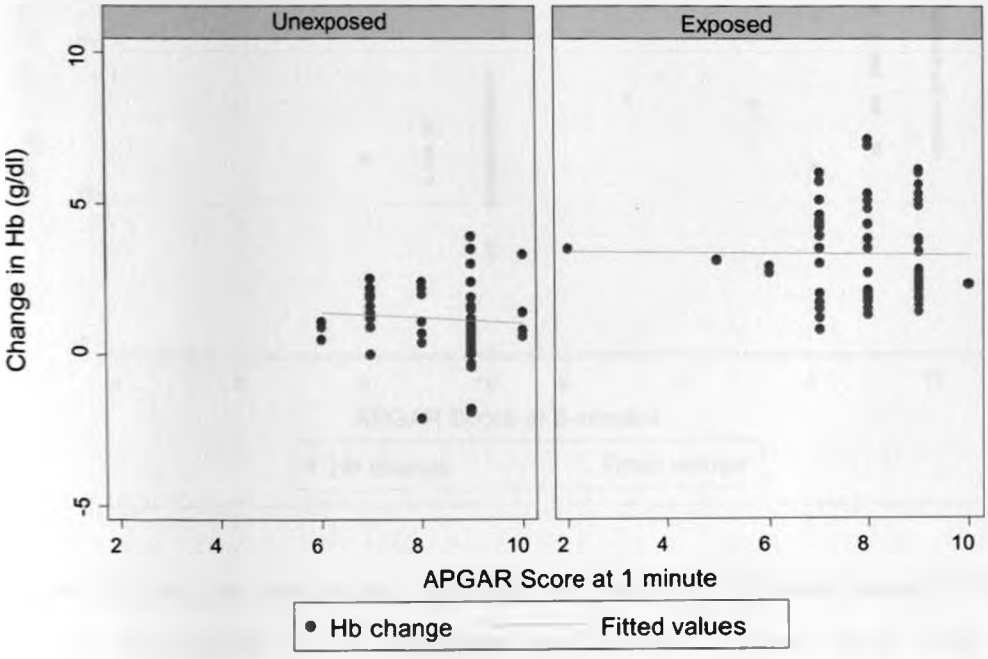


Figure 3 shows the scattergram depicting the correlation between the rate of Hb change (g/dl) per week and 1 minute Apgar score of the unexposed and the exposed. There was a weak negative correlation between change in HB and the 1 minute APGAR score in the exposed and unexposed arm. The Pearson coefficients are r= -0.0128 and -0.078 in the exposed and unexposed arms, respectively.

Figure 4: Correlation between change in Hb and 5 minute Apgar score of Unexposed and the Exposed.

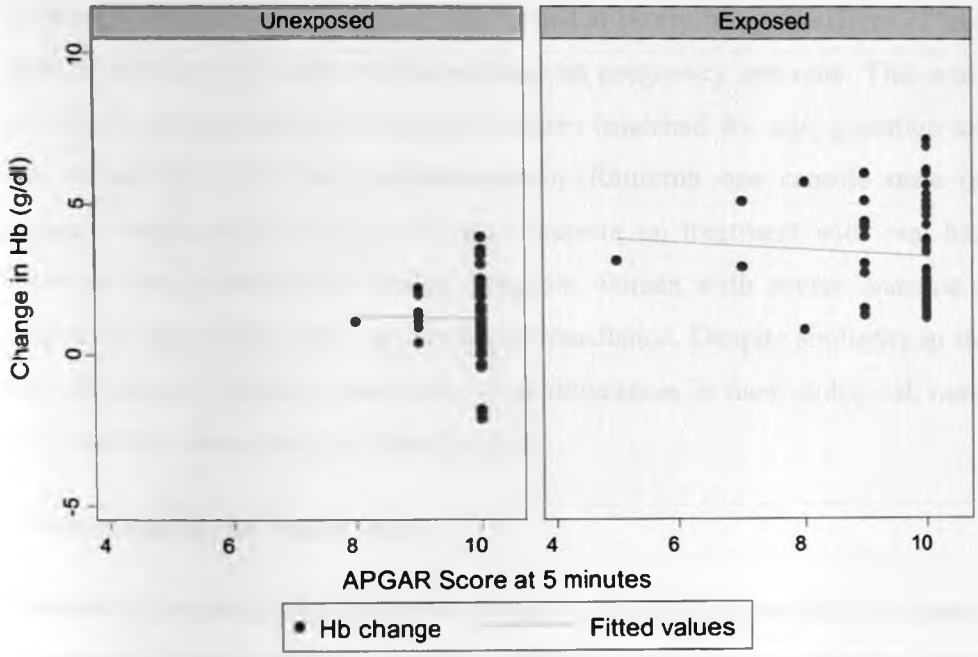


Figure 4 shows the scattergram depicting the correlation between change in Hb and 5 Minute Apgar score of the unexposed and exposed. There was a weak negative correlation between change in HB and the 5 minute APGAR score in the exposed and unexposed arm. The Pearson coefficients are r= -0.0677 and -0.021 in the exposed and unexposed arms, respectively.

DISCUSSION

This was a prospective cohort study that aimed at determining the effect of treatment of anaemia in pregnancy with oral haematinics on pregnancy outcome. This was done by comparing outcomes between pregnant women (matched for age, gestation and parity) with normal Hb on routine supplementation (Ranferon one capsule once daily) and pregnant women with mild to moderate anaemia on treatment with oral haematinics (Ranferon one capsule twice daily). Pregnant women with severe anaemia were not included in this study as they require blood transfusion. Despite similarity in the general characteristics of the two populations, some differences in haematological, maternal and foetal outcomes have emerged from the data.

Haematological response

Treatment of anaemia with double the dosage of prophylaxis resulted in a rapid increase in haematological parameters. Anaemic pregnant women on treatment had a more rapid rise in the Hb, MCV, MCH, Hct and MCHC in relation to the non-anaemic pregnant women on prophylaxis, with the Hb, MCV and MCH showing significant differences.

The mean rate of increase of haemoglobin concentration per week was 0.84g/dl for anemic pregnant women on treatment. This mean increase in Hb falls within the rate of increase in a patient responsive to treatment (when a patient is on oral iron therapy the haemoglobin should rise at the rate of approximately 2g/dl every three weeks).[22]

The mean increase in 4 weeks and mean rate of change per week of the mean corpuscular volume and mean corpuscular haemoglobin were much more among the exposed as compared to the unexposed ($P < 0.001$ in both instances). Although the mean rate of change per week of the haematocrit and mean corpuscular haemaoglobin concentration were higher among the exposed than among the unexposed, these differences were not statistically significant. Iron deficiency anaemia, is the commonest cause of anaemia in pregnancy and is characterized by a decrease in the haemoglobin, mean corpuscular volume, mean corpuscular haemoglobin, haematocrit and mean corpuscular haemoglobin

concentration. Oral iron therapy results in an increase of these parameters.[22] Haemoglobin reflects the overall oxygen carrying capacity while mean corpuscular haemoglobin reflects the individual capacity to contribute to the overall oxygen carrying capacity. A rise in both would presumably increase the oxygen carrying capacity more efficiently. In iron deficiency anaemia, the haemoglobin and haematocrit levels rise together. In this study in spite of having features of iron deficiency anaemia many women had mixed deficiency anaemia, however this was not addressed in the study. Mean corpuscular haemoglobin concentration is the most sensitive indicator of iron deficiency anaemia and the last to change in response to treatment.[3]

The period of follow up was short and therefore may not have provided adequate time for significant changes in the MCHC and Hct. In addition, although according to the study plan participants were to have repeat full haemogram and peripheral blood film at 8 weeks after recruitment, only two patients in the exposed arm had a repeat FHG and PBF at 8 weeks from admission to the study and therefore this could not be included in the data analysis.

Treatment of anaemia with oral haematinics effectively raised the Hb level; a majority of anaemic mothers had achieved a normal haemoglobin level by end of 4 weeks of treatment. This indicates that about four weeks are required for majority of anaemic pregnant women to correct the Hb, therefore early detection of anaemia is important.

An increase in haematological indices of pregnant women with normal Hb levels and on routine supplementation was noted. This shows that prophylactic iron supplementation not only prevents a fall, but also improves Hb levels during pregnancy.[7]

Maternal response

On maternal response, treatment resulted in increase in weight and BMI. The mean weight gain and BMI change were minimally less among the exposed than among unexposed. The differences in these changes were not statistically significant. A previous

study showed that anaemic women have a significantly low pre- and post-pregnancy weight.[14] The impact of anaemia is to decrease oxygen delivery, hence substrate utilization, 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.

The mean blood loss at delivery was slightly more among the exposed as compared to the unexposed. Similarly the average temperature at 24hours after delivery was slightly higher among the exposed than among the unexposed. However, in this study mode of delivery was not considered. None of the participants had a temperature >37.4°C. The differences in these parameters were not statistically significant. Anaemic pregnant women are at a higher risk of post partum haemorrhage and puerperal sepsis.[10,11,12] With correction of anaemia there is increased oxygen supply to the tissues including the uterus therefore preventing uterine atony and an overall improvement in the immune status. Correction of anaemia appears therefore to reduce the risk of infection which is prevalent in women delivering with uncorrected anaemia.

Foetal outcome

The foetal outcomes were comparable. The mean birth weight difference between the anaemic pregnant women on treatment and the non-anaemic pregnant women on routine supplementation was not statistically significant. Neonates born to anaemic mothers have a higher incidence of low birth weight.[10,11,12] In this study however, the timing of correction of anaemia seems to have allowed adequate time for growth of the foetus. Twenty eight weeks correspond to the beginning of exponential growth of the foetus, a period when the demand for oxidative process is high. In this study patients were recruited at a gestation of 28 to 34 weeks inclusive.

Apgar score may not have much difference because multiple factors in the antepartum and intrapartum period affect the Apgar score. No significant difference was found in the 1 and 5 minute Apgar scores between the exposed and unexposed. There was also no relationship between the degree of anaemia and gestation at admission to the study with the Apgar score. Anaemia is associated with a low Apgar score at birth due to the inability of the already compromised fetus to tolerate the decreased oxygen supply caused by the uterine contractions. This study shows that the Hb at birth is critical and therefore, early correction of anaemia before delivery ensures better foetal outcome.

Relationship between maternal response and foetal outcomes

There was a positive but weak correlation between the birth weights and maternal BMI changes in the exposed and unexposed arms. Similarly, mothers who had a Hb level of ≥11g/dl after 4 weeks of treatment delivered babies with higher birth weight compared to mothers who were still anaemic after 4 weeks of treatment, although there was no significant difference. This shows that improved maternal general status has a positive impact on foetal outcome. However, studies show that anaemia in pregnancy is associated with low birth weight. [10 11 12 13 14] For this reason, the interpretations of these results may be that there is a catch up effect on growth when anaemia is treated adequately giving credence to the improved substrate utilization.

However, there was a negative weak correlation between the Hb change and birth weight and the Hb change and Apgar score in both the exposed and unexposed arms. This is a paradoxical finding and may be attributed to the curtailment of normal volume expansion of pregnancy, which is important in decreasing the viscosity of blood and therefore affecting utero-placental blood flow. [23]

CONCLUSION

1. Oral haematinics are effective in the treatment of mild to moderate anaemia in pregnancy during the third trimester.
2. High dose oral haematinics are of benefit in the management of anaemia in pregnancy in the third trimester.
3. Correction of mild to moderate anaemia in pregnancy with oral haematinics results in maternal outcomes similar to those in women without anaemia in pregnancy.
4. Correction of mild to moderate anaemia in pregnancy with oral haematinics results in foetal outcomes similar to those in women without anaemia in pregnancy.

RECOMMENDATIONS

1. Early recognition of anaemia should be aggressively treated with high dose haematinics.
2. Routine supplementation with oral haematinics of all pregnant women should be encouraged.
3. Where possible a full haemogram instead of haemoglobin level alone should be done as part of the antenatal profiles to help in identifying possible cause of anaemia.
4. There is need for further research to establish the effects of treatment on early pregnancy (first and second trimester), post-delivery and the neonatal period.
5. Further research needs to be carried out in a study with greater power to establish outcomes like birth weight, as this study has inadequate power to do this.

REFERENCES

1. World Health Organisation 1999, "Reduction and Control of Iron Deficiency Anaemia in Women and Children" Report of the UNICEF/WHO regional consultation 1999.

2. Dechemy, H., Nathan, L., Goodwin, T. and Laufer, N. Diagnosis and Treatment Obstetrics and Gynecology. Tenth edition. New York. McGraw Hill 2003; **26**: 406-8.

3. Dutta D.C. Textbook of Obstetrics. Sixth edition. Calcutta. New Central Book Agency 2004; **19**:262-72.

4. Shalev, H., Arraham, G., Hershkovitz, R., H. et al. Pregnancy outcome in congenital dyserythropoietic anemia type I. European Journal of Haematology 2008; ISSN0902-4441.

5. Ministry of Health. Essential Obstetric Care Manual: for Health Service Providers in Kenya, Third Edition, 2006, Ministry of Health: Division of Reproductive Health.

6. Cogswell, M. E., Parvanta, I., Ickes, L.,Yip, R., and Brittenham, G.M. Iron supplementation during pregnancy, anemia and birth weight; a randomized controlled trial. American Journal of Clinical Nutrition 2003; **78**: 773-81

7. Singh, K., Fung, Y.F. and Arulkumaran S. The Role of prophylactic Iron supplementation in pregnancy. International Journal of Food Science and Nutrition 1998; **49(5)**: 383-9.

8. Mahomed, K. Iron and Folate supplementation in pregnancy. Cochrane Database of Systematic Reviews 2006; (3)

9. Meier R. P. Prevention of iron deficiency anaemia in adolescents and adult pregnancies. Journal of Medicine and Research 2003; **1 (1)**:29-36.

10. Karasahin, E., Ceyhan, S. T., Goktolga, U., Keskin, U. and Baser, I. Maternal anaemia and perinatal outcome. Perinatal Journal 2007; **15**:127-30.

11. Reveiz, L., Gyte, G. M. L. and Cuervo, L. G. Treatments for iron deficiency anaemia in pregnancy. Cochrane Database of Systematic Reviews: CD003094, 2007.

12. Marchant, T., Schellenberg, J. A., Nathan, R., Abdulla, S., Mukasa, O., Mshinda,H. et al. Anaemia in pregnancy and infant mortality in Tanzania. Tropical Medicine and International Health 2004; **9 (2)**: 262-6.

13. Fomulu, S.N. A 2 year retrospective controlled survey of maternal and foetal prognosis in anemia of pregnancy at Kenyatta National Hospital. MMed University of Nairobi, Thesis 1981.

14. Mahajan, S., Aalinkeel, R., Shah, P., Singh, S. and Kochupillai N. Nutritional anaemia dysregulates endocrine control of fetal growth. British Journal of Nutrition 2008; **100(2)** 408-17.

15. Marahatta, R. Study of anaemia in pregnancy and its outcome in Nepal Medical College Teaching Hospital, Kathmandu, Nepal. Nepal Medical College Journal NMCJ 2007;**9(4)** 270-4.

16. Kilbride, J., Baker, T., Parapia, L., Khoury, S., Shuqaidef, S. and Jerwood D. Anaemia during pregnancy as a risk factor for iron deficiency anaemia in infancy. A case control study in Jordan International Journal of Epidemiology.1999; **28**:461-468.

17. Noel, S.W. and Klaus, S. Intramuscular administration of iron dextran is inappropriate for treatment of moderate pregnancy anemia, both in intervention

research on underprivileged women and in routine prenatal care provided by public health service. The American Journal of Clinical Nutrition.2004;Editorial article pp 116

18. Juarez-Vazquez, J., Bonizzoni, E. and Aurello, S. Iron plus folate is more effective than iron alone in the treatment of iron deficiency anaemia in pregnancy. A randomized double blind clinical trial. An International Journal of Obstetrics and Gynaecology 2002; **109**: 1009-1014.

19. Khadija, J.J. Prevalence of anaemia amongst ANC attendants at Kakamega Provincial General Hospital. MMed University of Nairobi, Thesis 2006.

20. Sewe, P. Prevalence of anaemia in pregnancy among urban slum women at Dandora (II) Health Centre in Nairobi. MMed University of Nairobi Thesis 1998.

21. Mumia, S.A. Anaemia in pregnancy (foeto-maternal prognosis) at Kenyatta National Hospital, Nairobi. MMed University of Nairobi Thesis 1981.

22. Hoffbrand, A.V., Moss,P.A.H.,Pettit,J.E. Essential Haematology Fifth edition. Blackwell Publishing Ltd, 2006; **3:28**-29.

23. Cunningham, F.G., Levenno, K.J., Bloom, S.L., Hauth, J.C., Gistrap III, L. and Wenstrom, K.D. Williams Obstetrics. Twenty second edition. New York. McGraw Hill 2007; **51**: 1143-45.

APPENDICES

Appendix 1

CONSENT FORM

My name is Dr Jacqueline Chesang, a post-graduate student in the Department of Obstetrics and Gynaecology. I am carrying out a study on the treatment outcomes of anaemia in pregnancy. This entails comparing the treatment outcomes of those with anaemia in pregnancy and those without. Those with anaemia will be given haematinics at therapeutic dose while those without will receive routine supplementation. Blood samples will be drawn from all participants at admission into the study and at four weeks intervals for haematological studies. The patients will be followed up until 24 hours post delivery. The study will be done at no extra cost to the study participants. The results of the study may be used to improve the way we manage anaemic patients.

Participation in the study will not in any way change treatment offered to you as a patient within this hospital. Participation is voluntary and the information obtained will be confidential. Declining to participate or dropping out from the study will not influence your management. Treatment given will not harm you or your baby.

Consent

I have been explained to about the study and accept to participate. I have not been coerced or enticed in any way.

Participant's signature.....Date.....

In case of questions or any adverse events, please address the investigator or the following:

1. Study investigator:
   Dr. Jacqueline Chesang: Tel. 0721 280 318
2. Supervisors:
   Prof. Koigi Kamau, Chairman, Dept. of Obstetrics & Gynaecology, UON

Tel: 020-272 6360

Dr. Gichuru Kamau, Dept. of Obstetrics & Gynaecology, KNH.

Tel: 020-272 3830

Dr. G.W. Kitonyi, Dept. of Haematology & Blood Transfusion, UON

Tel: 0722 385 336

3. KNH-UON Ethics and Research Committee

   Tel: 020- 2726300 Ext 44102

Appendix 2

QUESTIONNAIRE

Serial number……..

Date……

CASES: TEATMENT GROUP (Hb 6-10g/dl) ( )

CONTROLS: SUPPLEMENTATION GROUP (Hb > 11g/dl) ( )

SECTIONA: SOCIODEMOGRAPHIC DATA

1. Age in completed years ☐☐
2. Marital status

   Married ( )

   Single ( )

   Separated/Divorced ( )

   Widowed ( )

3. Education level

   None ( )

   Primary ( )

   Secondary ( )

   Post-secondary ( )

4. Occupation

   Unemployed ( )

   Self employed ( )

   Gainful employment ( )

5. Number of previous pregnancies ☐☐

   Number of previous deliveries ☐☐

6. Date of your last normal menstrual period (LNMP) .....Not sure ( )
7. Gestation at admission into the study [ ][ ]
8. Height in centimeters at admission into the study [ ][ ][ ]

SECTION B: HAEMATOLOGICAL RESPONSE

9. Gestational age in relation to haematological indices and weight in the antenatal follow up period.

	GESTATIONAL AGE IN COMPLETED WEEKS												
	28	29	30	31	32	33	34	35	36	37	38	39	40
PARAMETRES													
Hb (g/dl)													
HCT (%)													
MCV (fL)													
MCH (pg)													
MCHC (g/dl)													
Weight (Kg)													
Weight gain													
BMI (Kg/m^2)													

* Gestation at admission

SECTION C: MATERNAL OUTCOMES

10. Gestation at delivery.....

    If before term state reason.....

11. Mode of delivery

    Spontaneous vaginal ( )

    Assisted vaginal ( )

Emergency caesarean section ( )

Elective caesarean ( )

12. Estimated blood loss during delivery

13. Fever (temperature >37.4°C) within 24 hours post delivery Yes ( ) No ( )

SECTION D: FOETAL OUTCOMES

14. Birth weight of the baby

15. Apgar score in:

1 minute ☐☐

5 minutes ☐☐

Appendix 3

LETTER OF APPROVAL

KENYATTA NATIONAL HOSPITAL
Hospital Rd along, Ngong Rd.
P.O. Box 20723, Nairobi
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP", Nairobi.
Email: KNHplan@Ken.Healthnet.org

Ref. KNH-ERC/ A/341

30th October 2009

Dr. Jacqueline Chesang
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Dr. Chesang

RESEARCH PROPOSAL: "EFFECT OF TREATMENT OF ANAEMIA IN PREGNANCY WITH ORAL HAEMATINICS ON PREGNANCY OUTCOMES AT KENYATTA N. HOSPITAL" (P163/6/2009)

This is to inform you that the Kenyatta National Hospital/UON Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 30th October 2009 - 29th October 2010.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

DR. L. MUCHIRI
AG SECRETARY, KNH/UON-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH/UON-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Obs/Gynae, UON
Supervisors: Prof. Koigi Kamau, Dept. of Obs/Gynae, UON
Dr. Gichuru Kamau, Dept. of Obs/Gynae, KNH
Dr. G. W. Kitonyi, Dept. of Pathology, UON