The effect of 61 days of combined iron (Chemiron®) and single iron therapy on haemoglobin, packed cell volume, platelets and reticulocytes during pregnancy. Preliminary report

G. O. Ajayi, E. O. Fadiran

Senior Lecturer/Consultant, Department of Obstetrics & Gynaecology, College of Medicine, University of Lagos, Idi-Araba; Senior Lecturer, School of Pharmacy, College of Medicine, University of Lagos, Idi-Araba (Lagos)

Summary

A 61-day short-term prospective study comparing the efficacy of Chemiron® capsules (Ferrous Fumarate 300 mg, Folic Acid 5 mg, Vitamin B12 10 ug, Vitamin C 25 mg, Magnesium sulphate, 0.3 mg and Zinc Sulphate 0.3 mg) with conventional ferrous gluconate and folic acid administration has shown that both haematinic regimens improve haematological indices in normal pregnant women. A significant rise in haemoglobin was seen in the Chemiron group on days 5 and 19 whereas a significant increase in packed cell volume was observed on days 5, 19 and 61. There were no significant differences between the mean value of platelets during the therapy period in either group.

A significant rise in the mean reticulocyte values could be demonstrated in the Chemiron group throughout the study period. This study further shows that Chemiron has a better haematological effect than Ferrous Gluconate at the dosage used.

Key words: Combined Iron (Chemiron®); Single iron therapy; Effect on pregnancy; Haemoglobin; Packed cell volume, Platelets and reticulocyte level.

Introduction

According to several studies at the end of pregnancy all women were found to have an iron deficiency; no iron could be found in the bone marrow in 85-90% of the cases (pre-latent iron deficiency) [19, 21, 29, 30]. A latent iron deficiency with reduction of serum iron is found in 40-50% of the cases; severe iron deficit leads to manifested iron deficit in 30% of the pregnant women with significantly low haemoglobin levels [11, 12, 13]. The risk to the mother and child as a result of a reduction in haemoglobin and reduced oxygen transport capacity will become more pronounced. It has been shown that patients with pregnancy anaemia are predisposed to pregnancy complications like premature contractions, bleeding, premature delivery, immaturity, intrauterine death and risk of infections [7, 8, 17]. As in the case of iron deficiency, folic acid deficiency results from increased demand and reduced intake during pregnancy [2-4, 11, 20, 23]. Those who are really involved are women with multiple pregnancies and who come from poor social classes (little meat and few vegetables).

The folic acid content of blood is low in about 30-50% of pregnant women. Results on incidence of folic acid deficiency with a value under 3 mg/ml lies between 0% and 30% [4, 16]. The main aetiological factors of anaemia in pregnancy include iron and folate deficiency in the diet, haemolysis from haemoglobinopathies and malaria, hookworm infestation, bacterial infection and malabsorption syndrome [24]. Fleming [9] was able to reduce the frequency of megaloblastic erythropoiesis from 56% to almost nil with folic acid supplementation. Folic acid deficiency can impair fetal growth either immediately or through the reduction of placental function. This can lead to abortion, fetal malformation and early placental separation [3, 8, 10-12, 15, 23, 24].

The demand for vitamin B12 is high during pregnancy and cannot be totally obtained through food. This leads to reduction of vitamin B12 levels in the serum. Over half of pregnant women have values under 80 µg/ml. The incidence of megaloblastic anaemia due to vitamin B12 deficiency is generally very low during pregnancy [2, 5, 16, 23, 25, 28]. In Europe and North America there is the opinion that the iron, folic acid and vitamin B12 content in their standard meals is enough to balance the need during the course of pregnancy. Megaloblastic anaemia is seldom seen and no routine diagnosis of folic acid and vitamin B12 during pregnancy is carried out. This is not the case in Nigeria where there is a high incidence of malnutrition. Since the latent iron, folic acid, and vitamin B12 therapy has not had a breakthrough in some countries.

In this study, we assess and compare the efficacy of administering single iron therapy and a combined iron, folic, acid, vitamin B12, magnesium and zinc (Chemiron® therapy during pregnancy in Nigerian women for a short period of 61 days.

Received January 7, 1998
revised manuscript accepted for publication March 20, 1998

Materials and Methods

A total of 19 patients attending the antenatal clinic of the Lagos University Teaching Hospital for the first time whose preliminary results were available were evaluated. They were divided into two groups and had no evidence of anaemia (>10 g/100 ml of Hb level).

Group 1 was made up of 6 patients who were treated with Chemiron®, a new haematinic preparation which contains ferrous fumerate (300 mg), folic acid (5 mg), vitamin B12 (10 mg), vitamin C (25 mg), magnesium sulphate (0.3 mg) and zinc sulphate (0.3 mg) - one capsule daily starting on the day of recruitment. The gestational ages ranged between 10 and 23 weeks (mean ± SD = 15.3 ± 4.80 weeks) at recruitment and their ages ranges between 18 and 37 years (mean ± SD = 27.8 ± 6.11 years). Their height and body weight ranged between 1.59 meters / 53.5 kg and 1.71 meters / 83.5 kg, respectively).

Group II consisted of 13 patients who were treated with ferrous gluconate (300 mg), one tablet twice daily and folic acid (5 mg), one tablet daily starting on the day of recruitment. The gestational ages ranged between 20 and 32 years (mean ± SD = 27.5 ± 3.45 years). Venous blood samples for base levels of haemoglobin, reticulocytes, packed cell volume and platelets were drawn between 9.00 a.m. and 10.00 a.m. from each patient studied (usually on a Wednesday when the investigating team were on emergency call). Group 1 was given Chemiron®, one capsule each to be taken orally after which venous blood was drawn again at 0' 30' and 90' (minutes) on days 5, 19, 33, 47 and 61. In group II, patients were given ferrous gluconate (300 mg) and folic acid (0.5 mg) to be taken orally after which venous blood samples were taken at 30 and 90 minutes on days 5, 49 and 61. They continued on their dosage until they delivered. The following parameters were studied: packed cell volume, haemoglobin, platelets and reticulocytes using the methods described according to Dacie and Lewis [25]. Patients with abnormal haemoglobin, overt infection, or those found to have a white blood count (WBC) greater than 10,000 µ/l and a sedimentation rate (SDR) more than 10-15 mm were excluded. Patients were told not to take their haematinic with coffee, milk, alcohol and soft drinks. Informed consent was obtained from all the patients participating in this on-going study. Routine statistical methods (Students' t-test, Newmann Keul procedure and Wilcoxon paired rank test) were used. Data are expressed as mean ± SD (standard deviation).

Results

Figures 1 to 4 show the mean haemoglobin, packed cell volume, platelet and reticulocyte values in group I (n = 6) treated with Chemiron®. One capsule contains ferrous fumerate (300 mg), folic acid (5 mg), Vitamin B12 (10 mg), Vitamin C (25 mg), magnesium sulphate (0.3 mg) and zinc sulphate (0.3 mg). Group II (n=13) was treated with ferrous sulphate and folic acid before starting treatment and during therapy at 0', 30', 90' on days 5, 19, 33, 47 until day 61.

Haemoglobin

There was a significant increase in haemoglobin on day 5 and day 19 in Group 1 (from 0=11.533 ± 0.501 to 12.256 ± 0.628 g/dl on day 5 and 12.283 ± 0.407 g/dl on day 19). There was no significant increase in haemoglobin level during the study period (0' minute = 10.862 ± 1.075 g/dl to the highest level on day 61 (11.300 ± 0.906 g/dl). Group 1 showed a significant difference (p) when the mean value of haemoglobin was compared to Group

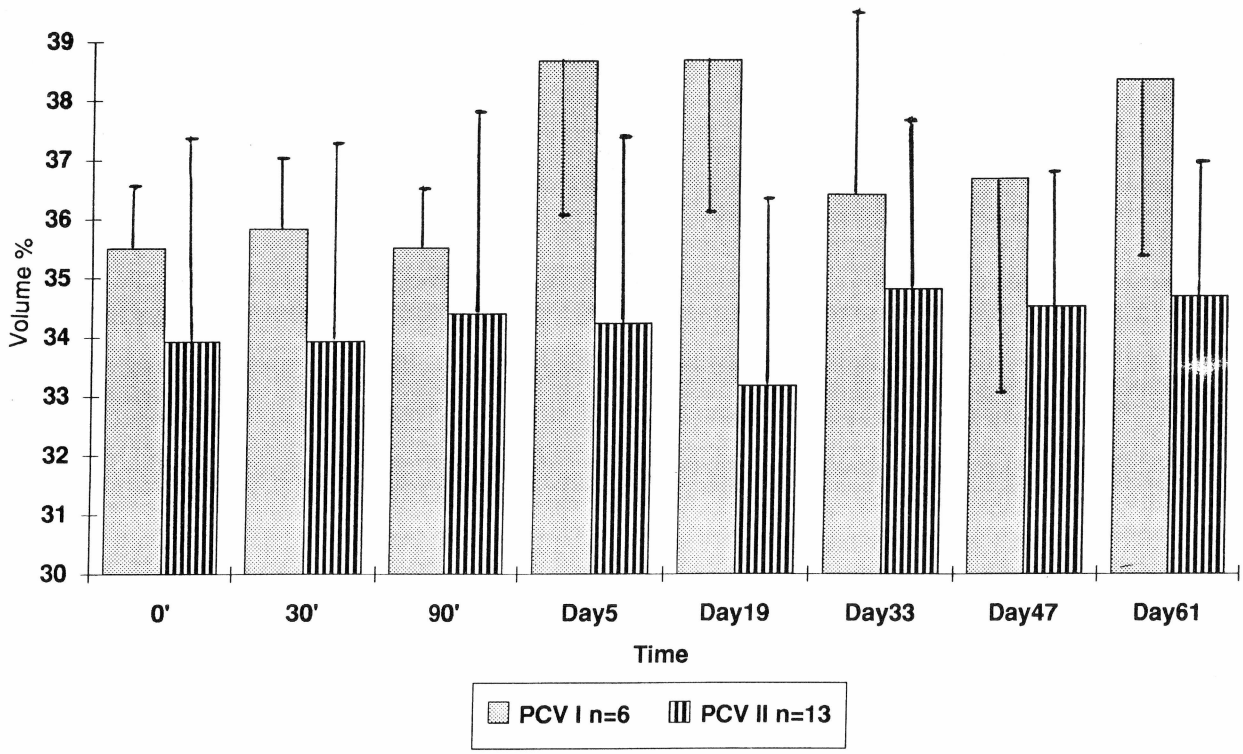

Figure 1. — Effect of combined iron therapy (Chemiron) and single iron therapy on packed red cell volume level during early normal pregnancy.

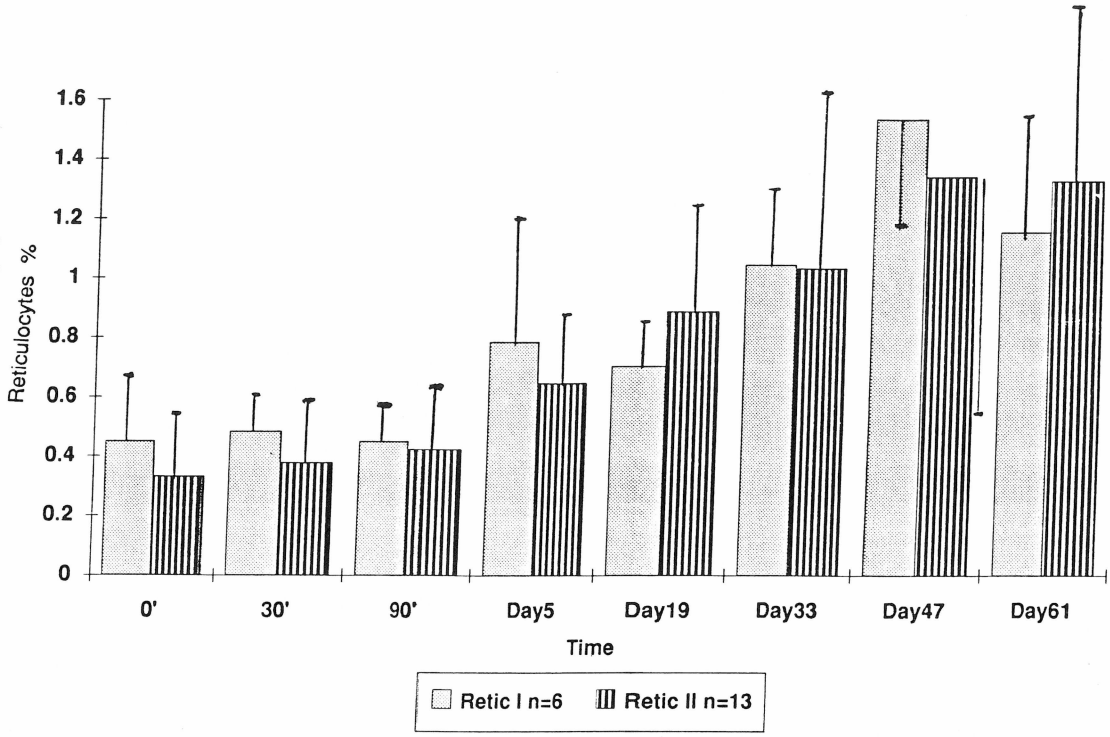

Figure 2. — Effect of combined iron therapy (Chemiron) and single iron therapy on reticulocytes level during early normal pregnancy.

II during the study period on day 5 and day 19 (n = 6/9) mean ± SD 12.250 ± 0.628 / 10.933 ± 1.005 g/dl + = 2.84 (n = 6/6) mean ± SD 12.283 ± 0.407 / 11.233 ± 0.969 + = 2.477 g/dl.

Packed cell volume

The packed cell volume in Group 1 increased from 35.5 ± 1.049 (Vol. % at 0 minute) to 38.667 ± 2.805 (Vol. % on day 5, on day 19 it was 38.667 ± 2.5832 (Vol. %) and 38.33 ± 3.077 (Vol. %) on day 61 (p). No significant differences between Group 1 and II were found during therapy on days 5, 19 and 61 (n = 6/9) 38.6767 ± 2.805 / 34.222 ± 3.38 Vol. %; (n = 6/6) 38.667 ± 2.682 / 33.167 ± 3.312 Vol. %); (n = 6/9) 38.333 ± 3.077 % / 34.667 ± 2.345%) p.

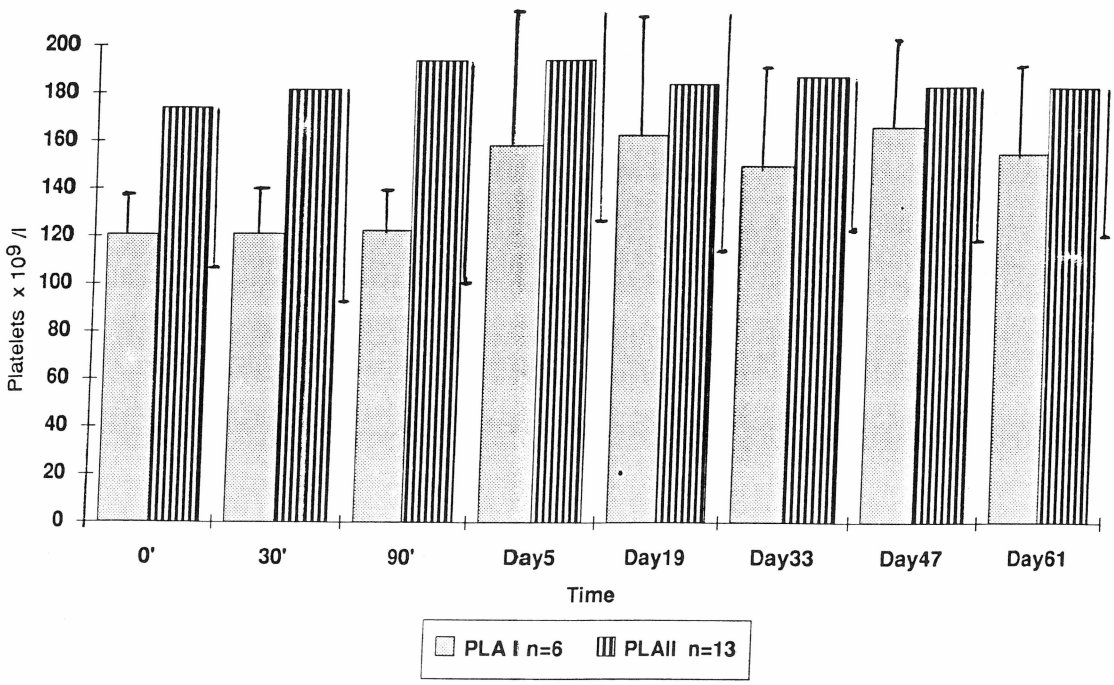

Figure 3. — Effect of combined iron therapy (Chemiron) and single iron therapy on platelet level during early normal pregnancy.

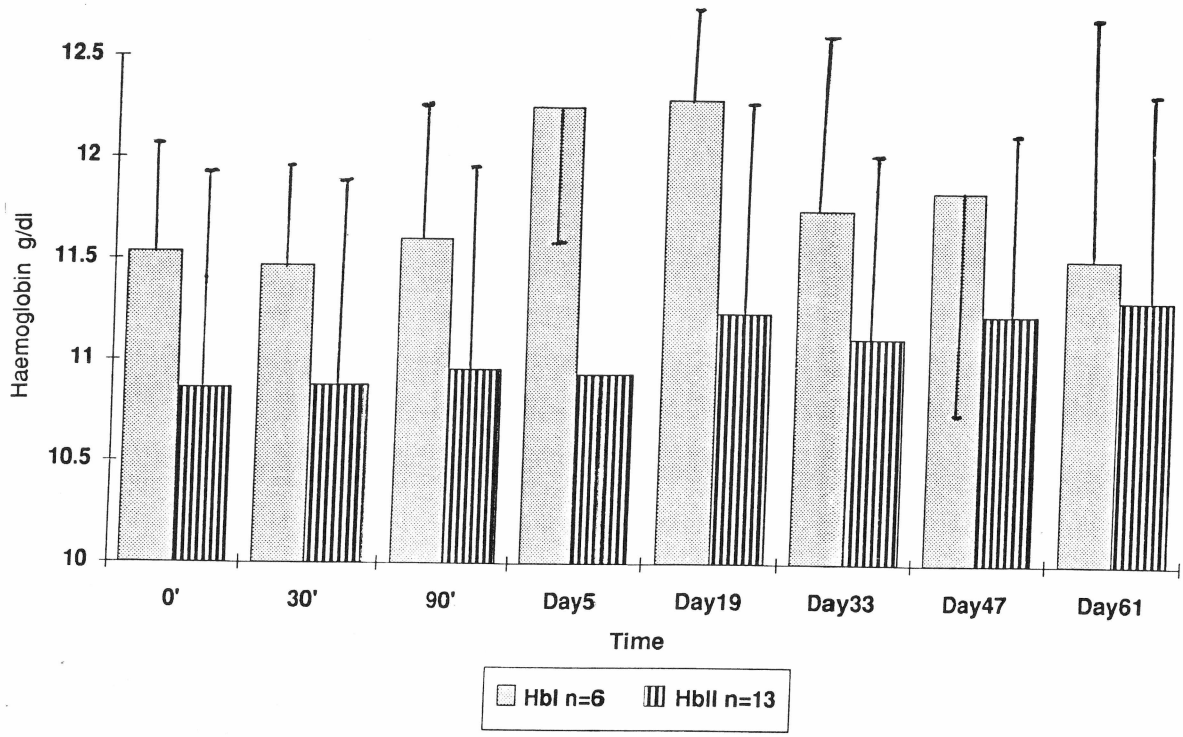

Figure 4. — Effect of combined iron therapy (Chemiron) and single iron therapy on haemoglobin level during early normal pregnancy.

Platelets

Group 1 showed an increase from 120.667 ± 16.765 to 154.167 ± 35.807 * 10 * * 9/L on day 61 but it was not significant. Whereas Group II showed less increase (0 minute = 173.846 ± 87.294 to 193.615 ± 87.238 * 10 * * 9/L at 90 minutes and 193.889 ± 63.100 * 10 * * 9/L on day 5). There was no significant difference between the mean values of platelets during the therapy period in either group.

Reticulocytes

Group 1 showed a significant increase in mean reticulocyte values from 0.450 ± 0.247% at 0 minute / (n = 6) 0.483 + 0.172% at 30 minutes p (n = 6) 0.783 ± 0.442% at day 5, (n = 3) 1.533 ± 0.351% at day 19, (n = 5) 1.040 ± 0.241% at day 33, (n = 3) 1.533 ± 0.351% at day 47, and (n = 6) 1.150 ± 0.367% on day 61. In Group II there was also a sigificant increase of reticulocytes at O' minutes, mean value 0.331 ± 0.206% (n = 13) 0.377 ± 0.213% at 30 minutes (n = 13), 0.423 ± 0.205% at 90 minutes (n = 9); 0.644 ± 0.201% at day 5 (n = 6), 0.883 ± 0.345% at day 19 (n = 10), 0.1030 ± 0.643% at day 33 (n = 8), 1.338 ± 0.930% at day 47 (n = 9), and 1.322 ± 0.676% at day 61. The mean gestational age of the group at the start of therapy was 15.3 ± 4.80 weeks and mean age of the patients 27.8 ± 6.11 years. The mean height and weight in this group was 1.64 ± 0.05 meters and 64.0 ± 10.8 kilograms, respectively. In group II the corresponding mean gestational age at the start of therapy was 16.4 ± 5.92 years, the mean height and weight was 1.66 ± 0.05 meters / 64.2 ± 12.2 kilograms, respectively.

Discussion

In the second trimester the demand for iron increases 3-7 mg per day. Although the absorption of iron increases, only 2-3 mg of iron can be absorbed from nearly 10 mg iron contained in a normal mixed diet. Our results support other studies by other authors recommending iron prophylaxis therapy in order to avoid the development of iron deficiency during pregnancy [1, 9, 18, 27, 31].

Since one-third of the women at the beginning of pregnancy develop a reduced iron depot it is necessary for early onset iron therapy. Although non-response has been shown not to be affected by the presence of folic acid, which is present in Chemiron, folic acid usage has been shown to protect against folic acid deficiency during pregnancy. The growing fetus needs large amounts of folic acid and vitamin B12 for its development. Both substances are coenzymes of DNA synthesis. A pregnant woman needs about 8 mg/day of folic acid and between 0.5 - 1.0 mg per day of vitamin B12, twice as high as in non-pregnant women. The recommended dosage of folic acid daily is between 3 to 5 mg.

Our results showed that during pregnancy combined iron, folic acid, vitamin B12, magnesium and zinc is preferable because iron deficiency often leads to folic acid and vitamin B12 deficiency and apart from this, pregnancy represents a hypomagnesemic and hypozincamic state. In this preliminary report of an on-going study, Chemiron® has been shown statistically to have a better response when compared to ferrous gluconate and folic acid by way of a significant by greater increase in haemoglobin, packed cell volume and reticulocytes value

during the treatment period. However in both groups there were no statistically significant differences between the gestational age at the start of the study, age of the patients, and height and weight of the patients which confirms previous reports by other authors [1, 7, 22, 26, 27]. However, it is hoped that a larger, evaluative series of haematological indices in this condition - now still in progress – may demonstrate conclusively the relationship between these substances and pregnancy.

References

[1] Agboola A., Akinsola S. A. and Olatunji T.: "Chemiron trial in pregnancy". *Nigerian Medical Practitioner*, 1988, *16*, 51.

[2] Ball E. W. C., Giles: "Folic acid and vitamin B12 level in pregnancy and their relation to megaloblatic anaemia". *J. Clin. Path.*, 1964, *17*, 165.

[3] Chanarin I., McFadyen I. R., Kyle R.: "The physiological macrocytosis of pregnancy". *Brit. J. Obstet. Gynecol.*, 1977, *84*, 504.

[4] Cole J. K., Kumter R. J., Kutleacte D.: "Serum folic acid levels and pregnancy in South Australia. A study of the factors associated with particular reference to racial groups and lactation". *Med. J. Austr.*, 1974, *1*, 421.

[5] Cooke J. D., Finch C. A., Smith N. J.: "Evaluation of the iron status in a population". *Blood.*, 1976, *48*, 449.

[6] Dacie J. V. and Oewis S. M.: "Practical Haematology". 7th Ed. Published by Churchill Livingstone, Edinburgh, 1993, *38*, 40, 50, 61.

[7] Fisher H., Tonndorf S., Seyffert C.: "Untersuchunger zur haufigkeit der schwangerschaft anaemia und ihrer beeinflussung durch folicombin". *Zentruabblatt Gynakol.*, 1989, *111*, 142.

[8] Fleming A. F., Martin J. D., Halnel R. F., Westlake A. J.: "Effects of haematology and fetal well being". *Med. J. Aust.*, 1974, *2*, 429.

[9] Fleming A. F., Chatuoan G. B. S., Hammon K. *et al.*: "The prevention of anaemia in pregnancy in primigravida in the Guinea Savanna of Nigeria". *Ann. Trop. Med. Parasitol.*, 1986, *80*, 211.

[10] Gilas C., Burton H.: "Observation on prevention and diagnosis of anaemia in pregnancy". *Brit. Med. J.*, 1960, *27*, 636.

[11] Goeltner E.: "Folsauremangel und schwangerschaft". *Med. Klin.*, 1971, *66*, 973.

[12] Goeltner E., Streigel H., Schuepler E., Leikan G.: "Der folsauregehalf des blutes in schwangerschaft und wochenbett". *Geburtsh. und Frauenheilk*, 1972, *32*, 510.

[13] Goeltner E.: "Iron requirement and deficiency in menstruating and pregnant women". In: "Iron metabolism and its disorders". Eds. H. Kief *et al.*, Excerpta Medica, Amsterdam, 1975, 159.

[14] Goeltner E.: "Haematologische erkrankungen in der schwangerschaft". *Gynaekologe*, 1979, *12*, 52.

[15] Goeltner E.: "Ein viertel der schwangeren ist anaemisch". *Z. Geburtshilfe und Perinatologie*, 1980, *75*, 491.

[16] Goeltner E.: "Kopuskulaeren elementen des blutes". In: "Physiologie der Schwangerschaft". Ed. Friedberg V. and Rathgen G. H. George Thieme Verlag, Stuttgart New York, 1980, 44-67.

[17] Haering M.: "Eisenmangel in der schwangerschaft und im wochembett". *Pro. Med.* (Munchen), 1973, *9*, 193.

[18] Harrison K. A.: "Maternal mortality in Nigeria". Presented at 1st conference of the Society of Gynaecology and Obstetrics of Nigeria at Abuja/Nigeria 1990.

[19] Hausmann, Kuse, Meinecke K. H., Martels H., Heinrich H. C.: "Diagnostische kritieren des praelatenten, latenten und manifesten eisenmangels". *Klin. Wschr.*, 1971, *49*, 1164.

[20] Harju E.: "Clinical pharmacokinetic of iron preparations". *Clin. Pharmacokinetic*, 1989, *17*, 6989.

[21] Heinrich H. C., Bartels H., Heinrich B., Kausmann K., Ruse R., Humke W., Mauss H. J.: "Intestinale 59-resorption und praelatenter eisenmangel waehrend der graviditat des menschen". *Klin. Wschr.*, 1968, *49*, 199.

[22] Hemmiriski E., Rimpalae Ulla: "Iron supplementation, maternal packed cell volume and fetal growth". *Archives of Disease in Childhood*, 1991, *66*, 422.

[23] Herbert V., Colman N., Spivack M. *et al.*: "Folic acid deficiency in the US Folatic assays in a prenatal clinic". *Amer. J. Obstet. Gyn.*, 1975, *175*.

[24] Hibbad B. M.: "Folates and the fetus". *S. Afri. Med. J.*, 1975, *49*, 1223.

[25] Huber H., Schlagelter K.: "Die megaloblataren schwangerschafts anaemia". *Internist*, 1976, *4*, 148.

[26] Ogunbode O., Otubu J. A. M., Briggs M. D. and Adeleye J. A.: "Chemiron – a new haematinic preparation. How effective during pregnancy". *Current Therapeutic Research*, 1992, *51*, 163.

[27] Papadia O. P., Papadia L., Brizio S. and Manusco S.: "Effects of routine iron supplementation in pregnancy". *Current Ther. Res. Clin.*, 1990, *48*, 348.

[28] Petri E.: "Blutgerrinung und Fibrinolyse". In: "Physiologie der Schwangerschafts" Eds. V. Friedbergang, G. H. Rathgen. George Thieme Verlag, Stuttgart, New York, 1980, 68.

[29] Primbs K.: "Eisenbehandlung waehrend der schwangerschaft eine vergleichsstudie". *Geburtsch U. Frauenheilk*, 1973, *33*, 552.

[30] Primbs J., Goeltner E., Lingenberg G.: "Eisen oder kombinierte eisenfolsaure-vitamin B12-behandlung in der schwangerschaft?". *Munch. Med. Wschr.*, 1977, *119*, 865.

[31] Ring D., Retzke U., Briedler H., Bueschke G.: "Eisen prophylaxe der schwangerschaft-luxus oder notwendigkeits?". *Geburtsch. U. Frauenheilk*, 1988, 590.

Address reprint requests to:
G. O. AJAYI M.D.
Senior Lecturer/Consultant
Department of Obstetrics and Gynaecology
College of Medicine, University of Lagos
Idi-Araba, Lagos