The effect of combined iron therapy (Chemiron®) and single iron therapy on the dexamethasone-estriol reaction test for placenta insufficiency during normal pregnancy

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Summary

Impaired uteroplacental perfusion has been shown to play a role in the pathogenesis of some complicated pregnancies with placenta insufficiency. Apart from this, lower oestrogen, magnesium and zinc are found in many of these conditions in the third trimester with placenta insufficiency.

In this study, we examined the effect of a 4 mg intravenous dexamethasone injection on estriol, since maternal cortisol or synthetic corticosteroids cross the placental barrier and inhibit the release of dehydroepiandrostesone sulfate in the fetal adrenals. Dexamathasone was found to suppress estriol levels in all groups but a significant difference in suppression was found between the Chemiron – a new combination hematinic – and the control single iron therapy groups.

Our preliminary results showed that Chemiron has a protective effect on the development of placenta insufficiency during the third trimester of pregnancy.

Key words: Combined Iron (Chemiron®); Single iron; Therapy; Placenta Insufficiency; Dexamethasone Estriol Reaction Test.

Introduction

Our earlier reports [6, 7] and those of other authors [17, 18] showed that the analysis of estriol response in the maternal serum or plasma after short-term suppression of fetal adrenals by dexamethasone may be helpful in differentiating between normal fetoplacental function and fetoplacental impairment in pathological pregnancies [26].

Lower levels of oestrogen may be associated with diminished uteroplacental perfusion. Pregnancies complicated by nutritive placental insufficiency may be associated with a diminished production of estrogen.

In late pregnancy, the placenta requires 19 steroids from the maternal and fetal adrenals for the biosynthesis of estriol (E3); 90.0-95.0% of the estriol produced in the fetoplacental unit is derived from fetal precursors and only 5-10% is of maternal origin. Dehydroepiandrosterone sulfate (DHAS) has been shown to be the major precursor for estriol in the fetoplacental unit.

Synthetic corticosteroid or maternal cortisol [6, 12, 13, 18, 34) are able to pass the placental barrier and inhibit the release of dehydroepiandrosterone sulfate (DHAS) in the fetal adrenals [5, 6, 10, 27, 32, 34, 37]. This inhibition of estriol production is reversible and time limited [6, 17, 18]. The information about uteroplacental blood flow in normal and anaemic pregnant women is still very scarce. This lack of information is also valid for the effect on this uteroplacental blood flow and nutritive placental function of most anti-anaemic drugs inspite of their widespread use during pregnancy. The major causes of anaemia in a developing country like Nigeria are iron deficiency, folic acid deficiency, hemoglobinopathies and malaria. In the drug market today, many hematinic preparations have been introduced. Many of them have not been assessed in controlled clinical trials. Recently a new hematinic preparation, Chemiron (ferrous fumarate 300 mg, folic acid 5 mg, vitamin B12 10 mg, vitamin C 25 mg, magnesium sulfate 0.3 mg and zinc sulfate 0.3 mg), has been introduced into the drug market in Nigeria and contains all the essential blood forming elements. In some studies, it has been shown that Chemiron has a greater hematologic response when compared with ferrous sulfate and folic acid as separate hematinics [1, 4, 30]. Certain essential minerals may serve a physiologic role in regulating the release and/or biologic activity of hormones and neuropetides involved in the menstrual cycle and pregnancy [19, 20, 25, 28, 33, 39] Zinc has been found to be involved in the regulation of progesterone [19] and prolactin activity [28] which is included in Chemiron therapy. Recent data indicate that zinc may play a critical role in endogenous opiate receptor binding in the central nervous system [33].

Although no specific role has been assigned to magnesium in the regulation or maintenance of pregnancy, it is involved in basal energy metabolism that changes over the course of pregnancy. Furthermore, it is believed that magnesium deficiency may be a possible cause of many pathological conditions of pregnancy [2, 8, 14, 25].

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 placenta separation [3, 12, 22, 23, 24].

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In this study we report the effect of different hematinic therapies including Chemiron®, a new combination haematical agent, on a Dexamethasone-Estriol Reaction Test for placental insufficiency during the third normal trimester of pregnancy.

Materials and Methods

A total of 25 patients were studied. Group I (n=9 patients) was treated with Chemiron, one capsule daily. If they reported any malaria attacks they were immediately given 3 tablets orally of Fansidar® (sulfadoxine 500 mg, pyrimethamine 25 mg) or Chloroquine and Phenergan (promethazine HCL) medications starting from the first trimester of pregnancy. The ages of the patients varied between 20 and 33 (25.8±4.3 years). Each capsule of Chemiron contained ferrous fumerate (300 mg), folic acid (5 mg), vitamin B12 (10 mg), vitamin C (25 mg), magnesium sulfate (0.3 mg), and zinc sulfate (0.3 mg). The gestational age in the Chemiron group ranged between 28 and 34 weeks. Group II constituted by 9 normal pregnant patients in the III trimester were treated with Fergon (ferrous gluconate, 300 mg) one tablet twice daily, folic acid (0.5 mg) one tablet daily and Daraprim (phrimethamine, 25 mg) from the first trimester of pregnancy. The ages of the patients varied between 22-31 years. (24.6±3.8 years (mean ± SD year). Gestational age ranged between 28 and 35 weeks. The third group was constituted by 7 normal pregnant patients treated with ferrous sulfate (200 mg) one tablet twice daily, folic acid (5 mg) once daily and Daraprim (phrimethamine, 25 mg) one tablet weekly, also starting from the first trimester. The ages of the patients varied between 23-35 years. 26.4 ± 4.8 (mean ± SD weeks). To perform the Dexamethasone-Estriol Reaction Test (Dexa-E3-R-Test) venous blood samples for basal estriol (E3) values were drawn at 8.00 a.m. from each patient studied.

Four mg of dexamethasone by intravenous injection (Decadron phosphate/MSD sharp Dohme-Lagos/Nigeria) were given. Blood samples were drawn again at 12:00, 16:00, and 20:00 p.m. and 8.00 a.m. on the next day (usually on a Wednesday when the investigating team were on emergency call), centrifuged and stored at –20°C, before determination of serum unconjugated estriol by radio-immuno-assay (RIA). The interassay ratio for estriol was between 8-12%.

The dexamethasone estriol reaction tests were performed in 25 women once from 28 to 35 gestational weeks in the 3 groups. The patients in group II and III served as controls. Routine statistical methods (Student's t-test, Newmann Keul procedure and Wilcoxon paired rank test) were used. Data are expressed as mean ± SD (Standard Deviation). Patients with abnormal haemoglobin, overt infection or those found to have white blood counts (WBC) greater than 10,000/U and a sedimentation rate (SDR) more than 10/15 mm were excluded.

Results

Fig. 1 shows the mean Dexamethasone-Estriol Reaction Test curves in normal III trimester pregnant patients on different types of hematinic regimens.

The Dexamethasone-Estriol Reaction Test during treatment with Chemiron® shows significant improvement when compared to the control group on single iron therapy (ferrous sulfate and ferrous gluconate ($p<0.05$, $p<0.01$) Fig. 1.

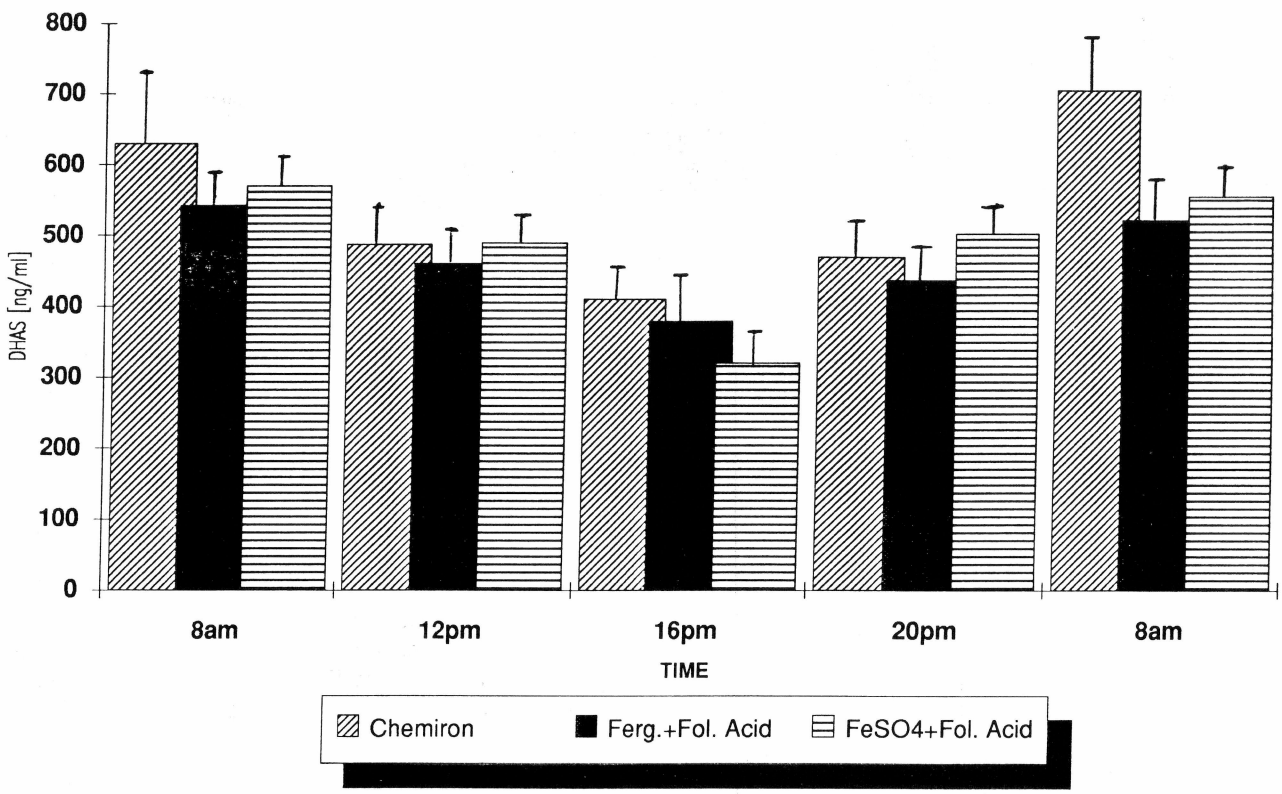

Figure 1. — Effect of 4 mg Dexamethasone Test for placenta insufficiency on plasma levels of dehydroepiandrosterone sulphate during different haematinic therapy.

Discussion

The pituitary adrenal system of a healthy fetus has been shown to be able to respond after transient suppression with a more pronounced output of adrenal estriol E3 precursors than does the adrenal system of a fetus of patients with placenta insufficiency [17, 18]. In this study treatment with Chemiron® was found to significantly improve the Dexamethasone-Estriol Reaction Test more than the single iron therapy with ferrous sulfate and ferrous gluconate.

Chemiron®, a new hematinic formula which contains ferrous fumarate (300 mg), folic acid (5 mg), vitamin B12 (10 mg), vitamin C (25 mg), magnesium sulfate (0.3 mg) and zinc sulfate (0.3 mg) differs in combination from the other treatment regimens by the presence of essential elements like vitamin C, vitamin B12, magnesium and zinc sulfate.

Recently, we showed that a significant reduction in the level of magnesium starts from the 2nd to the 15th week of pregnancy and remains low until birth in Nigerian women in a cross-sectional study, whereas in another study the lowest level was found in the 25th-28th gestational week [6, 7, 9].

The tap water in Lagos City in Nigeria was found to have different levels of magnesium [9]. A high demand for magnesium during pregnancy and adolescence has been reported by Seelig [31]. This high demand explains the reason for the decline in magnesium levels observed during pregnancy due to increased metabolism in the mother and the presence of a rapidly growing fetus.

Thus a woman with a normal magnesium level before pregnancy will during pregnancy have a relatively low plasma magnesium level if she does not increase her dietary magnesium intake.

The early onset of low levels of plasma magnesium and lower levels of drinking tap water in some parts of the city of Lagos could be a contributory factor to the high incidence of edema-proteinuria-hypertension gestosis-comple (preeclampsia/eclampsia/toxemia) with different severities of placental insufficiency. This hypomagnesiemia during pregnancy has been attributed to hemodilution [16] and to the effect of oestrogen [15].

During pregnancy serum/plasma zinc concentration has been reported to decrease with increased gestational age [29]. A result to be confirmed by an on-going study in Nigerian women. There are two possible interpretations. The first, again, is in plasma volume expansion and hypoalbuminemia [11, 21, 35, 36].

These findings further confirm a possible causal relationship between the condition of placenta insufficiency, low magnesium, zinc, and oestrogen levels during pregnancy, although the rest of the essential elements like folic acid, vitamin C, vitamin B12 could have an additional effect.

Our preliminary findings showed that Chemiron has a proctective effect on the development of placenta insufficiency during the third trimester of pregnancy using the Dexamethasone-Estriol Reaction Test.

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