Effect of combined iron therapy (Chemiron®) and single iron therapy on the dexamethasone-estriol test effect, on plasma dehydroepiandrosterone sulfate during normal pregnancy

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Summary

It is established that during human pregnancy maternal and fetal serum dehydroepiandrosterone sulfate (DHAS), which has been shown to arise mainly by adrenal secretion, serves as a substrate in the biosynthesis of placental oestrogen. The conversion to oestrogen is reflected by decreased DHAS and increased oestrogen concentration in the peripheral maternal blood.

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 levels are found in many of these conditions in the third trimester with placenta insufficiency.

In this study, we examined the effect of 4 mg Dexamethasone intravenously on dehydroepiandrosterone sulfate, since materal cortisol or synthetic corticosteroids cross the placental barrier and inhibit the release of dehydroepiandrosterone sulfate in fetal adrenals. Dexamethasone was found to suppress dehydroepiandrosterone sulfate levels in all groups but a significant difference in suppression was found between the Chemiron – a hematinic combination – and the single iron therapy control 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 Test; Dehydroepiandrosterone Sulfate Level.

Introduction

It is established that during human pregnancy maternal and fetal serum dehydroepiandrosterone sulfate (DHAS), which has been shown to arise mainly by adrenal secretion [1, 31], serves as a substrate in the biosynthesis of placental oestrogen [11, 14, 34]. The conversion to oestrogen is reflected by decreased DHAS and increased oestrogen concentration in peripheral maternal blood [35, 36, 40]. Recently our results and those of other authors have demonstrated a decrease in maternal serum or plasma concentrations of DHAS in the course of advancing pregnancy [8, 30, 33, 36] and a negative correlation has been found between gestational age and maternal DHAS levels [8, 30]. Furthermore, significantly lower mean levels of DHAS were found in the EPH-gestosis with placenta-insufficiency group when compared to normal women of the same gestational age with normal placenta function [8]. In many of these conditions impaired regional perfusion is considered to be the principle feature.

The administration of different types of drugs to eradicate or protect regional perfusion is popular. Gant in 1971 [19] demonstrated that labelled DHAS disappeared more slowly from the plasma of EPH-gestosis women, for example, than from the plasma of normal pregnant women at the same stage of pregnancy. Since the metabolic clearance rate of dehydroepiandrosterone sulfate (MCR-DHAS) appears to reflect among other things uteroplacental blood flow, one might presume from these results that uteroplacental blood flow is decreased in EPH-gestosis. Further studies by the same group have also shown that pharmacologic manipulation like treatment with hydrochlorothiacid, hydralazine hydrochloride and furosemide in hypertensive pregnancy was followed by an average decrease in metabolic clearance rate of dehydroepiandrosterone sulfate.

MCR-DHAS has been shown to be the major precursor for estriol in the fetoplacental unit [20, 21].

Synthetic corticosteroid or maternal cortisol [7, 17, 18, 37] is able to pass the placental barrier and inhibit the release of dehydroepiandrosterone sulfate (DHAS) in the fetal adrenals [6, 7, 12, 13, 28, 39]. 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 antianaemic 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

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B12 10 mg, vitamin C 2 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 was shown that Chemiron has a greater hematologic response when compared with ferrous sulfate and folic acid as separate hematinics [3, 4, 32].

Certain essential minerals may serve physiologic roles in regulating the release and or biologic activity of hormones and neuropeptides involved in the menstrual cycle and pregnancy [16, 22, 23, 27, 29, 38, 41] Zinc which is contained in Chemiron therapy, has been found to be involved in the regulation of progesterone [16] and prolactin activity [22].

Recent data indicate that zinc may serve a critical role in endogenous opiate receptor binding in the central nervous system [38].

Although no specific role has been assigned to magnesium in the regulation or maintenance of pregnancy, magnesium 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 [1, 10, 16, 27].

Folic acid deficiency can impair fetal growth either immediately or through the reduction of placental functioning. This can lead to abortion, fetal malformation and early placenta separation [5, 15, 24, 25, 26].

In this study, we report the effect of different hematinic therapies including Chemiron®, a new combination haematinic agent, on the Dexamethasone-Estriol Test effect on plasma dehydroepiandrosterone sulfate during the third normal trimester of pregnancy.

Material and Methods

A total of 25 patients were studied. Group 1 consisted of 9 patients treated with Chemiron (one capsule daily) and if they reported any malaria attack they were immediately given 3 tablets orally of Fansidar® (sulfadoxine 500 mg, pyrimethamine 25 mg) or Chloroquine and phenergan (promethazine HCL) medication 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 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). 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 (pyrimethamine 25 mg) from the first trimester of pregnancy. The ages of the patients varied between 22 and 31 years (24.6 ± 3.8 years (mean ± SD years). To perform the Dexametharone-Estriol Reaction Test (Dexa-E3-R-Test) venous blood samples for basal dehydroepiandrosterone sulfate values were drawn at 8.00 a.m. from each patient studied; 4 mg of dexamethasone by intravenous injection (decadrone 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 dehydroepiandrosterone sulfate by radio-immuno-assay (RIA). The interassay ratio was 8.3% and interassay ratio 5.9% for dehydroepiandrosterone sulfate. The Dexamethasone-Estriol Reaction Test was performed on 25 women once between 28 and 35 gestational weeks in the 3 groups. The patients in group II served as controls.

Routine statistical methods (Student's-test, Newman 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 curves of dehydroepiandrosterone sulfate response to the Dexamethasone-Estriol Reaction Test in normal III trimester pregnant patients on different types of hematinic regimens. The response of patients treated with Chemiron showed significantly more improvement when compared to the control group on single iron therapy (ferrous sulfate and ferrous gluconate, $p<0.05/p<0.01$). See fig. 1.

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 fetuses of patients with placenta insufficiency [18, 37]. During human pregnancy maternal and fetal serum/plasma dehydroepiandrosterone sulfate (DHAS), which has been shown to arise mainly from adrenal secretion, serves as a substrate in the biosynthesis of placental oestrogens including estriol [1, 14]. Recently decreases in the maternal serum/plasma concentration of DHAS in the course of advancing pregnancy [8, 35] have been reported. Significantly lower mean levels of dehydroepiandrostesone sulfate were found in conditions with impaired placenta perfusion when compared to normal pregnant women of the same gestational age studied [8].

In this study, treatment with Chemiron® was found to significantly improve the Dexamethasone-Estriol Reaction Test effect on dehydroepiandrostesone sulfate 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 the essential elements vitamin C, vitamin B12, magnesium and zinc sulfate. Recently in a cross-sectional study of Nigerian women we showed that a significant reduction in the level of magnesium starts from the 2nd to 15th week of pregnancy and remains low until delivery whereas in another study the lowest level was found in the 25th-28th gestational week. The drinking tap water in Lagos, Nigeria was found to have different

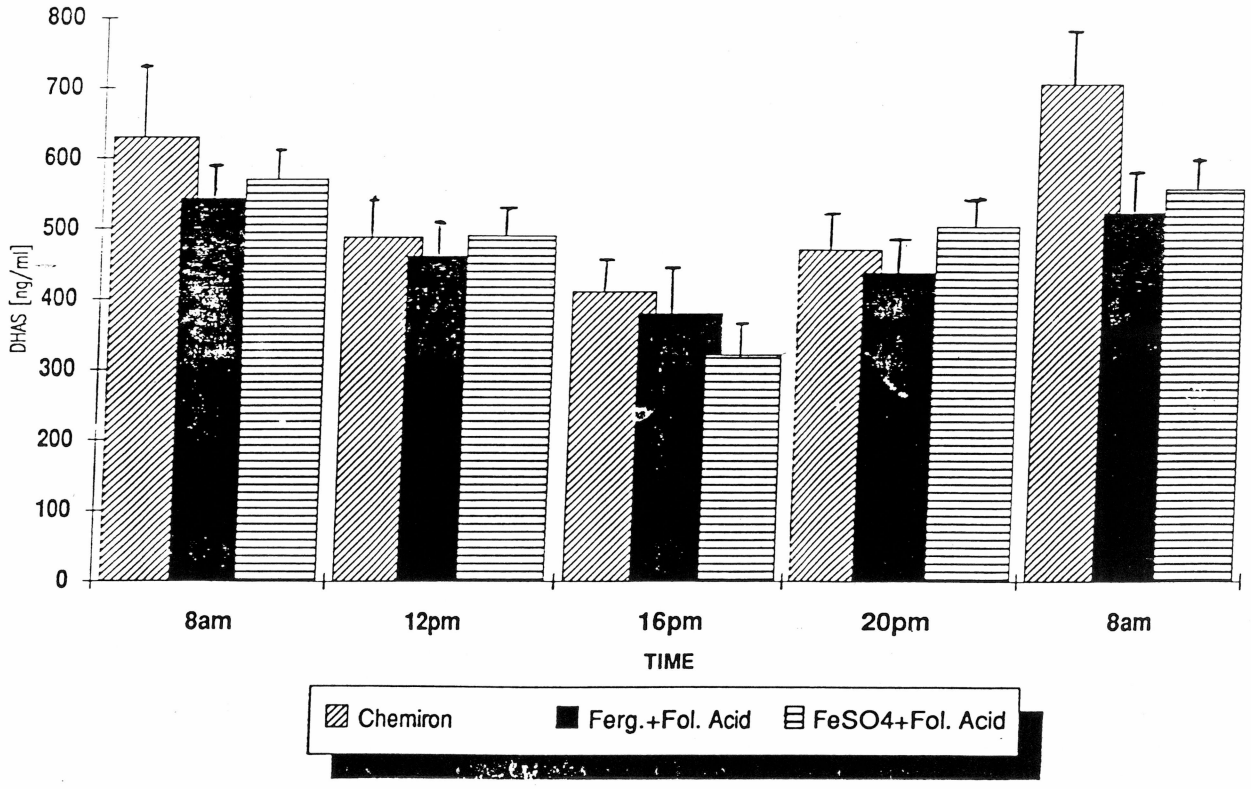

Figure 1. — Effect of 4 mg Dexamethasone Test for placenta insufficiency on plasma level of dehydorepiandrosterone sulphate during different haematinic therapies.

levels of magnesium [10]. High demand for magnesium during pregnancy and adolescence has been reported [16]. This high demand explains the reason for the decline in magnesium levels observed during pregnancy due to increased demand in the mother and 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 in the drinking water in some parts of the city of Lagos could be contributory factors to the high incidence of edema-proteinuria hypertension gestosis complex with different severity of placental insufficiency. This hypo-magnesiamia during pregnancy has been attributed to haemodilution [17] and to the effect of oestrogen [7]. During pregnancy serum or plasma zinc concentration has been reported to decrease with increased gestational age [38]. (A result to be confirmed by an ongoing study in Nigerian Women). There are two possible interpretations. The first again is plasma volume expansion followed by hypoalbuminemia [8, 10, 12, 15].

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

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