Serum changes of Ferroxidases and iron-binding capacity in pregnancy

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Summary: Serum changes of Ferroxidase I and II well as the total iron binding capacity (TIBC) and unsaturated iron binding capacity (UIBC) were measured thoughout their gestation in 32 normal pregnant women. Significantly higher concentrations for all the above mentioned parameters were found as pregnancy advanced. Moreover, a significant and positive correlation between the weeks of gestation and a) serum Ferroxidase I ($r:0.568$ $p<0.001$), b) serum Ferroxidase II ($r:0.619$ $p<0.001$), c) serum TIBC ($r:0.549$ $p<0.01$), and d) serum UIBC ($r:0.424$ $p<0.05$) was found. The parallel serum changes of both ferroxidase with those of TIBC and UIBC are also shown in this study. The correlation of Ferroxidase I with TIBC ($r:0.734$ $p<0.001$) and UIBC ($r:0.536$ $p<0.01$) as that of Ferroxidase II with TIBC ($r:0.634$ $p<0.001$) and UIBC ($r:0.513$ $p<0.01$) was significant and positive.

In conclusion, serum Ferroxidase I and II are progressively increased with serum TIBC and UIBC as pregnancy advances.

Key words: Ferroxidase, Iron-binding capacity; Pregnancy.

INTRODUCTION

Pregnancy is a condition which is characterized by significant physiological alternations. So circulatory, cellular and immunological changes occur during gestation. Moreover, pregnant women are at increased risk for hematological changes due to iron deficiency ([1]).

During pregnancy, iron is mainly mobilized from iron stores by the action of Ferroxidase I, which promotes its incorporation into transferrin in order to transfer iron for hemoglobin synthesis. The action of Ferroxidase II in non-pregnant women in relation to iron mobilization is minimal while the changes of serum Ferroxidase II during normal gestation are unclear. It is well known that during pregnancy an increase in total iron binding capacity (serum transferrin) occurs. However, the serum changes of transferrin in relation to the serum fluctuations of ferroxidase I as well as that of Ferroxidase II have not been well investigated.

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MATERIALS AND METHODS

A total of 32 normal pregnant women were included in this study. All women had received a daily oral dose of 300 mg of ferrous sulfate and hemoglobin concentration was no less than 10.5 g/100 ml throughout their gestation.

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XX, n. 2, 1993

Blood serum samples for Ferroxidase I, Ferroxidase II, total iron binding capacity (TIBC) and unsaturated iron binding capacity (UIBC) were measured in all patients.

For the parameters studied, blood samples were collected from fasting subjects in the morning. Ferroxidase I and II activity was estimated by a colorimetric method in which Fe^2 is used as a proper substrate and its oxidation to Fe^3 yields the total serum ferroxidase activity (μmol/L/min). By adding sodium aride, Ferroxidase I activity is inhibited and the remainder belongs to Ferroxidase II. The difference between total and Ferroxidase II activity represents Ferroxidase I activity (3). Serum TIBC and UIBC were measured by a colorimetric method in which transferrin is saturated with trivalent iron and the total iron which yields the TIBC is then determined. The difference between the TIBC and actual serum iron belongs to UIBC (4).

The levels of Ferroxidase I and II in non-pregnant normal women were 235±37.5 and 15.4±4.8 μmol/L/min respectively. The normal levels for TIBC range between 44.7 and 68 μmol/L (3, 4). Statistical analysis was carried out using the chi-square test and student's t-test to evaluate the differences between means in the three trimesters of pregnancy.

RESULTS

The mean serum value of ferroxidase I was 337.06±56.58 μmol/L/min in the first, and higher (mean 415.61±55.46) in the second trimester of pregnancy ($p < 0.01$). A further though not statistically significant increase was found in the third trimester of pregnancy (mean 467.81± 86.75 μmol/L/min). The serum changes of ferroxidase I from the beginning to the end of the pregnancy are shown in Fig. 1,

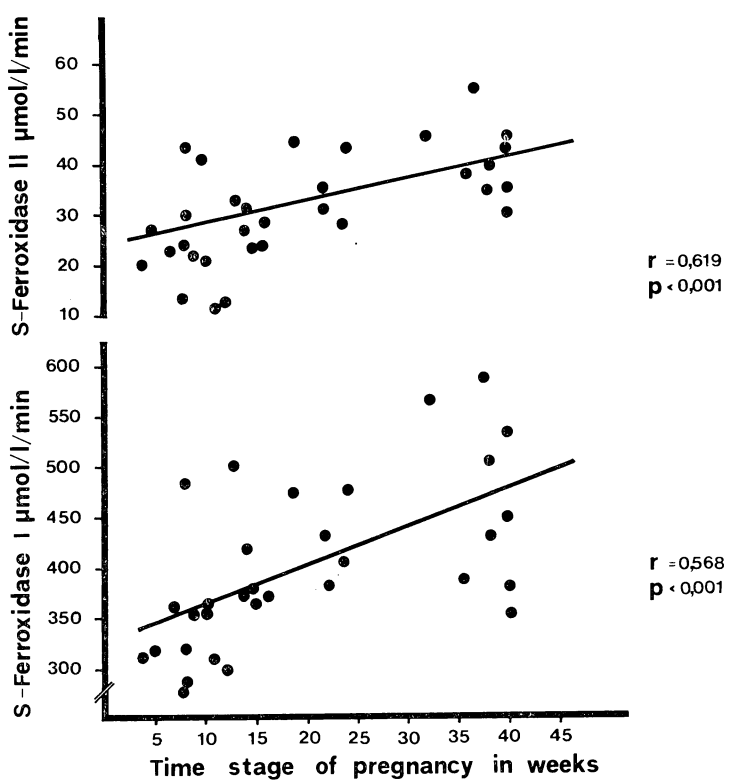

Fig. 1. — Correlation between serum activity of ferroxidase I and II and weeks of pregnancy.

where a significant and positive correlation between the weeks of gestation and ferroxidase I activity was found (r: 0.568 $p < 0.001$).

There were no statistically significant differences in mean values of ferroxidase II between the two first trimesters of pregnancy (24.52 ± 10.14 μmol/L/min and 31.94 ± 6.92 μmol/L/min respectively). The mean serum value of ferroxidase II was 41.08 ± 7.49 μmol/L/min in the third trimester, higher than that of the second ($p < 0.05$), as well as that of the first trimester of pregnancy ($p < 0.001$).

As is shown in Fig. 1, significant increase of ferroxidase II activity was observed as the pregnancy advanced (r: 0.619 $p < 0.001$). The mean serum value of TIBC was 60.90 ± 9.1 μmol/L/min in the first trimester and higher (71.64 ± 6.16 μmol/L/min) in the second trimester of pregnancy ($p < 0.01$). A further increase in the third trimester was not statistically difference (mean 74.42 ± 5.48 μmol/L/min). The levels of serum TIBC during pregnancy are shown in Fig. 2, where a significant and positive correlation between the activity of TIBC and the weeks of pregnancy is illustrated (r: 0549 $p < 0.01$). The mean serum values of UIBC was found 42.02 ± 16.33 μmol/L/min in the first and 52.06 ± 8.76 μmol/L/min in the second trimester of pregnancy (NS). The mean value of UIBC was 55.73 ± 7.55 μmol/L/min in the third trimester, not statistically significant different from that of second trimester, but higher than the mean value (42.02 ± 16.33 μmol/L/min) of the first trimester of pregnancy ($p < 0.05$).

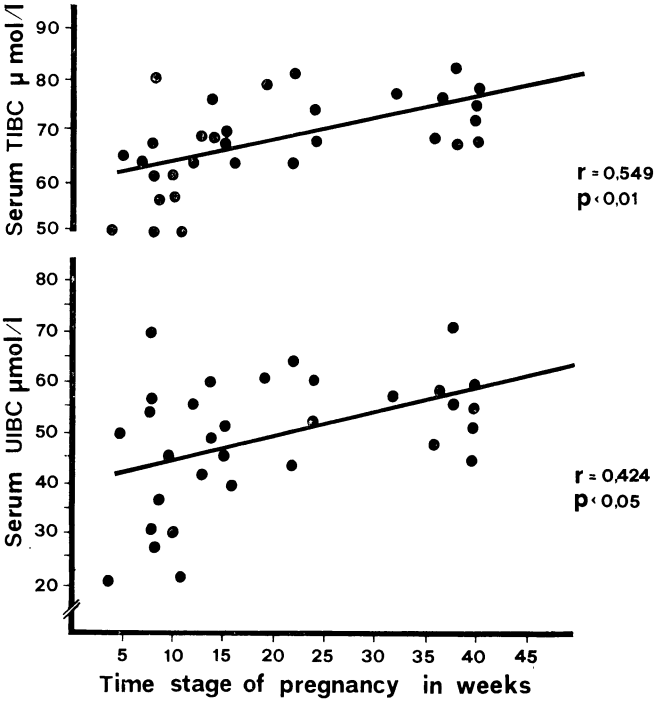

Fig. 2. — Correlation between serum levels of TIBC and UIBC and weeks of pregnancy.

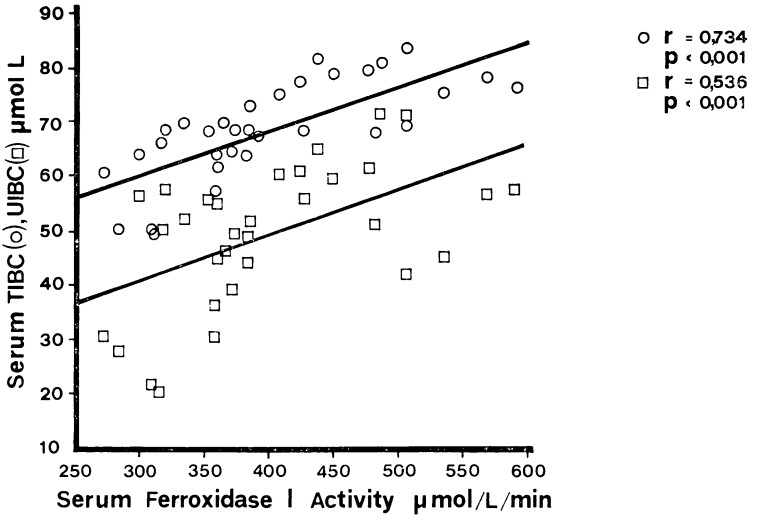

Fig. 3. — Correlation between ferroxidase I and TIBC and UIBC during normal gestation.

The serum levels of UIBC follow the alternation of levels of TIBC during normal pregnancy (Fig. 2, r: 0.549 $p<0.05$).

The parallel changes the activity of the ferroxidases with those of TIBC and UIBC are shown in Figs. 3 and 4. Fig. 3 shows a significant and positive correlation of ferroxidase 1 with serum TIBC (r: 0.734, $p<0.01$) and serum UIBC (r: 0.537, $p<0.01$). A significant and positive correlation of ferroxidase II with serum TIBC (r: 0.634, $p<0.001$) and serum UIBC (r: 0.513 $p<0.01$) is shown in Fig. 4.

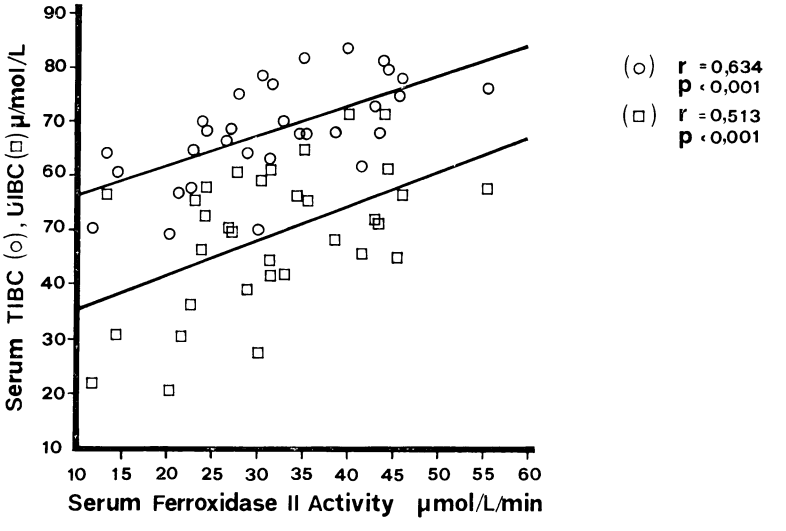

Fig. 4. — Correlation between ferroxidase II and TIBC and UIBC during normal gestation.

DISCUSSION

Ferroxidase I is a cuproprotein with an important biological role in the release and transfer of iron from storage cells to plasma transferrin. Ferroxidase II is also a cuproprotein, which contributes to approximately 7% of total ferroxidase activity in normal non pregnant women. However, there is evidence that the activity of ferroxidase II increases in the case of low serum activity of ferroxidase I ([2, 5]).

Because ferroxidase I and II are involved by iron oxidation in Fe^3-transferrin formation and ultimately in hemoglobin biosynthesis, a correlation between the serum changes of ferroxidase activity and serum-iron-binding capacity (TIBC) could in some conditions, be justified ([6, 7]). Pregnancy is a condition where iron is mobilized from the maternal circulation to the uterus in order to meet the increased demands for iron from the fetus and placenta. The major source of mobilized iron is derived from iron bound to maternal serum transferrin ([1, 8]).

It is well known that plasma transferrin concentration is usually increased with iron deficiency. This increase may occur before anemia develops and it is most extreme in severe iron depletion. There is also inverse relationship between hepatic synthesis of transferrin and parenchymal liver iron content ([1, 8, 9]).

During gestation the mother is at increased risk for the development of iron deficiency. This deficiency is associated with low serum levels of ferritin and high concentrations of total iron binding capacity despite of the normal levels of hemoglobin. In contrast, the fetus is iron sufficient with high serum ferritin and low iron binding capacity.

Our data showed a gradual increase of serum total iron binding capacity as pregnancy advanced, although none of our patients had lower than 10.5 g/100 ml hemoglobin. Moreover, our data incidadated a parallel increase of serum unsaturated iron binding capacity (UIBC).

It is also known that conditions of rapid hemoglobin synthesis, such as in growth or pregnancy, are associated with high serum ferroxidase activity.

During gestation a marked amount of iron is mobilized from the mother to the fetus. The increased mobilization of iron in pregnancy is accompanied by increased ferroxidase acitivity ([1, 2, 10]).

Apart from iron-deficient anemia, the estrogenic stimuli induces changes in serum transferrin and in serum ferroxidase activity. In pregnant women and in subjects receiving therapeutic doses of estrogens, high levels of serum transferrin and serum ferroxidase I have been demonstrated. Endogenous or exogenous estrogens also cause significant increase in serum copper levels and in this way many estrogens are contributed to an increased synthesis of ferroxidase I ([2, 10, 11, 12, 13]).

In our study elevated levels of ferroxidase I as well as ferroxidase II were observed. We could not find precise explanation in the literature, for the progressive increase of serum ferroxidase II activity in pregnancy, which was observed in this study. It seems that the increased serum ferroxidase II activity may be due to estrogenic stimuli as well as to the iron deficient anemia of the pregnancy.

Our results also indicate that under conditions of rapid hemoglobin synthesis such as pregnancy, the demands of ferroxidase activity for iron mobilization are not only met by ferroxidase I, but ferroxidase II also plays a significant role in this procedure.

Moreover, our results showed a parallel increase of serum ferroxidase I with the increase of serum transferrin. A positive correlation between serum ferroxidase II and serum transferrin during normal pregnancy was also found.

The findings of the present study may have practical interest since, instead of measurement of serum transferrin the measurement of serum ferroxidase I or serum ferroxidase II can show with great reliability the development of iron deficiency anemia during pregnancy.

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