increase in the urine protein reference range. Each laboratory should establish its own reference range for urinary protein.

References

Increased Serum Sulfate in Pregnancy: Relationship to Gestational Age
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Controlled-flow ion chromatography has significantly improved the precision with which inorganic sulfate (SO₄) can be measured in serum. In this study, we have shown that serum SO₄ is increased in pregnancy. The increase appears to follow gestational age, resulting in a 39% higher value by the middle of the third trimester. We suggest that this increase is a natural physiological process, which enhances SO₄ availability to the growing fetus and placenta.

Until recently, the relative imprecision of standard assay methods has prevented a detailed analysis of factors affecting concentrations of sulfate (SO₄) in the circulating blood (1). Renewed interest in this metabolite has been stimulated by the discovery of new classes of sulfate-conjugated molecules, including the tyrosine residues of selected proteins (2), bile acids, and an expanding family of glycolipids and glycoproteins (3).

Furthermore, new physiological roles for the sulfate-conjugation process have been described. The growing fetus is a net consumer of SO₄ (4), obtaining the metabolite as free inorganic SO₄ after transfer from maternal to fetal circulation via active transplacental transport (5, 6). Several earlier reports described an increase in SO₄ in the serum of pregnant women (7, 8), but offered little information about its relation to gestational age. We assayed serum SO₄ in 144 pregnant women and 44 non-pregnant controls. The aggregate data demonstrate a strong positive correlation between gestational age and SO₄ concentration, irrespective of the group into which the subject was categorized.

Materials and Methods

Samples were obtained from five groups of women: (a) controls, (b) pregnancy terminations, (c) clinic pregnancies, (d) high-risk pregnancies, and (e) women in labor. The 44 non-pregnant controls were laboratory staff volunteers, 17 to 44 years old. Pregnancy terminations (n = 28) were women of ages 13 to 39 years, who were admitted to hospital in the mid-second trimester for therapeutic abortion. All of these women were ostensibly in good health. Clinic pregnancies (n = 39) were healthy, ambulatory women, ages 15 to 35 years, who were seen for routine antenatal care at the walk-in clinic of the Grace Maternity Hospital. The 31 high-risk pregnancies were women of ages 19 to 38 years, who were admitted to hospital during the second and third trimester with potential obstetric complications. Patients with hypertension or renal failure were excluded. None of the women was in any acute distress at the time of study; a complete clinical description of this group appears elsewhere (9). The last group consisted of 46 women, ages 19 to 39 years, who were sampled at the time of delivery. A summary of their clinical features also appears elsewhere (9).

Methods

Blood sampling was not timed, although most specimens were taken during the morning hours. Serum was stored at −20 °C until analysis.

Inorganic sulfate was separated and quantified by controlled-flow ion chromatography according to procedures described previously (10). Sample serum were diluted with a 1 mmol/L solution of NaOH and injected directly. The D-10 Ion Analyzer (Dionex Instruments, Sunnyvale, CA) was equipped with two guard pre-columns. Chromatographic profiles of sera from pregnant women were quantified by peak height against known standards.

Statistical analyses included Student’s t-test, one-way analysis of variance, and multiple linear regression analysis. A MINTAS statistical package (University of Pennsylvania, 1981) was used for data reduction.

Results

Table 1 shows the statistics describing each group. Values for non-pregnant controls are not different from those we have described previously (10). Mean serum SO₄ was higher in all the groups of pregnant women as compared with controls. In the case of the pregnancy-termination group the difference was small, but the other groups were significantly higher (p <.05), as judged by one-way analysis of variance. Because there are differences among the mean gestational intervals for each of the four pregnancy groups, we used
multiple linear regression analysis to separate group effects from gestational effects on serum SO$_4$. This analysis showed that the strong positive correlation ($r = 0.67$, $p < .0001$) between gestation and serum SO$_4$ concentration remained after group effects were taken into account. A linear first-order regression equation fits the data as well as any other of the usual transformations (Figure 1). However, a visual assessment of the graphic data suggests that a larger sample might show a better curvilinear fit, in which the predicted serum SO$_4$ increases more rapidly after the middle or late second trimester.

**Discussion**

The advent of ion chromatography has led to a much improved precision in the assay of inorganic SO$_4$ in biological fluids (10). Pathophysiological changes in serum SO$_4$, as related to age, sex, and disease can now be reliably quantified. Tallgren (7), who first reported an increased serum SO$_4$ in 118 pregnant women, used a radiolabeled barium precipitation assay. He described a significant relationship to trimester and noted that concentrations were highest in the last trimester. However, he reported SO$_4$ concentrations that considerably exceed ours or those reported by Morris and Levy (8). Moreover, he suggested that concentrations were higher in the first trimester than in the second, an observation we cannot confirm. The data of Morris and Levy are based on a very small sample of third-trimester women ($n = 7$) and non-pregnant controls ($n = 9$). Their results, indicating a 23% increment in serum SO$_4$, are in accord with our data, although we predict a 39% increase for women by the middle of the third trimester.

Our conclusion that serum SO$_4$ increases as pregnancy advances leaves unanswered the questions of how and why. A partial explanation appears to be that inorganic SO$_4$ is more avidly reabsorbed by the maternal kidney, at least in the selected group of high-risk third-trimester pregnancies (9). The lack of significant differences between the groups of pregnant women—once the period of gestation is taken into account—suggests that the increase is a natural physiological one. The very gradual increase during the first half of pregnancy and the more substantial increase thereafter appear to match the exponential rise in fetal growth rate, further suggesting that maternal metabolism adapts to enhance SO$_4$ availability to the fetus (5, 6, 9).

Longitudinal studies of healthy women before, during, and after pregnancy may lend more weight to these ideas and offer further clues as to the mechanisms that regulate serum sulfate.

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