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Correlation of Neopterin Concentrations in Amniotic Fluid and Urine of Pregnant Women at Delivery

Bernhard Widner¹, Lothar C. Fuith², Maryan Czarnecki² and Dietmar Fuchs^{1*}

¹Institute for Medical Chemistry and Biochemistry, University of Innsbruck, Fritz Pregl Straße 3, A-6020 Innsbruck, Austria

²Department of Obstetrics and Gynecology, KH Barmherzige Brüder, A-7000 Eisenstadt, Austria

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Summary

Median neopterin concentration in amniotic fluid at delivery was 72 nM which is approximately 10-fold the maternal and fetal serum concentration. A strong correlation existed between neopterin concentrations in amniotic fluid and urine, except an unproportionally high level in amniotic fluid in one case with an intrauterine infection.

Key words : Neopterin, Pregnancy, Delivery, Amniotic fluid, Urine, Intrauterine infection, Feto-maternal interface

Introduction

Neopterin is produced by human monocytic cells upon stimulation with interferon- γ (1). Increased neopterin concentrations reflect the degree of Th-1 type immune response which is stimulated in, e.g. viral infections, malignant diseases, autoimmune disorders, or allograft rejection (2, 3). During pregnancy a moderate increase of neopterin concentrations in serum and urine and also in amniotic fluid of healthy pregnant women is observed, and neopterin concentrations usually raise with duration of gestation (4, 5). Increased neopterin concentrations during pregnancy indicate immune activation which likely represents an immunological adaptation process triggered by the allogeneic conceptus (4). Re-

cently, increasing concentrations of fetal neopterin with duration of gestation have been established, although no correlation was found between fetal and maternal neopterin concentrations (5). It is now interesting to know how neopterin produced by the fetus or by the mother in the feto-maternal interface, respectively, is excreted and whether there is an association between amniotic neopterin and the raise of neopterin concentrations in maternal urine.

Patients and Methods

Nineteen women, 20–38 years old (median 29.4 years) between 37th and 41st week of gestation at delivery were examined regarding their neopterin concentrations in amniotic fluid and urine. All individuals had singleton pregnancies, and cesarean sections were performed due to breech presentation and previous cesarean sections (11 subjects), hypertensive disorders and mild forms of pre-eclampsia (2 patients), and uterine contractions and signs of intra-

*Correspondence: Dr. Dietmar Fuchs, University of Innsbruck, Institute for Medical Chemistry and Biochemistry, Fritz Pregl Strasse 3, A-6020 Innsbruck, Austria, Tel.: +43 512 507 3519, Fax: +43 512 507 2865, e-mail: Dietmar.Fuchs@uibk.ac.at

amniotic infection or fetal asphyxia (6 patients). All cesarean sections were performed in general anaesthesia by using a transverse incision in the lower uterine segment. Concomitantly with the delivery of the fetus, 3-5 ml of amniotic fluid was aspirated from the uterine cavity. Before surgery, early morning urine specimens were collected. All specimens were frozen at -20°C until analysis. Measurements of neopterin concentrations in the amniotic fluid were performed by ELISA (Brahms Diagnostica, Berlin, Germany); neopterin concentrations in urine were determined via HPLC with a method described earlier (6).

Results

The median urinary neopterin level was 221 [195 - 346, interquartile range] $\mu\text{mol/mol}$ creatinine; in amniotic fluid the mean neopterin concentration was 69.0 [50.5 86.0] nM. Compared to healthy individuals (7) all subjects had increased urinary neopterin concentrations. Urinary and amniotic neopterin concentrations obviously did not differ between diagnostic categories (Kruskal Wallis test not significant). A significant correlation existed between the neopterin concentrations in urine and in amniotic fluid (Spearman rank coefficient of correlation $r_s = 0.47$, $P = .021$; Fig. 1). In one patient with an intra-uterine infection, the amniotic fluid was unclear and the neopterin concentration was very high (139 nM). When this outlier was excluded from the statistical evaluation, the correlation between neopterin in urine and amniotic fluid improved drastically ($r_s = 0.73$, $P = 0.0005$).

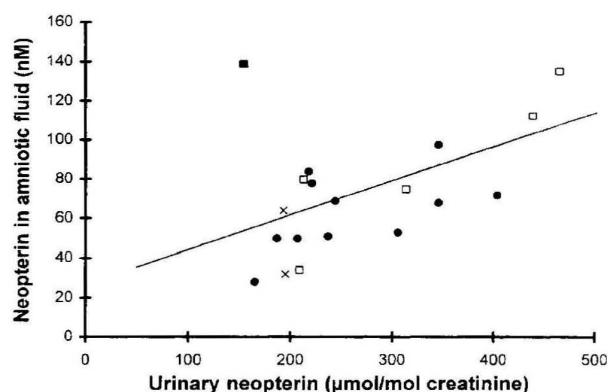


Figure 1. Correlation of neopterin concentrations in urine and amniotic fluid of patients who underwent cesarean sections. After elimination of the outlier ■, representing an intra-uterine infection, Spearman's correlation coefficient was 0.732 ($p < 0.0005$). Different symbols represent subgroups of patients, i.e. ●...breech presentation and previous cesarean sections, x...hypertensive disorders and pre-eclampsia, □ ...uterine contractions and fetal asphyxia.

Discussion

Neopterin concentrations in amniotic fluid are about 10-fold of the values normally found in serum of healthy controls (median 4.85 nM) or during pregnancy (median 6.9 nM in the 3rd trimester; ref 8). In contrast, neopterin concentrations in urine of pregnant women (280 $\mu\text{mol/mol}$ creatinine in the 3rd trimester; ref 9), similar like serum of pregnant women, are less than 2 times higher than in non-pregnant controls (7). Neopterin is exclusively excreted via the kidneys and its half-life in the circulation depends solely on renal clearance (10). The origin of increased neopterin production during pregnancy still remains unclear. In pregnancy reasonable immune activation is considered to take place at the fetomaternal interface as the fetus presents an allogeneic challenge for the maternal immune system, and this would match to the findings of high neopterin concentrations in amniotic fluid. On the other hand, basal levels of fetal neopterin excretion should accumulate in amniotic fluid and hence at least a part of the neopterin found in amniotic fluid may stem from the fetus. We are currently not able to distinguish between fetal and maternal sites of neopterin production when measuring neopterin concentrations in the amniotic fluid.

Although neopterin concentrations in amniotic fluid and maternal urine seem to correlate strongly in general, situations appear to exist, in which this correlation is abolished. In one patient with unclear amniotic fluid, the neopterin concentration in this was unproportionally high compared to urine. In this case, the site of immune activation seems to be located beyond the placenta, and the high neopterin concentration in the amniotic fluid most likely does not originate from the fetomaternal interface, rather its source is located within the amnion itself. One can assume that neopterin secreted into the amniotic fluid is excreted via maternal blood by renal clearance in a sustained way, which would provide an explanation for the unproportionally high neopterin value in this amniotic fluid. Neopterin as a sensitive parameter in gynecological infections has already been described: patients with bacterial vaginosis and with *Candida* vaginitis presented with significantly higher neopterin concentrations in vaginal secretions [11].

Amniocentesis is a measure which adheres to a pronounced risk of infection. From this point of view it seems not useful to generally establish the measurement of neopterin in amniotic fluid. However, amniocentesis as a usual procedure in high risk pregnancies would allow the measurement of neop-

terin as an accompanying determination to gain some information about the intra-amniotic immune status. Further investigations are required to evaluate a potential diagnostic value of neopterin measurement in amniotic fluid.

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