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Serum prolactin concentration in normal and small for gestational age fetuses

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ABSTRACT

Objectives To study fetal and maternal serum prolactin concentrations in appropriately-grown (AGA) fetuses and in small for gestational age (SGA) fetuses.
Design A cross-sectional study of 27 AGA and 27 SGA fetuses undergoing cordocentesis for prenatal diagnosis or for determination of fetal karyotype and acid-base balance. Serum prolactin concentration was measured by radioimmunoassay.
Setting Harris Birthright Research Centre for Fetal Medicine.
Results In the AGA group, both fetal and maternal serum prolactin concentration increased significantly with gestation ($P<0{\cdot}001$ and $P<0{\cdot}01$, respectively). In the SGA group, the fetal concentration of prolactin was significantly higher ($P<0{\cdot}05$), but the maternal serum prolactin concentration was not different from that of the AGA group.
Conclusions The finding of prolactin in the fetal circulation suggests that the anterior lobe of the pituitary is functioning from at least 12 weeks gestation. The increased serum prolactin concentration in SGA fetuses may be the consequence of hypoglycemic stress on the pituitary or the relative immaturity of the inhibitory hypothalamic–pituitary pathways.

Human prolactin is a member of the polypeptide hormone family which includes growth hormone and placental lactogen (Cooke *et al.* 1981; Wallis 1981). The only generally accepted function of prolactin in the adult human relates to the process of lactation. The hormone has been postulated, however, to have several important functions in the fetus, including lung maturation (Hauth *et al.* 1977; Gluckman *et al.* 1978), osmoregulation (Tyson 1982), and growth of the adrenal gland (Winters *et al.* 1975).

Prolactin has been detected in the pituitary gland of human fetuses from as early as 10 weeks gestation (Aubert *et al.* 1975). Existing data regarding changes in fetal prolactin secretion have been derived from blood samples obtained at termination of pregnancy or from cord blood at birth (Schenker *et al.* 1975, Kaplan *et al.* 1976, Suganuma *et al.* 1986). The results derived from such samples may not necessarily represent physiological levels in the undisturbed fetus; even data derived from elective cesarean section may be influenced by maternal fasting or transient hypotension which could alter placental perfusion and therefore affect the supply of oxygen and nutrients to the fetus (Morriss *et al.* 1974).

The aim of the present study was to investigate the maturation of fetal prolactin secretion in normal pregnancy and to examine possible changes in growth retarded fetuses using blood samples obtained by cordocentesis.

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Subjects and methods

Serum prolactin concentration was measured in 0·2 ml samples, obtained by cordocentesis (Nicolaides *et al.* 1986) at 17–37 weeks of gestation or cardiocentesis at less than 14 weeks gestation from 27 fetuses that were appropriately grown for gestation. The indications for cordocentesis (n=25) were: (a) prenatal diagnosis of blood disorders such as hemophilia A (n=8); (b) fetal karyotyping for women of advanced maternal age who booked late, those in whom amniocyte culture had failed or those with a low maternal serum alpha fetoprotein suggesting a significant risk of chromosomal defect (n=6); (c) karyotyping for fetal malformations such as mild hydronephrosis (n=7); and (d) fetal blood grouping in red blood cell isoimmunised pregnancies in which the fetal blood was subsequently found to be Coombs' test negative (n=4). In all cases, the fetal abdominal circumference and blood gases at the time of cordocentesis were within our reference ranges for gestation and the fetal karyotype was normal. Furthermore, the fetuses did not have the blood disorder or infection for which they were investigated. In addition, blood was obtained from two fetuses by cardiocentesis immediately before intracardiac injection of potassium chloride for embryo reduction in multi-fetal pregnancies.

Umbilical venous blood was also obtained by cordocentesis at 24–38 weeks' gestation from 27 women referred for fetal karyotyping and blood gas analysis because of ultrasonographic evidence of severe fetal growth retardation (fetal abdominal circumference 2–6 standard deviations

below the normal mean for gestation). All mothers were negative for antinuclear factor and showed no serologic evidence of recent toxoplasmosis, rubella, cytomegalovirus, or syphilis infections. The study was cross-sectional, and all fetuses were subsequently determined to be chromosomally normal.

The umbilical venous blood pO_2 and pH were measured by a blood gas analyzer (Radiometer ABL 330, Copenhagen, Denmark) immediately after collection in heparinized syringes. Kleihauer-Betke staining confirmed that all samples contained only fetal blood. The project was approved by the hospital ethics committee and informed consent was obtained from all the mothers.

For measurement of prolactin concentration, fetal and maternal blood (the latter obtained from an antecubital fossa vein immediately before fetal blood sampling) were collected into plain tubes, centrifuged for 10 min at 2000 rpm and the serum collected and stored at –20°C. Prolactin was measured by an immunoradiometric assay incorporating two high affinity monoclonal antibodies (Serono Diagnostics, Slough, UK). The inter- and intra-assay coefficients of variation were 3·4% and 1·6%, respectively.

Statistical analysis

Regression analysis was used to establish the reference range for fetal serum prolactin with gestational age. To determine differences between the maternal and fetal serum prolactin in the SGA and AGA groups, Students *t* test or the Mann Whitney *U* test were used as appropriate. Since fetal prolactin, pO_2 and pH change with gestational age, the individual values of the fetuses were expressed as the number of standard deviations (SDs) by which they differed from the respective normal mean for gestation (delta values) before applying Students *t* test or the Mann-Whitney *U* test.

Results

In the AGA group, both the maternal and fetal serum prolactin concentrations increased linearly with gestation (r=0·525, n=27, P<0·01; r=0·812, n=27, P<0·0001, respectively) (Fig. 1). There was no significant association between the fetal and maternal serum prolactin concentrations (r=0·391), and the mean fetal concentration (1421 mIU/l, range 207–4359) was not significantly different (t=–0·96, SEM=361·6) from the maternal (1921 mIU/l, range 391–4144).

Most fetal and maternal serum prolactin values were higher than the non-pregnant adult values (mean=165·5 mIU/l, range 53–520) (Fig. 1) established from the study of 68 pre-menopausal patients (Serono Diagnostics, Slough, UK).

In the SGA fetuses, the mean serum prolactin was significantly higher than in the AGA group (P<0·05), and the mean blood pO_2 and pH were significantly lower (P<0·0001 and P<0·0001, respectively) (Fig. 2). The mean maternal serum prolactin concentration (2378 mIU/l, range 1071–5084) was not significantly different from that in the AGA group.

Discussion

Prolactin is present in the fetal circulation from the first trimester of pregnancy, and the serum concentration, which is not related to that in the mother, is higher than in postnatal life. This finding, together with the demonstration of high circulating levels of thyroid stimulating hormone (Thorpe-Beeston *et al.* 1991), suggests that the anterior lobe of the pituitary is functioning from at least 12 weeks gestation.

The linear increase in fetal serum prolactin concentration with gestation, is consistent with the reported increase in pituitary weight from 10 weeks to term (Kaplan *et al.* 1976), and the demonstration of cytological differentiation and lactotrophs from as early as 12 weeks (Falin 1961; Pasteels *et al.* 1972). However, these findings are in contrast to those of previous studies which examined umbilical cord blood obtained after abortion or birth, and which reported an increase in serum prolactin concentration only after 21–30 weeks gestation (Aubert *et al.* 1975; Kaplan *et al.* 1976; Suganuma *et al.* 1986).

The increase in maternal serum prolactin concentration with advancing gestation is in agreement with the findings of previous studies (Schenker *et al.* 1975; Hercz 1985). This increase may be mediated by oestrogenic stimulation of lactotroph number and function (Aubert *et al.* 1975), and could be aimed at achieving lactation which is the only firmly documented action of prolactin.

In postnatal life, prolactin secretion is thought to be predominantly regulated by an inhibitory dopaminergic system. Thus, dopamine agonist drugs inhibit prolactin secretion and are used in the treatment of hyperprolactinemia. An increase in prolactin secretion is observed during pregnancy and lac-

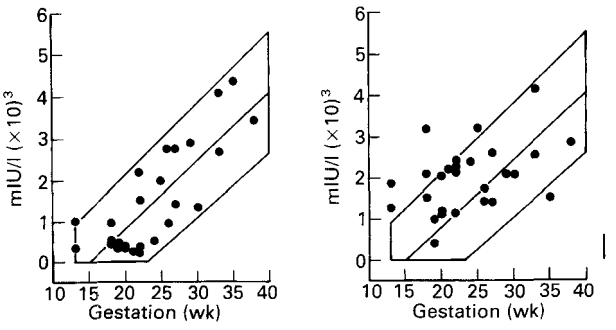

Fig. 1. Individual fetal and maternal serum prolactin concentrations in the normal group plotted on the fetal reference range for gestation (mean, 5th and 95th centiles). The vertical line on the right is the normal range in non-pregnant adults.

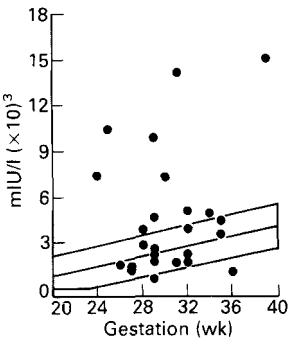

Fig. 2. Individual fetal serum prolactin concentrations in the small-for-gestational age group plotted on the fetal reference range for gestation (mean, 5th and 95th centiles).

tation, but also in renal failure, during episodes of stress or hypoglycaemia, after breast stimulation or following the administration of dopamine antagonists, estrogens, or thyrotropin releasing hormone (Moran-Campbell *et al.* 1984).

The findings that fetal and maternal serum prolactin concentrations are higher than in non-pregnant adults may be due to pregnancy-related stimulatory influences that are common to both the fetus and mother, but the lack of significant association between fetal and maternal levels suggests the presence of independent control mechanisms. Experiments in rats have demonstrated that the fetal pituitary has a high sensitivity to prolactin releasing factors, such as thyroid releasing hormone (Khorram *et al.* 1984). In the human fetus, however, it is unlikely that hypothalamic factors play a significant role in regulating prolactin secretion. Thus, Aubert *et al.* (1975) demonstrated that in anencephalic fetuses with no hypothalamus the circulating concentrations of prolactin are normal. Furthermore, several studies involving the administration of drugs to the mother, at timed intervals before delivery and measuring prolactin concentration in umbilical cord blood samples at birth, have demonstrated that fetal prolactin secretion is insensitive to TRH stimulation, and to both dopaminergic and H_2 receptor antagonism (Messinis *et al.* 1982a,b; Robuschi *et al.* 1982; Robuschi *et al.* 1984; Messinis *et al.* 1988; Roti *et al.* 1990).

The increased serum prolactin concentration in SGA fetuses is in agreement with the data of previous postnatal studies (Brimsmead & Liggins 1979; Taketani *et al.* 1984) and may result from increased synthesis or release of prolactin, either due to relative immaturity of the inhibitory hypothalamic–pituitary pathways, or in response to hypoglycemic stress (Woolf *et al.* 1977; Economides & Nicolaides 1989).

Hyperprolactinemia in growth retardation may mediate a series of beneficial adaptations in response to the hostile intrauterine environment of utero-placental insufficiency. Since prolactin stimulates somatomedin-like activity (Hill *et al.* 1977), growth of the fetal adrenal gland (Winters *et al.* 1975), enhances lung maturation (Hauth *et al.* 1977) and has antidiuretic properties (Pullano *et al.* 1989), hyperprolactinemia may represent an attempt to compensate for poor fetal growth, to enhance fetal maturation and to preserve extravascular volume.

Conclusion

Although the precise role of prolactin in intrauterine life remains unclear, the finding of high serum concentration in normal fetuses suggests that it may have an important role in fetal development. The hyperprolactinemia of growth-retarded fetuses could be considered as a response to a hostile intrauterine environment with possible beneficial effects.

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