Decidual, Amniotic Fluid, Maternal and Fetal Prolactin in Normal and Abnormal Pregnancies

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In the present studies, the content and the in vitro production of prolactin by decidua as well as the concentrations of prolactin in amniotic fluid, maternal and fetal serum in normal term pregnancies, induced abortions at various gestational ages, and in pregnancies complicated by diabetes mellitus, preeclampsia, chronic hypertension, and polyhydramnios were measured. Maternal and fetal prolactin levels varied considerably throughout gestation, but at term did not differ significantly between normal and abnormal pregnancies. Prolactin levels in amniotic fluid as well as decidual prolactin content and production were significantly lower only in pregnancies complicated by either hypertension or polyhydramnios. In both normal and abnormal pregnancies, decidual prolactin production correlated strongly with amniotic fluid concentrations. The present data suggest that 1) maternal and fetal prolactin levels do not differ significantly between normal and abnormal pregnancies, 2) the decidua is the principal source of amniotic fluid prolactin, and 3) the significantly lower levels of prolactin in amniotic fluid of pregnancies complicated by hypertension or polyhydramnios are probably due to adverse effects of these conditions on the synthesis and release of prolactin by decidua. ***(Obstet Gynecol 63:384, 1984)***

During normal human pregnancy, the prolactin levels in amniotic fluid and maternal and fetal serum reach the highest physiologic concentrations, with amniotic fluid levels being the greatest by far.[1–3] Although the biologic significance of this is not yet known, abnormal amniotic fluid prolactin concentrations have been reported to be associated with some pathological situations in which amniotic fluid volumes and fetal hydration are affected.[4,5] In addition, pregnancies complicated by hypertension have been reported by some authors to have abnormal maternal and fetal prolactin levels[6,7] while others have reported similar prolactin levels between normal and hypertensive pregnancies.[8,9] The sources of the circulating maternal and fetal prolactin are believed to be their respective pituitary glands, whereas the major source of prolactin in amniotic fluid is believed to be the decidua that lines the pregnant uterus.[10–12] A positive correlation between decidual prolactin and the concentrations of prolactin in amniotic fluid has recently been described in normal pregnancies,[12] but in abnormal pregnancies no information is available regarding decidual prolactin secretion and its relation to amniotic fluid prolactin levels.

Because of the previously mentioned controversies and the lack of information regarding decidual prolactin in pathological pregnancies, the authors have measured the concentration of prolactin in amniotic fluid, maternal and fetal serum, and determined the prolactin content and the in vitro production of prolactin by decidua in both normal pregnancies and pregnancies complicated by preeclampsia, diabetes mellitus, chronic hypertension, and polyhydramnios.

Materials and Methods

Appropriate informed consent, as approved by the Human Subject Review Committee of the University of Iowa College of Medicine, was obtained from all participants of this study, which included 20 women undergoing first-trimeter suction abortion (six to 16 weeks' gestation), 30 women undergoing second-trimester saline abortion (17 to 21 weeks' gestation), 30 women with normal, uncomplicated pregnancies, and ten women each with preeclampsia, insulin-dependent diabetes mellitus, chronic hypertension, and polyhydramnios. All diabetic patients were under the care of one of the authors (MWV), who controlled blood glucose strictly with two injections of insulin per day to achieve fasting blood levels between 70 and 110 mg/100 ml and postprandial levels between 80 and 130 mg/100 ml. All hypertensive patients had been diagnosed and treated for essential hypertension before pregnancy. Although the majority of them had been

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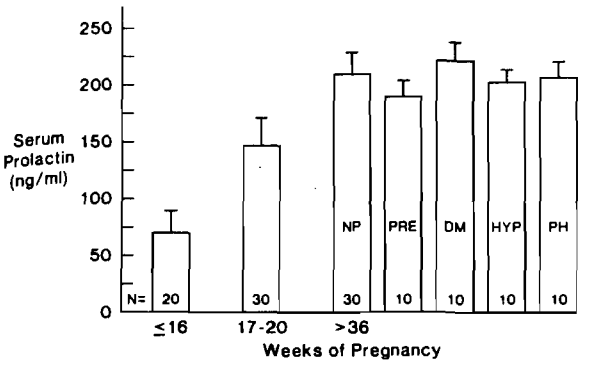

Figure 1. Mean (± SEM) maternal serum prolactin concentrations during the first and second trimesters of pregnancy, and in normal and abnormal pregnancies at term. Term: NP = normal; PRE = preeclampsia; DM = diabetes mellitus; HYP = chronic hypertension; PH = polyhydramnios.

on antihypertensive medication before and sometimes during pregnancy, only three of these patients were on antihypertensive medication at the time of admission into the labor and delivery unit. One patient was taking α-methyldopa, 2 g/day, and the other two patients were taking α-methyldopa, 1 g/day and hydrochlorothiazide, 50 mg/day. The diagnosis of polyhydramnios, with amniotic fluid volumes estimated at greater than 2000 ml, was made clinically in all patients with excessive uterine enlargement associated with difficulty in palpating fetal parts. Seven of these patients underwent ultrasonographic studies that confirmed the clinical diagnosis, and three patients underwent amniocentesis during the latter part of the third trimester with removal of excess amniotic fluid to relieve maternal discomfort. Four of the patients with polyhydramnios also had insulin-dependent diabetes mellitus, but they were not included in the group of patients with diabetes mellitus. No other causes for polyhydramnios were evident in the other patients.

The preeclampsia was mild to severe in these patients, and all were treated with intravenous magnesium sulfate from 12 to 36 hours before delivery. Except for abortions, only pregnancies of greater than 36 weeks' gestation with normal infants were included in the study to avoid differences that might have been attributed to fetal maturity or fetal abnormalities.

Samples of maternal peripheral blood, fetal cord blood, amniotic fluid, and decidual explants were obtained during the immediate peripartum period. The serum and amniotic fluid samples were frozen and stored until assayed for prolactin in the same batch to avoid interassay variability. Decidual content and production of prolactin were measured before and after 24-hour incubation of 300-mg samples of freshly obtained explants of decidua dissected from the maternal surface of the chorion immediately after delivery of the placenta.[13] Prolactin concentrations were measured by specific radioimmunoassay based on the technique of Sinha et al,[14] and the mean intraassay variability was 7.5%. The statistical analyses of results were performed by the Student *t* test and linear regression analyses.

Results

Figure 1 shows maternal serum prolactin levels throughout pregnancy and at term in normal and abnormal pregnancies. As reported,[1-3] maternal serum prolactin concentrations increase progressively throughout gestation, reaching the highest levels after the 36th week of pregnancy. At term, although maternal prolactin levels varied considerably from patient to patient, they did not differ significantly between normal and abnormal pregnancies. Similarly, fetal prolactin levels from normal pregnancies did not differ from abnormal pregnancies at term. Figure 2 shows the mean prolactin concentrations in amniotic fluid throughout gestation in normal pregnancies, and after 36 weeks of abnormal pregnancies.

Amniotic fluid prolactin levels were highest between 17 and 20 weeks' gestation ($P < .01$). After 36 weeks' gestation, they declined to levels similar to those obtained during the first trimester. At term, the amniotic fluid prolactin levels in pregnancies complicated by chronic hypertension or polyhydramnios were significantly lower than normal pregnancies or pregnancies complicated by either diabetes mellitus or preeclampsia ($P < .01$).

Figure 3 shows decidual prolactin content and production from normal and abnormal term pregnancies.

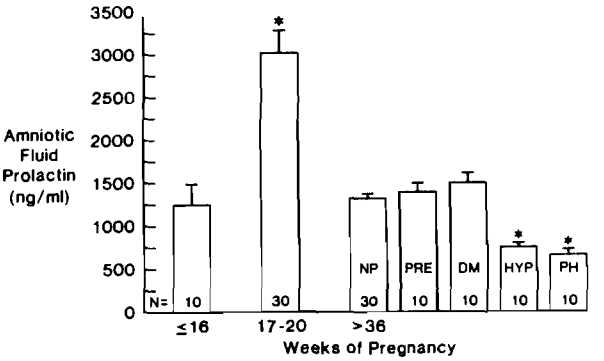

Figure 2. Mean (± SEM) prolactin concentrations in amniotic fluid during the first and second trimesters of pregnancy, and in normal and abnormal pregnancies at term. *Significantly different from normal pregnancies ($P < .01$ by Student *t* test). Abbreviations as in Figure 1.

As with amniotic fluid prolactin levels, decidual prolactin content and production in pregnancies complicated by either chronic hypertension or polyhydramnios were significantly lower than normal pregnancies and pregnancies complicated by diabetes mellitus or preeclampsia ($P < .01$).

Because the initial content of prolactin in decidua seemed to parallel the amount of prolactin produced after 24 hours' incubation, correlation analyses were carried out between initial prolactin content and production after 24-hour incubation. Significant correlations were found between the initial tissue content of prolactin and its production in both normal ($r = .559$, $P < .001$) and abnormal pregnancies ($r = .499$, $P = .00104$). This suggests that the capacity of the decidua to produce prolactin in vitro can be predicted from its initial content.

To further test the hypothesis that the decidua is a major source of amniotic fluid prolactin, regression analyses were carried out between the amount of prolactin produced by the decidua after 24-hour incubation in vitro and prolactin concentrations in the amniotic fluid of normal and abnormal pregnancies. These correlations were highly significant, as shown in Figures 4 and 5, further supporting the hypothesis that the decidua is the major source of prolactin in amniotic fluid.

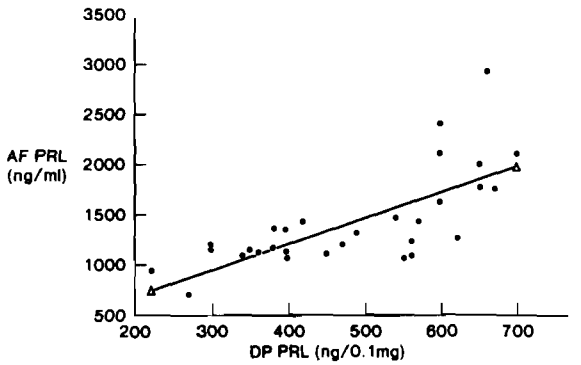

Figure 4. Correlation of decidual production of prolactin (*DP PRL*) in vitro and amniotic fluid prolactin (*AF PRL*) concentrations in normal pregnancies. $r = .711$; $P < .001$.

Discussion

Besides preparing the breast for lactation, the biologic roles of the high levels of prolactin in human pregnancy remain speculative. Because prolactin has been reported to antagonize the pressor effects of angiotensin and norepinephrine in laboratory animals,[15,16] it has been postulated that the high levels of prolactin during pregnancy may be protective against the development of hypertension, and that gestational hypertension may develop in patients with decreased prolactin levels.[17] Although Yuen et al[6] reported decreased maternal plasma prolactin levels in pregnant women with either preeclampsia or chronic hypertension, no difference in maternal prolactin levels between normal and hypertensive pregnant women or pregnancies complicated by diabetes mellitus or polyhydramnios have been found in this and other studies.[8,9] Therefore it seems that maternal prolactin levels in pregnancy are not helpful in the evaluation of pathological pregnancies.

Fetal prolactin may be important in fetal lung maturation during the latter part of pregnancy.[7-18] In the present study, cord prolactin levels did not differ between normal and abnormal pregnancies. Grosso et

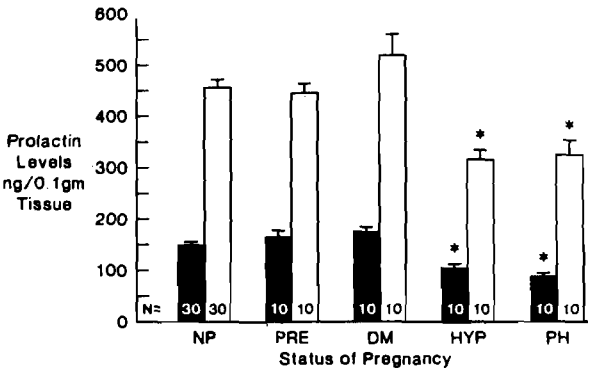

Figure 3. Mean (± SEM) prolactin content (*black columns*) and production (*white columns*) by decidua in normal and abnormal pregnancies at term. *Significantly different from normal pregnancies ($P < .01$ by Student t test). Abbreviations as in Figure 1.

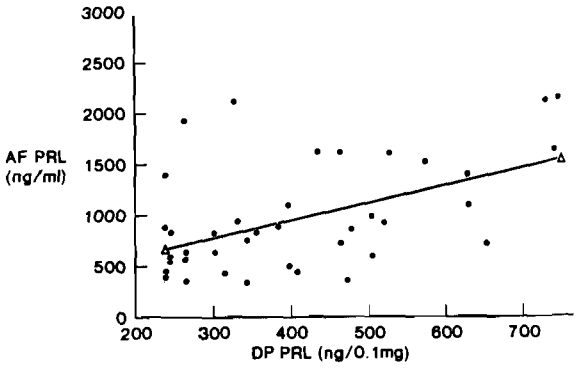

Figure 5. Correlation of decidual production of prolactin (*DP PRL*) in vitro and amniotic fluid prolactin (*AF PRL*) concentrations in abnormal pregnancies. $r = .480$; $P = .002$.

al[7] reported that cord prolactin levels in infants of preeclamptic and hypertensive women were higher than in infants of normotensive women delivered between 30 and 39 weeks of gestation, but the differences were insignificant at later gestational ages. The failure to find any differences in cord prolactin levels between normal and abnormal pregnancies after 36 weeks' gestation may be due to the relatively small number of patients in each of the abnormal groups or to the fact that the present study included only full-term pregnancies with completely normal infants, thus avoiding differences that might be attributed to prematurity and/or fetal anomalies.

In agreement with previous reports,[1–3] the amniotic fluid prolactin levels in these studies were several times higher than either maternal or fetal levels, with the highest concentrations occurring at midgestation. Although amniotic fluid prolactin levels from patients with diabetes mellitus or preeclampsia did not differ from those in patients with normal pregnancies at term, patients with chronic hypertension or polyhydramnios had amniotic fluid prolactin concentrations significantly lower than normal. Similar findings have been reported by Freisen et al[4] and Josimovich[5] in small numbers of patients with polyhydramnios, and by Yuen et al[6] in patients with chronic hypertension. The decreased amniotic fluid prolactin levels in patients with polyhydramnios could be attributed to either a dilutional effect or to a decreased transfer of prolactin from either maternal or fetal serum. But the present findings that decidual prolactin content and production are similarly reduced in pregnancies complicated by either chronic hypertension or polyhydramnios suggest that the underlying dysfunction lies with the decidua. The report by Rosenberg et al[12] of a high correlation between decidua prolactin content and production with amniotic fluid prolactin concentrations observed in the present studies in both normal and abnormal pregnancies strongly support the conclusion that the decidua is the most important source of prolactin in amniotic fluid. Therefore, the decreased prolactin production by decidua is most likely responsible for the decreased levels of amniotic fluid prolactin observed in pregnancies complicated by polyhydramnios or chronic hypertension. What causes the decidua from these pregnancies to produce less prolactin is not known. It is possible that in chronic hypertension the vascular supply to the endometrium may be diminished, causing the decidua to be less productive. The reason similar changes were not observed in preeclamptic women may be related to the duration of the vascular compromise, which is much longer in chronic hypertension than in preeclamptic patients. Prolactin production by decidua of pregnancies complicated by polyhydramnios may be adversely affected by either the increased intrauterine pressure or the excessive stretching of the decidua by the greatly enlarged uterus. However, these are merely speculations and need to be further evaluated.

In conclusion, the authors' findings revealed that: 1) maternal and fetal prolactin levels, although varying considerably throughout gestation, do not differ significantly between normal and abnormal pregnancies; 2) amniotic fluid prolactin levels correlate with decidua prolactin content and secretion in both normal and abnormal pregnancies, and differ from normal only in those pregnancies complicated by chronic hypertension and polyhydramnios; and 3) the strong correlations of decidua prolactin production with amniotic fluid prolactin concentrations in both normal and abnormal pregnancies further support the concept that the decidua is the principal source of amniotic fluid prolactin.

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