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Maternal plasma and amniotic fluid 17β-estradiol, progesterone and cortisol concentrations in women with successfully and unsuccessfully treated preterm labor

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Abstract. Maternal plasma and amniotic fluid (AF) were obtained for measurement of 17β-estradiol, progesterone and cortisol concentrations from 40 patients with preterm labor and intact membranes at 28–32 weeks of gestation: 20 delivered preterm and the remaining 20 patients responded to tocolytic treatment and delivered at term. Maternal plasma and AF concentrations of these hormones were measured with specific commercially available radioimmunoassay kits. Maternal plasma and AF 17β-estradiol concentrations were significantly higher in women who delivered preterm than in those who delivered at term, 8.0 ng/ml vs 3.5 ng/ml and 0.85 ng/ml vs. 0.6 ng/ml, respectively. No significant differences were found between groups in maternal plasma and AF progesterone concentrations. Maternal plasma cortisol concentrations were higher in the preterm delivery group than in the term group (235 ng/ml vs. 55 ng/ml, respectively). No significant differences were found in AF cortisol concentrations between groups.

Key words: Labor-Amniotic fluid – Plasma-17β-estradiol – Progesterone – Cortisol

Introduction

The endocrine changes associated with parturition are poorly understood (Challis 1971, Turnbull 1977, Thurburn 1979, Myers 1993). In sheep, there are systemic changes in sex steroid hormones before and during labor (Liggins 1973), but similar changes were not observed in humans (Myers 1993). In contrast, a local change in the amniotic fluid (AF) progesterone/estrogen ratio has been demonstrated in patients with term and preterm labor (Romero 1988, Neuman 1992, Mazor 1993, 1994). Indeed, while no significant changes occurred in AF progesterone levels,

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AF estrogen concentrations increased both in term and preterm parturition. These changes play an important role in controlling myometrial contractility (Mitchell 1984, 1987, 1993; Romano 1987).

In a previous study, we demonstrated that human labor at term was associated with a significant increase in cortisol concentrations in both maternal plasma and AF (Ohana 1995). In women in labor at 32–36 weeks gestation, only maternal plasma cortisol concentrations were higher than the plasma cortisol levels in patients not in labor, while AF cortisol levels were not significantly different in the two groups (Mazor 1994).

Since the metabolism of sex steroid hormones and cortisol seems to be different in term and preterm labor, we decided to investigate whether the changes in hormones levels observed in women with preterm labor between 32–36 weeks' gestation, can also be found in patients with preterm labor at a lower gestational age. Hence, the purpose of the present study was to determine maternal plasma and AF concentrations of 17β-estradiol, progesterone and cortisol in women in preterm labor at 28–32 weeks of gestation and to look for differences between patients who delivered preterm and those who went on to deliver at term.

Materials and methods

The study population consisted of patients admitted to the Soroka Medical Center, with a diagnosis of preterm labor, intact fetal membranes, and an otherwise normal singleton gestation who had undergone amniocentesis for the assessment of the microbiologic status of the amniotic cavity and/or fetal lung maturity. A cross sectional study was conducted according to the gestational age at admission and the patient's response to medical treatment for premature labor. Group 1 (preterm delivery group) consisted of women admitted with preterm labor between 28 to 32 weeks of gestation who delivered preterm ($n=20$). Group 2 consisted of 20 patients admitted with preterm labor who responded to tocolytic treatment and went on to deliver at term (term delivery group). The latter group of patients was identified by searching our stored aliquots of plasma and AF from patients who had had an amniocentesis in preterm labor with intact membranes for bacteriological or fetal lung maturity studies.

Preterm labor was defined as the presence of uterine contractions occurring with a frequency of two or more in 10 minutes associated with cervical effacement or dilation. Rupture of membranes was excluded by speculum examination and a Nitrazine test. Maternal plasma and AF samples were obtained before the start of tocolytic therapy. Ritodrine was used intravenously as the tocolytic agent, according to a protocol described by Daftary (1992). No patients received bethamethasone prior to amniocentesis or venepuncture. AF was obtained by transabdominal amniocentesis under ultrasonographic guidance. Written informed consent was obtained from all patients included in this study.

Gram stain examination and cultures for aerobic anaerobic bacteria were performed immediately after AF collection. Patients with positive Gram stain examination or positive culture for microorganisms were excluded from the study, as well as, those with meconium stained or blood stained amniotic fluid.

In both groups, samples of maternal plasma were obtained immediately after AF collection. AF and maternal blood were centrifuged at 700 *g* and 800 *g*, respectively, for 10 min and the supernatants were frozen in polypropylene tubes at –20 °C until assayed. Samples of AF and maternal plasma were not subjected to freeze-thaw cycles before assay.

Commercially available radioimmunoasay (RIA) kits (Diagnostic Products Corp, Los Angeles, CA) validated for direct AF and blood analysis of 17β-estradiol, progesterone and cortisol, were used to measure maternal plasma and AF steroid hormone concentrations (Mazor 1994). The RIA kit for cortisol was highly specific with a sensitivity of 10 ng/ml. The total inter-assay and intra-assay coefficients of variation for cortisol were 5% and 7%, respectively. A commercial preparation of conjugated estrogens was assayed from 50,000 to 500,000 pg/ml. Cross reactivity was approximately 0.1% (Mazor 1994). The intra-assay and inter-assay coefficients of

variation were 6% and 10% for 17β-estradiol, and 5% and 12% for progesterone, respectively. Our laboratory participates in the Wellcome quality control program for hormone assays.

The following clinical information was obtained from patient records after their delivery: maternal age, maternal weight, parity, gestational age at admission and at delivery mode of delivery, birth weight, Apgar scores at 1 and 5 min and sex of baby. Statistical analysis was conducted with True Epistat 4.0 (Epistat Services, Richardson, TX). Either unpaired Student *t*-testor Mann-Whitney *U* test were used for comparison of continuous variables. A two tailed $p<0.05$ was considered significant.

Results

Table 1 describes the clinical characteristics of patients in both groups and there were no significant differences in maternal age, maternal weight, parity, mode of delivery, Apgar scores ≤7 at 1 and 5 minutes and sex of the infants.

Maternal plasma and AF 17β-estradiol concentrations in both groups are shown in Fig. 1. The median (range) maternal plasma 17β-estradiol concentration was significantly higher in women with preterm labor who delivered preterm than in those who delivered at term [8.0 ng/ml (2.8–23.6) vs. 3.5 ng/ml 81.2–7.1) respectively, $p=0.00068$]. This significant difference between groups was also detected in AF 17β-estradiol concentration, [0.85 ng/ml (0.5–1.9) vs. 0.6 ng/ml (0.3–0.8), respectively $p=0.000088$] but no significant differences were noted in maternal plasma and AF progesterone concentrations (Fig. 2).

Figure 3 shows maternal plasma and AF progesterone/17β-estradiol ratios in both groups. We found a significant decrease in the maternal plasma and AF ratios in women who delivered preterm as compared to those delivered at term [maternal plasma; 9.6 ng/ml (7.2–59.5) vs. 25.7 ng/ml (7.6–100), respectively, $p=0.001$; AF; 24.4 ng/ml 813.2–88) vs. 45.7 ng/ml (11.1–94), respectively, $p=0.00938$].

Table 1. Clinical and obstetric variables of patients in preterm labor

Variable	Preterm delivery (n = 20)	Term delivery (n = 20)	Significance
Maternal age (yrs ± SD)	25.9 ± 6.6	28.7 ± 5.2	NS
Maternal weight (kg ± SD)	67.5 ± 11.2	69.2 ± 9.4	NS
Gestational age at admission (wk ± SD)	30.3 ± 1.1	30.5 ± 1.1	NS
Gestational age at delivery (wk ± SD)	32.6 ± 2.4	38.7 ± 1.3	$P<0.0001$
Birth weight (gr ± SD)	2013 ± 534	3014 ± 417	$P<0.0001$
Parity (mean ± SD)	3.1 ± 2.9	2.6 ± 1.2	NS
Mode of delivery (n)			
Vaginal	16	17	NS
Cesarean section	4	3	NS
Apgar Score ≤7 (n)			
1 min	6	4	NS
5 min	2	0	NS
Sex of baby (n)			
Male	11	12	NS
Female	9	8	NS

NS, Not significant

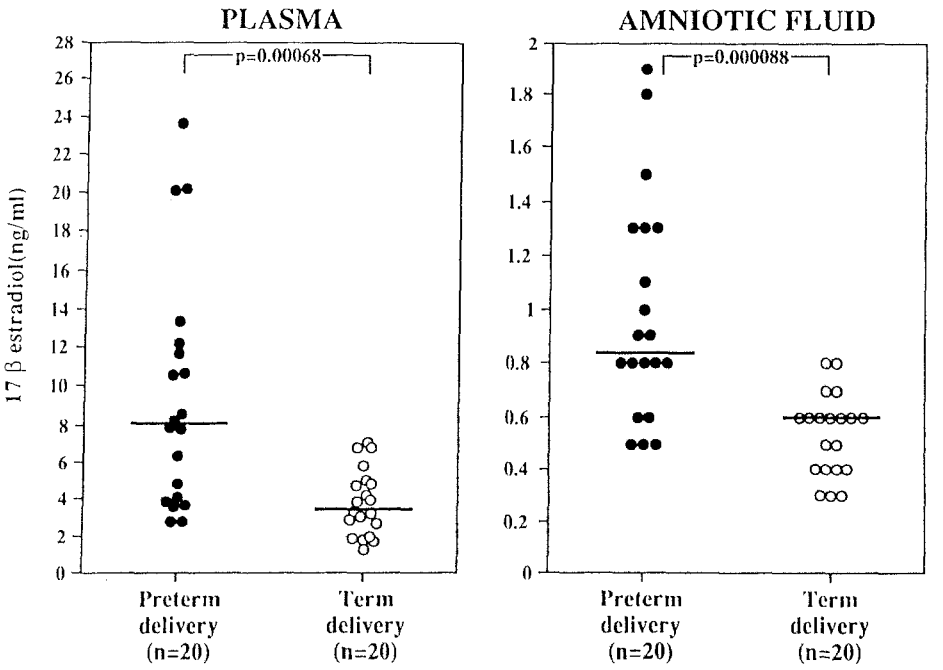

Fig. 1. Maternal plasma and amniotic fluid 17β-estradiol concentrations in patients with preterm labor according to gestational age at delivery. *Cross bars*, Median of these concentrations

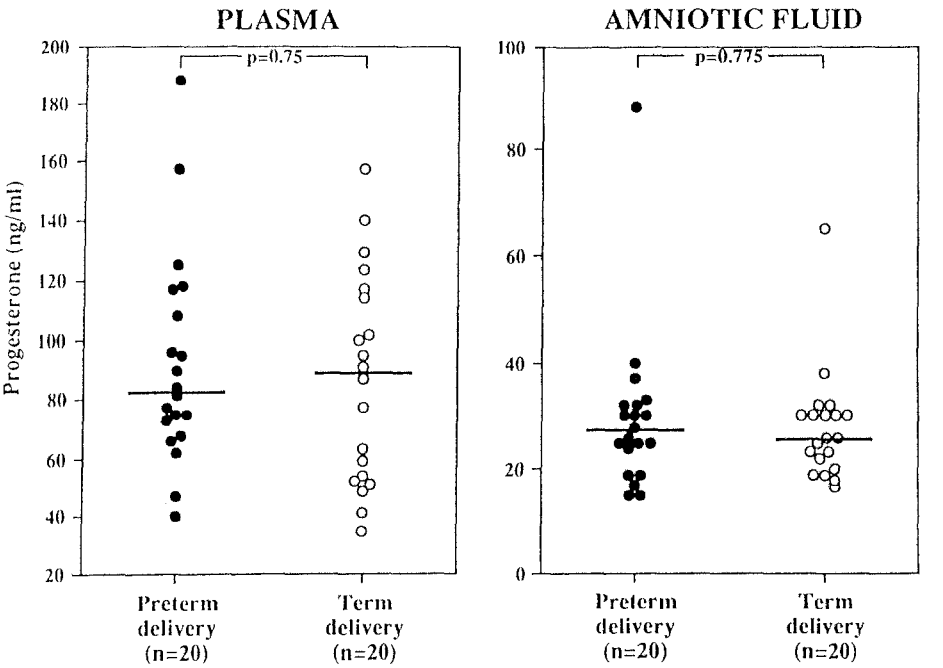

Fig. 2. Maternal plasma and amniotic fluid progesterone concentrations in patients with preterm labor according to gestational age at delivery. *Cross bars*, Median of these concentrations

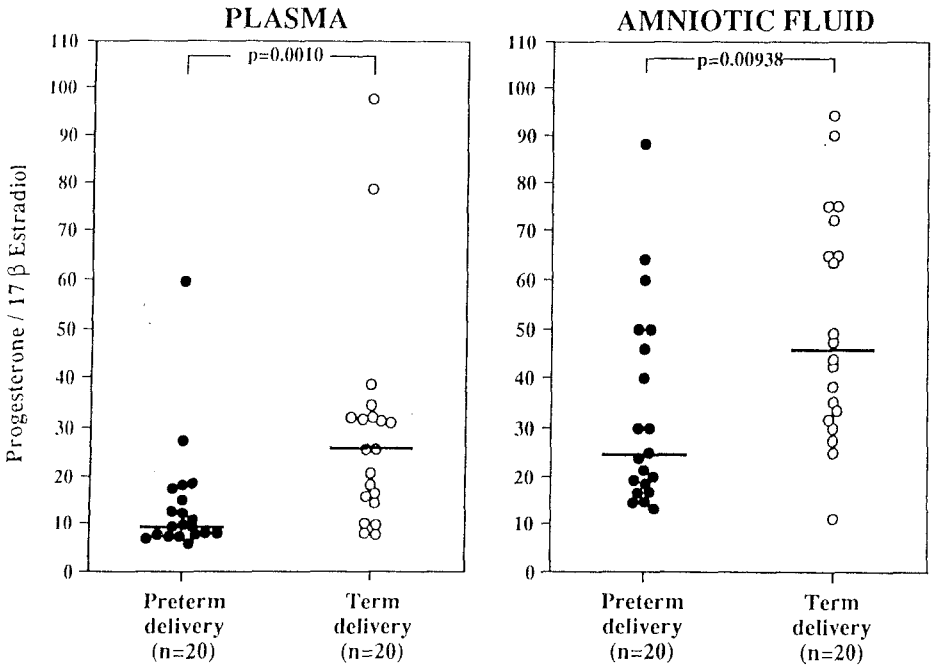

Fig. 3. Maternal plasma and amniotic fluid progesterone/17β-estradiol ratio in patients with preterm labor according to gestational age at delivery. *Cross bars*, Median of these concentrations

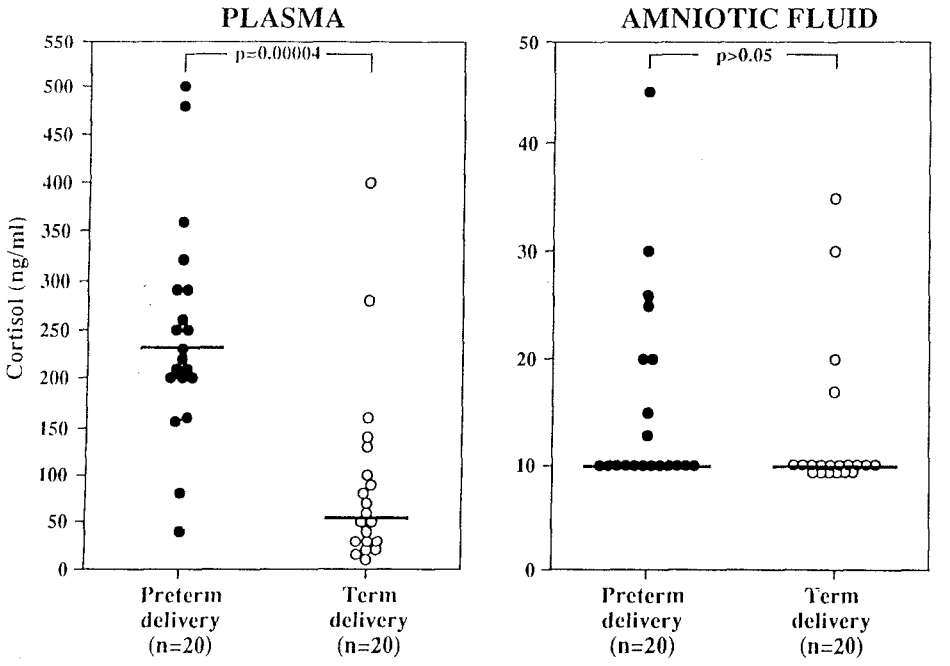

Fig. 4. Maternal plasma and amniotic fluid cortisol concentrations in patients with preterm labor according to gestational age at delivery. *Cross bars*, Median of these concentrations

Figure 4 shows maternal plasma and AF cortisol concentrations. There were no significant differences in AF cortisol but maternal plasma cortisol concentration was higher in the preterm delivery group, 235 ng/ml (40–500) than in the term delivery group, 55 ng/ml (10–400), $p = 0.00004$.

Discussion

In most mammals, parturition is a process associated with a significant change in progesterone and estrogen concentrations (Myers 1993). Estrogens have an important role in the process of parturition by inducing the formation of gap junctions (Garfield 1980), oxytocin receptors in the myometrium (Alexandrova 1980) and by increasing prostaglandin biosynthesis in intrauterine tissues (Olson 1983, Schatz 1983). Recently, it has been demonstrated that term and preterm labor are associated with a significant increase in AF 17β-estradiol levels (Romero 1988, Neuman 1992, Mazor 1993, 1994). Moreover, the increase in estrogen concentrations was also detected in maternal plasma in patients with preterm labor who delivered preterm. It should be stressed, however, that progesterone concentrations remained unchanged both systemically and locally in preterm and term labor as compared to those in patients not in labor (Romero 1988, Mazor 1993, 1994). The results of this study strongly support our previous observations on the changes in 17β-estradiol and progesterone concentrations in maternal plasma and AF. These observations lend further support to the hypothesis that human term and preterm labor is associated with changes in the progesterone/17β-estradiol ratio (Romero 1988, Mazor 1993, 1994).

The role of cortisol in human parturition is controversial. Casey et al. (1981) demonstrated that despite the massive increase in cortisol secretion observed during term labor, the effect of cortisol on prostaglandin biosynthesis does not always lead to an increase in prostaglandin concentration. Other investigators (Hong 1976, Hirata 1980) have shown that cortisol can inhibit arachidonic acid release from phospholipid by reducing phospholipase activity, leading to decreased prostaglandin concentration. In contrast, other studies performed in vitro, demonstrated that cortisol administration can enhance prostaglandin concentration (Potesio 1988, Gibb 1990). In a recent study, we demonstrated that human labor at term was associated with a significant rise in maternal plasma and AF cortisol levels (Ohana 1995). On the other hand, our group showed that although maternal plasma cortisol and dehydroepiandrosterone-sulfate (DHEA-S) concentrations were higher in women in preterm labor who delivered preterm, no similar findings were noted in AF of these patients (Mazor 1995). The stress phenomenon associated with the process of labor is very likely to be the explanation for our findings. The results of the present study strongly suggest that the findings observed in the preterm birth occurring near term (Mazor 1994) are similar to those found in women at an earlier gestational age and are different from those in labor at term. Further studies are required to clarify the precise role that cortisol plays in human parturition.

A possible limitation of our study is its cross sectional design. A longitudinal study is required to determine maternal plasma and AF 17β-estradiol and cortisol concentrations before and during preterm labor. However, such an approach may arise ethical issues as they would require repeated invasive procedures.

In summary, our results show that patients with preterm labor who failed therapy and delivered preterm have higher maternal plasma 17β-estradiol and cortisol

concentrations than those who delivered at term. This rise in maternal plasma cortisol may be attributed to the stress effects of labor.

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