Antenatal dexamethasone therapy does not affect circulating concentrations of insulin-like growth factor binding protein-1

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In animals, dexamethasone administration during pregnancy leads to fetal growth restriction due to enhanced expression of insulin-like growth factor binding protein-1 (IGFBP-1). In humans, there is also a significant inverse correlation between maternal and fetal concentrations of IGFBP-1 and birth weight. During pregnancy, maternal IGFBP-1 is derived from the decidualized endometrium. We have studied the effect of dexamethasone on circulating concentrations of IGFBP-1 in 12 pregnant women who received dexamethasone therapy for fetal lung maturation in anticipation of premature delivery before 34 completed weeks of gestation. Blood samples were collected before dexamethasone administration, at 24 h and 48 h after the course of dexamethasone, and within 24 h of delivery, for the measurement of IGFBP-1. There was no significant change in plasma IGFBP-1 concentrations at 24 and 48 h following dexamethasone therapy, and at delivery (P = 0.666, 0.307 and 0.398, respectively). Therefore, antenatal dexamethasone therapy does not influence decidual synthesis of IGFBP-1.

Key words: decidua/dexamethasone/insulin-like growth factor binding protein-1

Introduction

It is now well established that administering corticosteroids prior to preterm delivery reduces the incidence of respiratory distress syndrome in the new-born (Liggins and Howie, 1972; Crowley, 1995). The efficacy of neonatal surfactant therapy is also enhanced by antenatal exposure to corticosteroids and there is an associated reduction in the risk of intravascular haemorrhage, necrotizing enterocolitis, neonatal hyperbilirubinaemia and neonatal death (Sinclair, 1994). Therefore, most pregnant women are now given corticosteroids whenever preterm delivery is anticipated.

In animals, dexamethasone administration during pregnancy leads to fetal growth restriction due to the enhanced expression of insulin-like growth factor binding protein-1 (IGFBP-1; Price et al., 1992). IGFBP-1 is thought to modulate the paracrine influence of insulin-like growth factor I (IGF-I) on placental growth and nutrient uptake (Fant et al., 1986), and so to reduce fetal growth (Rutanen et al., 1988; Wang and Chard, 1992). During pregnancy in the human, maternal IGFBP-1 is derived mostly from the decidualized endometrium (Rutanen et al., 1985, 1988). A significant inverse correlation between maternal and fetal concentrations of IGFBP-1 and birth weight has been identified with concentrations being significantly higher in the presence of fetuses that are small for gestational age or in whom there is intrauterine growth restriction (Wang et al., 1991; Hills et al., 1996; Ostlund et al., 1997).

Given the animal evidence suggesting that dexamethasone enhances circulating concentrations of IGFBP-1 and leads to growth restriction, this study was performed to examine the effect of antenatal dexamethasone, given to induce fetal lung maturation, on maternal circulating concentrations of IGFBP-1. This was thought to be a justifiable investigation in humans given the current trend for repeated administration of dexamethasone, which may have an effect on fetal growth.

Materials and methods

A longitudinal study was performed on 12 pregnant women who received dexamethasone therapy for fetal lung maturation in anticipation of premature delivery before 34 completed weeks of gestation, but who were not in labour. The obstetric problems that threatened premature birth were preterm rupture of membranes (n = 4) and antepartum haemorrhage due to placenta praevia (n = 4) and of unknown origin (n = 4). These women served as their own controls.

A standard regimen of dexamethasone (David Bull Laboratories, Mulgrave, Victoria, Australia) that comprised two doses of 12 mg intramuscular injections at 12 h intervals was administered to all women. The number of women (n = 12) was chosen on the basis of an earlier study by Miell et al. (1993) who reported a mean baseline serum IGFBP-1 concentration of 42.9 ± 8.2 µg/l, and demonstrated that it fell by a mean difference of 14.9 µg/l following short-term dexamethasone administration; this was statistically significant (P < 0.001; Miell et al., 1993). Power calculations showed that a study demonstrating a comparable difference would require a total group size of 10 with an α of 0.05 and a β of 0.2.

All women gave informed consent to the study, which was approved by the Riverside Research Ethics Committee. Blood samples were collected before starting the dexamethasone therapy, at 24 and 48 h after completing therapy, and within 24 h of delivery. The samples were collected between 0800 and 2200 to avoid the nocturnal peak of circulating IGFBP-1 (Baxter and Cowell, 1987). Samples were centrifuged at 1560 g for 30 mins to separate plasma, which was stored at −20°C until analysed in a single batch. Measurement of IGFBP-1 was as described by Wang et al. (1991). Statistical analysis was performed using the Statistics Package for Social Sciences (SPSS). Changes in IGFBP-1 levels from pre-therapy values were
assessed by Wilcoxon matched-pairs signed-ranks test separately for each post-therapy stage.

Results

The mean (± SD) age of subjects was 33.2 ± 5.3 (range 24–40) years; parity ranged from zero to four. The median gestational age at administration of the first dose of dexamethasone was 29 (range 23–33) weeks. The median gestational age at delivery was 34 (range 25–41) weeks, with a median interval between dexamethasone therapy and delivery of 18 (range 2–117) days. The mean birth weight was 2.345 ± 0.859 kg and the mean birth weight percentile was 60 ± 26.

There was no significant change in plasma concentrations of IGFBP-1 at 24 and 48 h following dexamethasone therapy, and at delivery (P = 0.666, 0.307 and 0.398, respectively) (Table I).

Discussion

Serum concentrations of IGFBP-1 increase rapidly during pregnancy and reach a peak at 12–13 weeks of gestation; thereafter they remain high but without significant change until term (Wang et al., 1991; Hills et al., 1996). The bulk of the maternal circulating IGFBP-1 in pregnancy is believed to result from synthesis by the decidualized endometrium (Rutanen et al., 1985; Bell, 1989). IGFBP-1 is thought to act systemically, or locally, to modulate the mitogenic actions of IGF-1 on placental growth and secondarily on fetal growth (Wang and Chard, 1992). Indeed, Miell et al. (1997) assessed IGFBP-1 concentrations in early pregnancy in maternal serum and embryological fluid, and found maternal serum to contain mainly phosphorylated isoforms of IGFBP-1 whereas IGFBP-1 in coelomic fluid was almost exclusively non-phosphorylated. Phosphorylated IGFBP-1 is inhibitory to the bioactivity of IGF-1 (Jones et al., 1991, 1993), hence, these data suggest a mechanism whereby circulating maternal IGFBP-1 suppresses fetal growth. The presence of significant quantities of non-phosphorylated IGFBP-1 in coelomic fluid would allow potentiation of the mitogenic effects of insulin-like growth factors (IGF) in the early human gestational sac (Miell et al., 1997).

Price and colleagues (1992) administered a daily intraperitoneal injection of 100 µg dexamethasone for 5 days to rats, beginning on gestational day 15 (term = 22 days), and showed fetal concentrations of IGFBP-1 to be significantly higher than in controls. They concluded that increased IGFBP-1 concentrations may be important in the aetiology of dexamethasone-induced fetal growth retardation (Price et al., 1992). In the present study we have demonstrated that dexamethasone administered to women in whom premature delivery is anticipated does not affect maternal concentrations of IGFBP-1, possibly due to the relatively shorter duration and lower dosage of dexamethasone administration than was used by Price et al. (1992).

Miell and colleagues (1993) studied the effect of short-term dexamethasone treatment on the serum concentrations of IGF and their binding proteins in men, and showed suppression of IGFBP-1 concentrations after dexamethasone administration. They suggested that this effect was due to a dexamethasone-induced rise in insulin levels, as IGFBP-1 concentrations are known to be inversely related to those of insulin (Holloy et al., 1988; Suikkari et al., 1989). Also, dexamethasone has been shown to inhibit production of IGFBP-1 in human fetal liver explants (Lewitt and Baxter, 1989). Indeed, in the non-pregnant state, the predominant source of IGFBP-1 is the liver (Hossenlopp et al., 1987; Scharl et al., 1996). In contrast, in the non-pregnant rat, dexamethasone elicits a rise in both serum IGFBP-1 and hepatic IGFBP-1 mRNA concentrations (Luo et al., 1990). The conflicting results in the non-pregnant state may be due to a species difference in the response to dexamethasone. In humans, differences between males and pregnant females may be due to the fact that in males the liver is the predominant source of circulating IGFBP-1, while in females it is produced by the decidua. Alternatively, such differences may be due to variations in regulatory mechanisms of IGFBP-1 production during pregnancy.

The lack of change in plasma concentrations of IGFBP-1 following antenatal dexamethasone therapy suggests that the drug does not influence decidual synthesis of IGFBP-1. Such lack of effect may explain the fact that, in contrast to animal studies, there is no evidence of fetal growth retardation following antenatal dexamethasone therapy in humans (Lamont et al., 1983), a view supported by our finding of a mean birth weight centile of 60. While this is reassuring, further studies are required to see whether repeated dexamethasone dosage to women in whom the threat of premature delivery persists might have a different outcome.

References


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