Effect of antenatal dexamethasone therapy on maternal plasma human chorionic gonadotrophin, oestradiol and progesterone

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Introduction

It is now common practice to administer dexamethasone to pregnant women whenever delivery before 34 weeks is anticipated. This reduces the incidence of respiratory distress syndrome in the new-born (Liggins and Howie, 1972; Crowley, 1995), enhances the efficacy of neonatal surfactant therapy, and reduces the associated risk of intravascular haemorrhage, necrotising enterocolitis, neonatal hyperbilirubinaemia and neonatal death (Sinclair, 1994). However, there has been some concern about adverse maternal effects of corticosteroid therapy with reports of infection due to altered immune response, pulmonary oedema, altered blood glucose control and adrenal suppression (Crowley, 1995).

Dexamethasone administration has been shown to suppress maternal and fetal adrenal production of the oestrogen precursor, dihydroepiandrosterone sulphate (DHEAS), and so lead to reduced circulating concentrations of oestrogen (Ylikorkala et al., 1978). Dexamethasone has been reported to have inhibitory (Mano and Chou, 1981), and direct stimulatory (Wilson and Jawad, 1982) effects on placental human chorionic gonadotrophin (HCG) production in vitro. However, it does not appear to affect the circulating or amniotic fluid concentrations of HCG (Ylikorkala et al., 1978; Haning et al., 1989). Earlier in-vivo studies involved the administration of dexamethasone at different dosages and duration. Currently, it is common practice to administer 12 mg of dexamethasone given twice, 12 h apart. The aim of this study was to determine whether the current regimen of dexamethasone administration affects placental hormone concentrations by measuring maternal circulating concentrations of HCG, oestradiol and progesterone before and after dexamethasone administration.

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 delivery comprised labour (n = 5), severe pre-eclampsia (n = 1), and antepartum haemorrhage due to placenta praevia (n = 3) and of unknown origin (n = 4). These women served as their own controls. It was felt that, to detect changes in a group of women, it was better to use them as their own control rather than carry out a cross-sectional comparison with another group. Therefore, a separate control group was not studied. A standard regimen of dexamethasone comprised two doses of 12 mg intramuscular injections, 12 h apart after completing therapy. Blood samples were collected before starting the dexamethasone therapy, 24 h, and 48 h after completing therapy for the measurement of the plasma concentrations of human chorionic gonadotrophin (HCG), oestradiol and progesterone. There was a progressive fall in the plasma concentrations of HCG following dexamethasone therapy (P = 0.049 and P = 0.034, 24-h and 48-h post therapy respectively). There was an initial fall in the plasma concentrations of oestradiol after dexamethasone therapy (z = 3.059; P = 0.002, 24-h post therapy), which recovered by 48 h (P = 0.239). There was no difference between the plasma concentrations of progesterone at the three time points. The effect of dexamethasone on HCG concentrations suggests that it has a direct inhibitory effect on placental hormone synthesis or secretion. Further studies are needed to define the mechanism of action of dexamethasone on placental HCG production.

Key words: dexamethasone/HCG/oestradiol/progesterone

Abstract

The aim of this study was to determine whether the current regimen of dexamethasone administration to induce fetal lung maturation affected the circulating concentrations of placental hormone. A standard regimen of dexamethasone comprised two doses of 12-mg intramuscular injections, 12 h apart was administered to 12 pregnant women who were not in labour. The obstetric problems that threatened premature delivery comprised labour (n = 5), severe pre-eclampsia (n = 1), and antepartum haemorrhage due to placenta praevia (n = 3) and of unknown origin (n = 4). These women served as their own controls. It was felt that, to detect changes in a group of women, it was better to use them as their own control rather than carry out a cross-sectional comparison with another group. Therefore, a separate control group was not studied. A standard regimen of dexamethasone comprised two doses of 12 mg intramuscular injections, 12 h apart after completing therapy. Blood samples were collected before starting the dexamethasone therapy, 24 h, and 48 h after completing therapy for the measurement of the plasma concentrations of human chorionic gonadotrophin (HCG), oestradiol and progesterone.
Assays

Progesterone and oestradiol were measured by an enzyme-linked immunosorbent assay using the ES700 automated assay system (Boehringer Mannheim UK Ltd, Lewes, East Sussex, UK). The sensitivity of the assay was 37 pmol/l and 0.64 nmol/l for oestradiol and progesterone respectively, and the inter-assay precision was 6.1–14.4% and 3.5–10.3% for oestradiol and progesterone respectively. HCG was measured by an in-house radioimmunoassay using rabbit polyclonal anti-HCG and [125I]-labelled HCG with polyethylene glycol-accelerated second antibody separation. The sensitivity of the assay was 1 IU/l, with an intra- and inter-assay precision of 6% and 10% respectively.

Results

The subjects had a mean age of 32.7 (± 5) years (range 24–40 years); parity ranged from 0 to 4. The median gestational age at administration of dexamethasone was 28 weeks (range 24–33 weeks).

The plasma concentrations of HCG at the three time points were significantly different ($\chi^2 = 11.17$; df $= 2$; $P = 0.004$). There was a significant and steady fall in the plasma concentrations of HCG that was first evident 24 h after completion of dexamethasone therapy ($z = 1.961$; $P = 0.049$). By 48 h after completion of dexamethasone therapy, the plasma concentrations of HCG had fallen further when compared with the pre-therapy concentrations ($z = 2.118$; $P = 0.034$) (Table I). The plasma concentrations of oestradiol were significantly different at the three time points ($\chi^2 = 15.5$; df $= 2$; $P = 0.0004$). Dexamethasone therapy led to a fall in the plasma concentrations of oestradiol which was significant 24 h after completion of therapy ($z = 3.059$; $P = 0.002$). Forty-eight hours after completion of dexamethasone therapy, the plasma concentrations of oestradiol had recovered so that they were not significantly different from the pre-therapy concentrations ($z = 1.176$; $P = 0.239$) (Table I). There was no difference in the plasma concentrations of progesterone at the three time points ($\chi^2 = 1.167$; df $= 2$; $P = 0.558$), and the individual post-therapy concentrations were not different from the pre-therapy concentrations ($z = 0.863$, $P = 0.388$; and $z = 0.235$, $P = 0.814$; 24 and 48 h post therapy respectively) (Table I).

Discussion

This study has demonstrated, for the first time, a fall in the maternal plasma concentrations of HCG following dexamethasone therapy. This is contrary to the findings of Haning et al. (1989). In their study of 33 subjects with a median gestational age of 32 completed weeks, 14 subjects received 5 mg of dexamethasone every 12 h intramuscularly for up to four doses (a total of 20 mg), while 19 had a placebo in a similar vehicle (Haning et al., 1989). There was no significant change from the baseline value observed in either the controls or subjects in the circulating concentrations of HCG 6 h after the last dose of dexamethasone (Haning et al., 1989). Even though the circulating concentrations of dexamethasone begin to fall 6 h after completion of dexamethasone therapy (Collaborative Group on Antenatal Steroid Therapy, 1981), its maximum effect may not be evident until much later. Indeed, our findings of a progressive decrease in the concentrations of HCG following dexamethasone therapy, and the lack of change demonstrated by Haning et al. (1989) are consistent with this theory. The relatively lower dose and more prolonged nature of the regimen used by Haning and colleagues may have contributed to the lack of change in circulating concentrations of HCG (Haning et al., 1989).

Ylikorkala et al. (1978) studied 10 women with a mean gestational age of 34.1 weeks who were treated with dexamethasone in doses of 12, 8 and 4 mg on 3 consecutive days to induce fetal lung maturity, and found that the mean concentrations of HCG in the amniotic fluid did not change 3 days after the completion of dexamethasone therapy. It is thought that amniotic fluid HCG is secreted from the trophoblasts directly (Ozturk et al., 1988). However, there is a strong correlation between the maternal serum and amniotic fluid concentrations of HCG (Chen et al., 1993), which may either reflect a common source or the possibility that HCG diffuses from the maternal circulation into the amniotic fluid. Therefore, if dexamethasone does indeed inhibit placental secretion of HCG, a similar pattern of change in the concentrations of HCG in both maternal serum and amniotic fluid would have been expected. However, as the plasma concentrations of HCG were not measured in the study by Ylikorkala et al. (1978), it is possible that the plasma concentrations of HCG had returned to normal 3 days after the completion of dexamethasone therapy. Alternatively, if HCG does diffuse from the maternal

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**Table I.** Plasma concentrations of human chorionic gonadotrophin (HCG), oestradiol and progesterone before and after dexamethasone therapy

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Median (range)</th>
<th>Pre-therapy (a)</th>
<th>Post 24 h (b)</th>
<th>Post 48 h (c)</th>
<th>Two-tailed P-value (z value)*</th>
<th>a versus b</th>
<th>a versus c</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG (IU/l)</td>
<td>20 406.5 (5232–66 639)</td>
<td>19 311.5 (3788–105 348)</td>
<td>13 310.5 (2814–105 492)</td>
<td>0.049 (1.961)</td>
<td>0.034 (2.118)</td>
<td>0.863</td>
<td>0.084</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>57 711 (24 487–97 714)</td>
<td>24 540 (9002–36 822)</td>
<td>42 405 (16 446–89 642)</td>
<td>0.002 (3.059)</td>
<td>0.239 (1.177)</td>
<td>0.814</td>
<td>0.235</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>281 (190–857)</td>
<td>336 (168–811)</td>
<td>314 (170–582)</td>
<td>0.388 (0.863)</td>
<td>0.814 (0.235)</td>
<td>0.814</td>
<td>0.235</td>
</tr>
</tbody>
</table>

*Wilcoxon matched-pairs signed-rank test.*
circulation in the amniotic fluid, it is possible that it takes more than 3 days for equilibration to occur.

The findings of this study also contrast with the majority of tissue culture data, where dexamethasone has been reported either to have no effect or to stimulate increased HCG secretion in cultured human term placenta (Wilson and Jawad, 1982; Ling, 1983). However, Mano and Chou demonstrated that dexamethasone inhibited HCG synthesis in simian virus 40 tsA mutant-transformed human first trimester placenta cells, though there was no effect on term placental cells (Mano and Chou, 1981). Therefore, the effect of dexamethasone on the production or secretion of HCG may alter with gestation, and the inhibitory effect shown in this study may reflect the fact that our subjects had a median gestational age of 28 weeks, as compared with a median gestation age of 32 weeks and the mean gestational age of 34.1 weeks in the studies by Haning et al. (1977) and Ylikorkala et al. (1978) respectively.

During pregnancy, glucocorticoid therapy results in a transient decrease in the circulating concentrations of oestrogen (Kauppila et al., 1976; Ohrlander et al., 1977). Glucocorticoids do this by suppressing the maternal and fetal adrenal secretion of DHEAS, which is the main precursor of oestrogen (Ylikorkala et al., 1978). The findings of this study that dexamethasone administered to induce fetal lung maturity leads to an initial fall in the concentrations of oestradiol is in agreement with the findings of others (Kauppila et al., 1976; Ohrlander et al., 1977; Ylikorkala et al., 1978). However, in this study, a complete recovery 48 h after completion of therapy was found while, in the other studies, recovery occurred 3 to 6 days after completion of therapy (Kauppila et al., 1976; Ohrlander et al., 1977; Ylikorkala et al., 1978). Ohrlander et al. (1977) found the lowest level of oestradiol was obtained 3 days after completion of therapy, and recovery was complete 6 days after completion of therapy. This may reflect differences in dexamethasone administration, as Ohrlander et al. (1977) administered 12 mg of dexamethasone on three consecutive days with a total dosage of 36 mg, in contrast to two injections of 12 mg dexamethasone administered 12 h apart. Our data suggest that the current dexamethasone regimen leads to a transient suppression of adrenal secretory functions with rapid recovery of the circulating concentrations of oestradiol. The data presented here suggest that there will be little or no adrenal suppression if delivery occurs more than 24 h after dexamethasone therapy.

The mechanism by which dexamethasone modulates HCG secretion is unknown. There are two lines of evidence to indicate that the secretion of HCG is partially under fetal endocrine control. First, unlike human placental lactogen and pregnancy specific beta 1-glycoprotein, which are also secreted by the syncytiotrophoblast and which rise progressively in relation to the trophoblast mass, HCG rises exponentially to a peak at 8 to 10 weeks gestation, and then falls to a plateau for the remainder of the pregnancy (Braunstein et al., 1980). Second, unlike other hormones secreted by the syncytiotrophoblast which have similar concentrations in both male- and female-bearing pregnancies, the concentration of HCG in maternal peripheral blood (Broditsky et al., 1975; Haning et al., 1989), and placental tissue (Hobson and Wide, 1974; Wide and Hobson, 1974) is higher in female-bearing pregnancy than in male-bearing pregnancy. There is evidence that HCG production is inhibited by a steroid originating in the fetal adrenal (Haning et al., 1982), and administration of DHEAS to placental explants in vitro inhibited the stimulatory effect of gonadotrophin-releasing hormone on HCG secretion (Haning et al., 1989). Therefore, we expected that dexamethasone administration to pregnant women would stimulate HCG production by reducing the concentration of DHEAS from both maternal and fetal adrenals. However, this study has demonstrated a significant fall in the plasma concentrations of HCG, accompanied by a fall in the plasma concentrations of oestradiol following dexamethasone administration. This suggests that dexamethasone directly inhibits the synthesis or secretion of HCG. Another possibility is that dexamethasone could exert its effect through inhibition of the production of pro-inflammatory cytokines (Telleria et al., 1998), which are known to stimulate HCG production (Matsuzaki et al., 1995; Sawai et al., 1995).

This study confirms the findings of earlier studies that dexamethasone administered to induce fetal lung maturation does not alter the plasma concentrations of progesterone (Kauppila et al., 1976; Ohrlander et al., 1977; Ylikorkala et al., 1978). It has been suggested that this is because the breakdown of cholesterol, the main precursor of placental progesterone, is not inhibited by glucocorticoids (Ylikorkala et al., 1978).

One of the major concerns about dexamethasone therapy is that it may have lasting effects on fetal endocrine and metabolic processes. This study has shown that dexamethasone has significant effects on placental hormone concentrations, which implies that it may have effects on other aspects of placental function. Further studies are necessary to define the mechanisms and extent of the effect of dexamethasone on placental function.

References


Received on June 8, 1998; accepted on October 13, 1998