The metabolic effect of antenatal corticosteroid therapy

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The use of antenatal dexamethasone to mature the fetal lung in pregnancies likely to deliver before 34 weeks is almost universal. It reduces the incidence of respiratory distress syndrome in the newborn and results in an overall improvement in neonatal morbidity and mortality. Although considered to be generally safe, there are concerns about adverse maternal and fetal effects. In a series of studies, we have found that antenatal dexamethasone administration is associated with reduced placental hormone production and maternal bone formation, impaired glucose tolerance and altered function of the hypothalamic–pituitary–adrenal axis. In this article, we have compared our data with other reports in the human and reviewed the relevant animal data. We conclude that further studies on the long-term effects of antenatal dexamethasone therapy in the human are warranted with particular emphasis on the long-term effects on the fetus.

Key words: antenatal corticosteroids/dexamethasone/fetal growth/metabolic effects/respiratory distress

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Introduction

Dexamethasone administration prior to preterm delivery reduces the incidence of respiratory distress syndrome and enhances the efficacy of surfactant therapy in the new-born. In addition, there is an associated reduction in the risk of intraventricular haemorrhage, necrotizing enterocolitis, neonatal hyperbilirubinaemia and neonatal death (Sinclair 1994). Thus, overall, there is a marked reduction in neonatal morbidity and mortality associated with the administration of dexamethasone. It acts by accelerating lung maturation, speeding up the thinning of the double capillary loop to form the thin gas exchanging walls of alveoli and enhancing the production of surfactant by the type II pneumocytes (Liggins and Howie, 1972; Bunton and Plopper, 1984; Massaro et al., 1985; Adamson and King, 1988; Crowley, 1995). Hence, most pregnant women are given corticosteroids whenever delivery before 34 weeks is anticipated.

Recently, concern has been expressed about the potential adverse effects of dexamethasone administration. There are reports of infection due to immune suppression, pulmonary oedema, impaired blood glucose control and adrenal suppression in the mother (Crowley, 1995). In addition, animal data suggest that dexamethasone has adverse effects on the fetus and that these effects persist into adulthood. These include reduced fetal growth, impaired glucose tolerance, high blood pressure and altered function of the hypothalamic–pituitary–adrenal axis (Price et al., 1992; Dodic et al., 1998; Nyirenda et al., 1998).

Impaired placental function

Dexamethasone administration has been associated with growth restriction in animal and recently in human studies (French et al., 1999). The reduced fetal growth may be due to impaired placental function or altered fetal metabolism. Dexamethasone has been reported to induce abnormal placental development in the sheep (Cox et al., 1999a) and typical changes of growth restriction in the human placenta (Salafia et al., 1997).

There are conflicting data relating to the effect of dexamethasone on placental hormone production and/or secretion. In earlier studies, dexamethasone administration did not affect the circulating or amniotic fluid concentrations of human chorionic gonadotrophin (HCG) (Ylikorkala et al., 1978; Haning et al., 1989) or human placental lactogen (HPL) (Ylikorkala and Kauppila, 1974; Ylikorkala et al., 1978). In contrast, HPL concentrations were reported to decrease significantly 1 week after cessation of dexamethasone therapy, suggesting a direct depression of placental function (Lange and Anthonsen, 1980).

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and pregnancy specific which suggest that the secretion of HCG is partially under fetal account for the differences observed.

gestational age at which we administered dexamethasone that our study and the earlier studies, it is probably the earlier differences in the dosage and regimen of dexamethasone between placental cells (Manu and Chou, 1981). Thus, although there were differences in the dosage and regimen of dexamethasone between our study and the earlier studies, it is probably the earlier gestational age at which we administered dexamethasone that accounted for the differences observed.

The mechanism by which dexamethasone modulates HCG secretion is unknown. However, there are two lines of evidence which suggest that the secretion of HCG is partially under fetal endocrine control. Firstly, unlike human placental lactogen (HPL) and pregnancy specific β₂-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 8–10 weeks gestation, and then falls to a plateau for the remainder of the pregnancy (Braunstein et al., 1980). Secondly, 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 pregnancies than in male bearing pregnancies. In addition, there is evidence that HCG production is inhibited by a steroid originating in the fetal adrenal (Haning et al., 1982), and the addition of dihydriopandrostosterone sulphate (DHEA-S) to placental explants in vitro is reported to inhibit the stimulatory effect of gonadotrophin-releasing hormone (GnRH) on HCG secretion (Haning et al., 1982). Therefore, dexamethasone administration to pregnant women might be expected to stimulate HCG production indirectly by reducing the concentration of DHEA-S from both maternal and fetal adrenals. However, this hypothesis was not proven by our recent demonstration of a significant fall in the plasma concentrations of HCG, despite an accompanying fall in those of oestradiol following dexamethasone administration (Table I) (Ogueh et al., 1999a). Thus, our data suggest that dexamethasone has a direct inhibitory effect on the production or secretion of HCG by the placenta. However, it is possible 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 (Sawai et al., 1995; Matsuzaki et al., 1995).

The reduction in HCG concentrations following dexamethasone administration may explain why steroids are useful in the management of hyperemesis gravidarum (Nelson-Piercy and De Swiet, 1994). However, no data are available about the impact of prednisolone administration on HCG concentrations and in contrast to dexamethasone, prednisolone is not thought to cross the placenta. Thus, if HCG concentrations fall secondary to an effect in the fetus, then prednisolone may not have the same effect.

Fetal partial oxygen pressure (pO₂) concentrations have been shown to fall for >24 h post-dexamethasone administration in the sheep. This may be due to changes in fetal haemodynamics, the increase in fetal glucose concentrations (which then require more oxygen to metabolize) or impaired gas transfer across the placenta (Bennett et al., 1999). However, placental vascular resistance is reported to fall which should improve oxygen transfer (Wallace and Baker, 1999) and the fall in pO₂ preceded the increase in fetal glucose concentrations, thus it may be alterations in placental function which are responsible. The fall in pO₂ is small, but if the fetus is already hypoxic such a fall could be significant. Dexamethasone has been reported to induce apoptosis and to reduce rates of mitosis in several cell lines (Carson et al., 1973; Johnson et al., 1997). Such effects could be responsible for impaired placental function and the reported changes in histology (Salafia et al., 1997).

### Table I. Plasma concentrations of HCG, oestradiol and progesterone before and after dexamethasone therapy. Values are given as median and range, with percentage change in parentheses

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Pre-therapy</th>
<th>Post-24 h</th>
<th>Post-48 h</th>
<th>P value (2 tailed)</th>
<th>NS = not significant (Wilcoxon Matched-Pairs Signed-Rank Test).</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCG (IU/l)</td>
<td>20406.5 (100)</td>
<td>19311.5 (95)</td>
<td>13310.5 (65)</td>
<td>0.049 0.034</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5232–66639</td>
<td>3788–105348</td>
<td>2814–105492</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>57711 (100)</td>
<td>24540 (43)</td>
<td>42405 (73)</td>
<td>0.002 NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24487–97714</td>
<td>9082–36822</td>
<td>16446–89642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>281 (100)</td>
<td>336 (120)</td>
<td>314 (112)</td>
<td>NS NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>190–857</td>
<td>168–811</td>
<td>170–582</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Immuno reactive IGF-1 concentrations (Gourmelen, 1996, despite normal or moderately increased serum in those with endogenous glucocorticoid excess due to Cushing's disease, which is known to suppress hepatic IGF-1 synthesis (Hollinger, 1988; Suikkari, 1989; Clemmons, 1991). Also, dexamethasone administration to non-pregnant rats increases both serum IGFBP-1 and hepatic IGFBP-1 mRNA concentrations (Luo et al., 1990), and has been suggested that the decreased IGF bioactivity associated with glucocorticoid excess is due to the presence of serum inhibitors of IGF actions, e.g. IGFBP-3 (Unterman and Phillips, 1985; Ooi, 1990; Clemmons, 1991).

Price et al. demonstrated that in rats dexamethasone administration during pregnancy leads to fetal growth restriction (Price et al., 1992). They administered a daily i.p. injection of 100 μg dexamethasone for 5 days to seven rats beginning on gestational day 15 (term = 22 days) and showed that, compared with a control group, the fetal IGFBP-1 concentrations and maternal IGFBP-1 mRNA were significantly higher in the treatment group (Price et al., 1992). It is believed that IGFBP-1 reduced the paracrine influence of IGF-I on placental growth and nutrient uptake (Fanti et al., 1986), and so led to impaired fetal growth (Rutanen et al., 1985; Wang and Chard, 1992).

Similarly, in the human, the bioactivity of serum IGF-I is consistently inhibited in patients treated with glucocorticoids and in those with endogenous glucocorticoid excess due to Cushing's disease, despite normal or moderately increased serum immunoreactive IGF-1 concentrations (Gourmelen et al., 1982; Caufriez and Copinschi, 1986; Miell et al., 1993). However, in contrast to the animal data, short-term dexamethasone treatment in the human male leads to a reduction in IGFBP-1 and IGFBP-2 concentrations and an increase in IGFBP-3 concentrations (Miell et al., 1993). The suppression of IGFBP-1 is thought to be due to a dexamethasone-induced rise in insulin concentrations (Miell et al., 1993), which is known to suppress hepatic IGFBP-1 synthesis (Holly et al., 1988; Suikkari et al., 1989; Clemmons, 1991). Also, dexamethasone may have a direct effect on IGFBP-1 synthesis, since it inhibits production of IGFBP-1 in human fetal liver explants (Lewitt and Baxter, 1989), the liver being the predominant source of IGFBP-1 in the non-pregnant state (Hossenlopp et al., 1987; Scharf et al., 1996). Regardless of the mechanisms involved, it is apparent that, in contrast to the rat, there are no dexamethasone-induced increases in IGFBP-1 concentrations in man (Miell et al., 1993), and therefore induction of this binding protein cannot be implicated in the mechanism of glucocorticoid-induced inhibition of IGF-I bioactivity. In the circulation, IGFBP-3 is proteolysed by serine proteases to two major fragments. The larger 22/25 kDa fragments has low affinity for IGF-I and weakly inhibits IGF-I mitogenic effects, whilst the smaller 16 kDa fragment does not bind to IGF-I, but inhibits IGF-I bioactivity to a similar extent as intact IGFBP-3 (Lalou et al., 1996, 1997). Hence, IGFBP-3 proteolysis may inhibit IGF-I-stimulated mitogenesis by a mechanism independent of IGFs.

In the human, maternal serum concentrations of IGF-I gradually rise throughout pregnancy, and the source of this increase is thought to be the maternal liver (Hills et al., 1996). On the other hand, the serum concentration of IGFBP-1 increases rapidly to reach a peak at 12–13 weeks gestation; but then does not change until term (Wang et al., 1991; Hills et al., 1996). The bulk of the maternal circulating IGFBP-1 in pregnancy is believed to be derived from the deciduized endometrium (Rutanen et al., 1985; Bell, 1989). IGFBP-1 is thought to act systemically, and/or locally, to inhibit the mitogenic actions of IGF-I on placental growth and so to reduce fetal growth (Wang and Chard, 1992).

Indeed, maternal serum mainly contains phosphorylated isoforms of IGFBP-1 which have an inhibitory effect on IGF-I bioactivity (Jones et al., 1991, 1993). However, in a longitudinal study of pregnant women who received dexamethasone therapy for fetal lung maturation in anticipation of premature delivery before 34 completed weeks gestation, there was no significant change in the IGFBP-1 bioactivity, concentrations of IGF-1 and IGFBP-1, or IGFBP-3 protease activity 24 and 48 h after administration of dexamethasone (Table II: Ogueh et al., 1998a, 2000). The lack of change in the IGF axis following dexamethasone therapy during human pregnancy may be due to the relatively shorter duration and lower dosage of dexamethasone administered when compared with other studies in rats (Price et al., 1992; Ogueh et al., 1998a, 2000). Nevertheless, it may explain why, in contrast to animal studies, there is no evidence of fetal growth restriction following antenatal dexamethasone therapy in humans (Lamont et al., 1983; Ogueh et al., 1998a). However, multiple courses of antenatal corticosteroids appears to be associated with significant reduction in birth weight and head circumference in human pregnancy (French et al., 1999). The mechanism of this effect of multiple courses of antenatal corticosteroids is unclear, but it is likely to be independent of the maternal GH-IGF axis.

**Suppression of the hypothalamic–pituitary–adrenal axis**

Oestradiol concentrations fell rapidly following dexamethasone administration and had only recovered partially at 48 h post-treatment (Table I). The transient decrease in the circulating concentrations of oestrogen following dexamethasone administration in pregnancy has been reported previously (Kauppila et al., 1976; Ohrlander et al., 1977). Steroids do this by suppressing the maternal and fetal adrenal secretion of DHEA-S, the main precursor of oestrogen (Ylikorkala et al., 1978). Complete recovery of the circulating concentrations of oestrogen has been reported to occur 3–6 days after completion of therapy (Kauppila et al., 1976; Ohrlander et al., 1977; Ylikorkala et al., 1978). Repeated betamethasone treatments suppress the normal gestational age-associated increase in oestriol concentrations (Hendershott et al., 1999).

Antenatal dexamethasone administration did not alter the plasma concentrations of progesterone as previously reported (Table I; Kauppila et al., 1976; Ohrlander et al., 1977; Ylikorkala et al., 1978). This has been suggested to be because the breakdown
of cholesterol, the main precursor of placental progesterone, is not inhibited by glucocorticoids (Ylikorkala et al., 1978).

Maternal plasma corticotrophin-releasing hormone (CRH) concentrations were increased by betamethasone administration suggesting that hypothalamic and placental CRH regulation differs (Korebrits et al., 1998), but confirming earlier in-vitro data which suggested that steroids enhanced placental CRH synthesis (Jones et al., 1978). It is uncertain whether the increase in maternal CRH is significant, although CRH may play a role in the onset of labour and dexamethasone administration has been suggested to increase the risk of preterm delivery in multiple pregnancy (Elliot and Radan, 1995).

In the rat, glucocorticoid excess during pregnancy has a strong inhibitory effect on the structure and function of the fetal and neonatal adrenal glands (Hristic et al., 1997; Manojlovic et al., 1998). However, in a study looking at the infants of mothers given short courses of dexamethasone antenatally to mature the fetal lungs, Ng et al. could not demonstrate any effect on the response to corticotrophin-releasing hormone (CRH) at 7 days of age (Ng et al., 1997a). Although dexamethasone administered postnatally to preterm infants as treatment for chronic lung disease or to wean off the ventilator has been demonstrated to suppress adrenal function, and the effect may persist after stopping the steroids (Ford et al., 1997; Ng et al., 1997b).

There is scant evidence of long-term effects of dexamethasone administration during pregnancy. The only convincing data are those of Trautman et al. who demonstrated psychological differences between controls and children whose mothers took dexamethasone during pregnancy for congenital adrenal hyperplasia (Trautman et al., 1995).

Reduced insulin sensitivity

Steroids reduce insulin sensitivity and both acute and chronic steroid administration result in increased circulating insulin concentrations (Miell et al., 1993; McMahon et al., 1988). In an earlier study, the administration of dexamethasone to pregnant women was found not to affect the circulating concentrations of insulin and glucose (Tuimala et al., 1975). However, only 1 mg of dexamethasone was administered orally four times daily for an average of 7.8 days, which is substantially different from the current regimen of 12 mg of dexamethasone twice 12 h apart. Our data show that the current regimen of dexamethasone administration induces a transient increase in the concentrations of glucose and insulin 24 h after completion of dexamethasone therapy (Ogueh et al., 2000). Although, the fetus is also exposed to higher concentrations of glucose (Tuimala et al., 1975). However, only 1 mg of dexamethasone was administered orally four times daily for an average of 7.8 days, which is substantially different from the current regimen of 12 mg of dexamethasone twice 12 h apart. Our data show that the current regimen of dexamethasone administration induces a transient increase in the concentrations of glucose and insulin 24 h after completion of dexamethasone therapy (Ogueh et al., 2000). Although, the fetus is also exposed to higher concentrations of glucose (Bennett et al., 1999) and so probably insulin, the transient nature of these changes may mean that they are not significant. However, in animal studies, a single treatment of thyroid hormone at a specific point in fetal development, leads to a permanent resetting of the hypothalamic–pituitary–thyroid axis (Pracyk et al., 1992). Thus, even a transient

Table II. Maternal plasma concentrations of insulin-like growth factor (IGF)-1, IGF bioactivity, insulin-like growth factor binding protein (IGFBP)-3 protease activity, insulin, glucose and insulin resistance index, before and after dexamethasone therapy. Values are given as median and range, with percentage change in parentheses.

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Pre-therapy</th>
<th>Post-24 h</th>
<th>Post-48 h</th>
<th>P value (2 tailed)</th>
<th>$P$ value (2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(a)</td>
<td>(b)</td>
<td>(c)</td>
<td>a versus b</td>
<td>a versus c</td>
</tr>
<tr>
<td>IGF bioactivity (IU/ml)</td>
<td>1.05 (100)</td>
<td>1.25 (119)</td>
<td>1.61 (153)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>0.52–1.27</td>
<td>0.44–1.37</td>
<td>0.85–2.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGFBP-3 (%) protease activity</td>
<td>77.8 (100)</td>
<td>78.2 (101)</td>
<td>76.8 (99)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>73.5–81.3</td>
<td>75.5–83.3</td>
<td>69.2–81.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF-1 (nmol/l)</td>
<td>38.7 (100)</td>
<td>40.2 (104)</td>
<td>41.5 (107)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>25.9–48.1</td>
<td>31.7–43.3</td>
<td>34.7–48.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin (mU/l)</td>
<td>12.8 (100)</td>
<td>22.4 (175)</td>
<td>20.9 (163)</td>
<td>0.041</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>8.1–20.6</td>
<td>11.8–29.8</td>
<td>14.3–57.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>4.3 (100)</td>
<td>5.6 (130)</td>
<td>4.6 (107)</td>
<td>0.021</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3.9–4.8</td>
<td>4.2–6.9</td>
<td>3.9–5.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRI</td>
<td>1.75 (100)</td>
<td>5.15 (294)</td>
<td>3.25 (186)</td>
<td>0.050</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>1.19–3.99</td>
<td>1.95–8.67</td>
<td>2.03–15.12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant (Wilcoxon Matched-Pairs Signed-Ranks Test); IRI = insulin resistance index (glucose × insulin/25).
increase of glucose and insulin may be sufficient to permanently alter fetal glucose homeostasis if this were to occur at a critical point in fetal development. Such a coincidence is more likely with the practice of administering repeated doses of dexamethasone to women at continued risk of preterm delivery. Indeed, in recent animal studies, dexamethasone administered to pregnant rats and sheep in late pregnancy produced fasting hyperglycaemia, reactive hyperglycaemia, and hyperinsulinaemia on subsequent glucose loading in the offspring. This effect was not present if the dexamethasone was administered in the first or second week of gestation in the rat. Therefore, excessive glucocorticoid exposure late in pregnancy may predispose the offspring to glucose intolerance in adulthood (Nyirenda et al., 1998; Cox et al., 1999b).

**Bone metabolism**

In the non-pregnant state, corticosteroids cause osteoporosis by inhibition of collagen synthesis; this results in a drop in both bone mass and bone mineral density (Cutroneo et al., 1981; Oikarinen et al., 1996). This adverse effect has been confirmed by measuring the biochemical markers of bone turnover, which are the single most sensitive method for monitoring acute changes in bone metabolism (Godschalk and Downs, 1988; Prummel et al., 1991; Taylor et al., 1994). As type I collagen is mainly synthesized in the bone, the circulating concentration of its pro-peptide, carboxy terminal pro-peptide of type I pro-collagen (PICP) directly correlates with the rate of bone formation, and serves as a marker of bone formation (Melkko et al., 1990). Similarly, the serum concentrations of cross-linked carboxy terminal telopeptide of type I collagen (ICTP, a marker of bone resorption) before and after dexamethasone therapy. Values are given as median and range, with percentage change in parentheses

<table>
<thead>
<tr>
<th>Bone marker</th>
<th>Pre-therapy (µg/l)</th>
<th>+ 24 h (µg/l)</th>
<th>+ 48 h (µg/l)</th>
<th>Delivery (µg/l)</th>
<th>P value (2 tailed)</th>
<th>P value (2 tailed)</th>
<th>P value (2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICP</td>
<td>114.5 (100)</td>
<td>83 (72)</td>
<td>100.5 (88)</td>
<td>121 (106)</td>
<td>0.001</td>
<td>0.014</td>
<td>0.044</td>
</tr>
<tr>
<td>ICTP</td>
<td>4.05 (100)</td>
<td>4.05 (100)</td>
<td>4.4 (109)</td>
<td>4.7 (116)</td>
<td>NS</td>
<td>0.059</td>
<td>0.006</td>
</tr>
</tbody>
</table>

NS = not significant (Wilcoxon Matched-Pairs Signed-Ranks Test).

Osteocalcin, another marker of bone formation decrease with daily doses of prednisolone as low as 2.5 mg (Caporali et al., 1991; Nielsen et al., 1991). Intermittent treatment does not seem to reduce the bone loss, but bone mass usually recovers when treatment is stopped altogether (Laan et al., 1993).

So far no skeletal problem has been clinically evident during or after pregnancy in women treated with corticosteroid for fetal lung maturity in anticipation of premature delivery, possibly due to a relatively short course of the therapy. In order to investigate the possibility that maternal bone metabolism was altered by dexamethasone administration we measured the circulating concentrations of carboxy terminal pro-peptide of PICP, a marker of bone formation) and ICTP, a marker of bone resorption. We found that, within 24 h of completion of dexamethasone therapy, there was a significant drop in the concentrations of bone formation marker PICP, which started to rise by 48 h post-therapy, but remained significantly lower than the pre-therapy concentrations (Table III; Ogueh et al., 1998b). The PICP concentrations continued to increase to become higher than pre-therapy concentrations at the time of delivery, suggesting a complete recovery from the suppression and further increase in bone formation. On the other hand, the plasma ICTP concentrations showed a trend towards rise by 48 h post-therapy, which continued until delivery when concentrations were significantly higher compared with pre-therapy concentrations, suggesting an increase in bone resorption (Table III; Ogueh et al., 1998b).

During normal pregnancy, PICP initially decreases to a nadir at 12 weeks gestation but subsequently increases to peak at 38 weeks gestation (Puistola et al., 1993; Khashigir et al., 1996). Dexamethasone therapy reverses this trend of PICP, and is associated with an increase in ICTP concentrations (Ogueh et al., 1998b). The relatively short duration of corticosteroid therapy may explain the transient nature of these changes, but the potential of corticosteroid-induced suppression of bone formation is powerful enough to be evident against a background increase in the rate of bone formation in pregnancy. The dexamethasone-induced change in the PICP and ICTP concentrations in pregnancy is similar to that reported in the non-pregnant state.
(Oikari et al., 1992; Packe et al., 1992). However, in pregnancy the effect is transient, and postpartum bone mineral density in women who had antenatal dexamethasone therapy is similar to that of a control group of women who did not have dexamethasone therapy (Table IV; Ogueh et al., 1999b). Nevertheless, any subclinical bone changes with corticosteroid therapy during pregnancy might enhance any future risk of osteoporosis, particularly in those women who already have low bone density at the beginning of their pregnancy (Khastgar and Studd, 1994).

Cardiovascular system

Recent animal studies have linked fetal exposure to excess maternal glucocorticoids with the later occurrence of cardiovascular disorders, particularly hypertension. Dodic et al. subjected two groups of pregnant ewes to treatment with dexamethasone for 48 h, and found that glucocorticoid exposure in early pregnancy resulted in a significantly higher basal mean arterial pressure in the lambs at 4, 10 and 19 months after birth (Dodic et al., 1998). However, there was no alteration in the vascular sensitivity to noradrenaline, angiotensin II and adrenocorticotropic hormone (ACTH), nor did it affect the basal or ACTH-induced concentrations of cortisol or basal renin plasma concentrations in the lambs at any age (Dodic et al., 1998).

Conclusions

It is clear that current practice of administering corticosteroids to induce fetal lung maturation prior to delivery before 34 weeks gestation has significant effects on the maternal metabolism. This has been demonstrated by the effects of dexamethasone on the circulating concentrations of IGF, HCG, oestadiol, glucose, insulin, and insulin resistance. However, the long-term effects of these changes on the mother and newborn are unknown, and the effects of repeated administration of dexamethasone to pregnant women are yet to be determined.

There is now evidence to support the hypothesis that events in fetal life may permanently alter the structure and function of an individual, programming later adult disease. Reduced birth weight and thinness at birth are associated with higher blood pressure in later life, and glucose intolerance and non-insulin dependent diabetes mellitus respectively (Clark 1998). Animal studies suggest that this may be due to programming of the hypothalamic–pituitary–adrenal axis. Given that our data suggest that dexamethasone has marked effects on maternal metabolism, studies of its effects on the offspring’s later blood pressure and glucose tolerance are warranted.

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