The Role of Cortisol in Preparing the Fetus for Birth

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Abstract. The glucocorticoids, cortisol and corticosterone, have a unique function in the fetus in inducing a wide range of enzymes before birth that have little or no function during fetal life but on which survival after birth is dependent. The loss of the placenta at birth deprivs the fetus of a source of oxygen, glucose and heat (among many other things) for which alternatives must be available immediately if survival is to be assured. In anticipation of these needs several organs undergo maturational changes in late pregnancy aimed at meeting these requirements. The lungs mature structurally and functionally, becoming distensible and capable of coping with high surface tension when air enters the alveoli with the first breath. In the liver, glycogen accumulates and gluconeogenesis is initiated to meet the demands for glucose until feeding begins. There is an increase in the production of tri-iodothyronine and catecholamines in preparation for the sharp increase in metabolic rate and thermogenesis associated with breathing and the cold environment. All these dramatic maturational events are regulated by cortisol as are numerous others in most organ systems that contribute to neonatal well-being but on which survival is less dependent. Pharmacological manipulation of these systems before birth has made a substantial contribution to improving human health.

Introduction

Jim Goding's life and mine ran remarkably parallel courses over a decade or more. He was born 11 years before me but I caught up some of the difference when he spent some lost years as a prisoner of war. When I was graduating from Medical School, he was Superintendent of Prince Henry's Hospital. We were both late starters in research. Jim's first publication was in 1956 at the age of 41 (Coats et al. 1956) and mine was in 1959 at the age of 33. We both trained as surgeons and applied those surgical skills to research; Jim adapted hypophysectomy, adrenalectomy and transplantation of the ovary and uterus to the adult sheep whereas I performed hypophysectomy and adrenalectomy in fetal sheep. In 1967, we both reported our first results; experiments with autotransplanted uterus and ovaries (Goding et al. 1967) and fetal hypophysectomy (Liggins et al. 1967). Jim Goding's interest was to find the factors regulating the end of the oestrous cycle, whereas my interest was to find the factors regulating the end of pregnancy. Our respective research in sheep inevitably led us into the field of prostaglandins, culminating in 1971 when Jim and his colleagues described the luteolytic effects of prostaglandin $F_2\alpha$ (PGF$_2\alpha$) (McCracken et al. 1971) and Susan Grieves and I described the uterine release of PGF$_2\alpha$ preceding parturition (Liggins and Grieves 1971). His early death in 1973 deprived Jim of the opportunity of sharing in the discovery of ovine trophoblastic protein, the prostaglandin-inhibitory protein that inhibits luteolysis, whereas I was fortunate to isolate gravidin, the prostaglandin-inhibitory protein that we think inhibits parturition in women (Wilson et al. 1988).

This review does not address the initiation of parturition because a recent James Goding Lecturer delivered a thought-provoking paper on that subject (Thorburn 1991). My topic is a by-product of the initiation of parturition which can be broadly described as preparation for birth. Preceding parturition, fetal organs undergo accelerated maturation which facilitates the transition from intrauterine to extrauterine life. These changes are more or less (depending on species) tightly coupled to the mechanism initiating parturition and the common factor is cortisol. For example, the foal is mature at birth over a wide span of gestation lengths provided that the onset of parturition is spontaneous (Silver et al. 1984). In the fetus, the well-known regulatory action of cortisol on enzyme activity in adults has a unique opportunity to induce activity in enzymes that are dormant although the relevant genes have passed the programmed time when transcription first becomes possible.

At least in the fetal lung, the maturational response to cortisol is enhanced by tri-iodothyronine ($T_3$) and prolactin. This discussion will be largely confined to cortisol but the possibility of synergism of cortisol,
particularly with $T_3$ and prolactin, in other organs should not be overlooked.

In most species investigated to date, late pregnancy is characterized by rising concentrations of cortisol in the fetal circulation; when the newborn is precocious and must be self-sufficient to survive (e.g. sheep) concentrations rise sharply prepartum (Fig. 1) whereas slower increases are characteristic of those species in which the newborn is immature and highly dependent on maternal care (e.g. rodents and human). The mechanism by which increasing activity of cortisol is achieved also varies; in fetal sheep, the concentration of both total and free cortisol rises as a result of an increased rate of secretion (Fairclough and Liggins 1975) whereas in fetal rats, rising concentrations of free cortisol are due mainly to falling concentrations of cortisol-binding globulin (CBG). Nevertheless, there is little evidence of species specificity in the spectrum of enzymes inducible by cortisol with the exception of placental 17α-hydroxylase which is inducible in some species (e.g. sheep) (Fig. 2) and absent or noninducible in others (e.g. human). This exception is fundamental to species differences in the mechanism initiating labour. The presence of a cortisol-inducible placental 17α-hydroxylase permits the fetal hypothalamic–pituitary–adrenal system to regulate placental steroid production (Flint et al. 1975) whereas its absence deprives the fetus of this form of control. Indeed, in the latter case, no alternative mechanism initiating parturition is known and current hypotheses generally postulate a system in which the chorionic membrane and placenta interact in a paracrine fashion with the adjacent decidua, the contribution of the fetus being no more than permissive.

Interest in cortisol as the 'maturational hormone' dates back to the origins of fetal physiology when Jost (1947) reported his observations on the effects of decapitating fetal rabbits. The role of cortisol in the small intestine was acknowledged soon afterwards (Moog 1953). The impetus to investigate the hypothesis that cortisol has a general function in inducing fetal maturation came with the discovery of corticosteroid-induced maturation of the fetal lung (Liggins 1969; Kotas and Avery 1971) which also drew attention to the potential for therapeutic intervention with antepartum corticosteroid administration. The remainder of this paper reviews organ systems in which maturation effects of cortisol have been demonstrated.

### Thyroid

The thyroid is a good example of the way in which cortisol converts a system in anticipation of birth from one meeting the needs of fetal life to one meeting the needs of extrauterine life. Autonomy of fetal thyroid function

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**Fig. 1.** The first demonstration of a rise prepartum in fetal corticosteroid levels. The concentration of total corticosteroids in plasma of fetal sheep in late pregnancy. Note that the rise occurs also in fetuses delivered prematurely. (Bassett and Thorburn 1969.)

**Fig. 2.** Effect of infusion of dexamethasone for 45 h on placental steroid 17α-hydroxylase in fetal sheep. Western blot analysis of cytochrome P450c17, in microsomal preparations. Lanes 1–3, untreated controls; lanes 4–7 dexamethasone-treated. (Flint et al. 1988.)
Fetal Cortisol

is assured by the more or less complete impermeability of the placenta to maternal thyroid hormones. The fetus develops in a constant thermoneutral environment; the thyroid must supply the requirements of basal metabolism but is not required to increase secretion rate in response to acute changes in metabolic rate. On the other hand, the thyroid must grow and develop the potential for the demand for T₃ after birth when the metabolic rate rises sharply to maintain body temperature in a cold environment and to cope with breathing. These conflicting demands are resolved in two ways.

(1) The thyroid maintains a relatively high rate of secretion of thyroxin (T₄) but deiodination of T₄ is predominantly to biologically inactive reverse T₃ (rT₃) rather than to T₃ (Fig. 3).

(2) The placenta maintains a high metabolic clearance rate (MCR) of T₃.

The switch from the fetal to the newborn state near term is controlled by cortisol which stimulates outer-ring deiodination of T₄ in the liver (Wu et al. 1978) and reduces the MCR of T₃ by inhibiting placental deiodination (Fraser and Liggins 1989) (Fig. 4). Thus, fetal plasma concentrations of T₃ rise concurrently with those of cortisol. Loss of the placenta at birth is associated with a further marked rise in circulating T₃ (Fig. 2). The dramatic increase in neonatal requirements for thyroid hormones is met by a surge of thyrotrophin-stimulating hormone and increased secretion of T₄ and T₃.

**Lung**

The response of the immature fetal lung to cortisol is complex, involving stimulation not only of surfactant synthesis and secretion but also of connective tissue maturation, alveolar epithelial differentiation, lung liquid resorption, glycogenolysis and antioxidant enzymes. Provided that certain other hormones (T₃ and prolactin) are present in adequate amounts, fetal sheep infused with sufficient cortisol to increase circulating levels to those normally present at term respond within 72 h with

**Fig. 3.** Patterns of cortisol and thyroid hormones in plasma of fetal sheep in late pregnancy. T₃, tri-iodothyronine; T₄, thyroxin; RT₃, reverse T₃.

**Fig. 4.** Effect of infusion of cortisol on the metabolic clearance rate of tri-iodothyronine (T₃) and thyroxin (T₄) in fetal sheep. (Fraser and Liggins 1989.)
advancement from gross immaturity to morphological and functional maturity approaching that at term (Liggins et al. 1987).

**Surfactant**

Surfactant has a lipid component, disaturated phosphatidylcholine, and a protein component consisting of at least four proteins—surfactant protein (SP) A (SP-A), SP-B, SP-C and SP-D. The synthesis of both components is stimulated by cortisol (Fig. 5). Several enzymes in the phosphatidylcholine biosynthetic pathway including cholinephosphotransferase, phosphatidate phosphatase, lysocereithin acyltransferase and phosphatidate cytidyltransferase have been reported inconsistently and depending on species to be stimulated by glucocorticoids (see Rooney 1985). The rate-limiting enzyme that consistently responds to glucocorticoids is cholinephosphate cytidyltransferase, the activity of which correlates well with the rate of synthesis of phosphatidylcholine in fetal lungs. The effect of glucocorticoid may be direct in part but may also be mediated by fibroblast-pneumocyte factor secreted by fibroblasts adjacent to Type II cells (Smith and Post 1989) and by increased fatty acid synthesis resulting from enhanced fatty acid synthase activity (Gonzales et al. 1990; Batenburg and Elfring 1992).

The mRNAs for the surfactant proteins SP-B and SP-C, which accelerate surfactant film formation, increase during exposure of human lung in vitro to glucocorticoids (Liley et al. 1989) (Fig. 6). The mRNA for SP-A which is probably concerned with the movement of surfactant into and out of the alveolus has a biphasic response to glucocorticoid, being inhibited at high concentrations and stimulated at low concentrations (Liley et al. 1988).

**Structural Maturation**

Experimental evidence points increasingly to structural changes being at least as important as surfactant in determining the compliance of the lung in the term newborn or the preterm corticosteroid-treated newborn (Schellenberg 1986). The lungs of fetal sheep, monkeys and rabbits that have become highly compliant after treatment with cortisol may contain little alveolar surfactant and are unstable (Beck et al. 1981; Liggins et al. 1984; Ikegami et al. 1987). The increase in collagen and elastin content of fetal lung that normally precedes birth is reproduced in immature fetuses by treatment with cortisol (Schellenberg et al. 1987) but it is likely that thinning of septae and other architectural changes are equally important.

**Alveolar β-adrenoceptors**

Two developmental responses necessary to prepare the fetal lung for its function as an organ of gas exchange, the

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**Fig. 5.** Diagram illustrating multiple points of action of cortisol on the biosynthetic pathway of pulmonary surfactant.

**Fig. 6.** Effect of various steroids on mRNAs of the surfactant proteins, SP-B and SP-C in explants of human lung. Cont, control; E2, 17β-oestradiol; DHT, dihydrotestosterone; HP, 17α-hydroxyprogesterone; F, cortisol; E, cortisone; B, corticosterone; Dex, dexamethasone. * P < 0.05 vs. control. (Liley et al. 1989.)
release of surfactant and reabsorption of alveolar water, can be stimulated by β-adrenergic agonists (Lawson et al. 1978; Olver et al. 1981). The sensitivity of the responses increases greatly in late pregnancy and can be induced prematurely by treatment with cortisol which specifically increases the concentration of alveolar β-adrenergic receptors (Barnes et al. 1984).

**Glycogenolysis**

Unlike the liver, in which glucocorticoids promote glycogen deposition, the response in the fetal lung is glycogenolysis (Bourbon and Jost 1982) (Fig. 7). Glycogen accumulation in the lung appears to be independent of hormones and is unaffected by fetal hypophysectomy. The function of glycogenolysis probably provides substrate for phospholipid synthesis (Brehier and Rooney 1981).

**Antioxidants**

Free-radical scavengers are not important in the protected fetal environment but assume an important function with the onset of air-breathing. Infusion of cortisol into immature fetal sheep stimulates the activity of superoxide dismutase, catalase and glutathione peroxidase (Walther et al. 1991).

**Cortisol–cortisone Interconversion**

In fetuses of many species, cortisol is extensively converted to cortisone by 11β-hydroxysteroid dehydrogenase resulting in higher concentrations of cortisone than cortisol in fetal plasma (Murphy 1981). In the lung, however, the reaction is mainly reductive (Nicholas and Lugg 1982). Although production of cortisol from cortisone in the lung is small compared with adrenal secretion, local production could contribute to lung maturation. Glucocorticoids increase the activity of the enzyme suggesting a mechanism by which the effects of rising plasma cortisol levels may be amplified in lung tissue (Smith et al. 1982).

**Small Gut**

Although the fetus consumes large volumes of amniotic fluid, digestion is not required and waste materials accumulate in the large bowel as meconium. It seems likely that cortisol-dependent maturation of the small gut occurs before birth but most studies have been made in suckling rats, rabbits or mice in which corticosteroid treatment results in morphological maturation and induction of sucrase, alkaline phosphatase and Na⁺/K⁺ATPase (Moog 1953; Guiraldes et al. 1981). Prenatal treatment in rats elicits a precocious appearance of jejunal sucrase (Celano et al. 1977) and alkaline phosphatase (Ross and Goldsmith 1955). Alkaline phosphatase is induced also in fetal rabbits (Lee et al. 1976). An extensive morphological study in fetal sheep infused with physiological amounts of cortisol at 0.7 of gestation found advanced villus enterocyte kinetics (Trahair et al. 1987) suggesting that investigation of potential cortisol-inducible enzymes in tissues from this species may be rewarding.

**Liver**

Reports of the effects of glucocorticoids on liver enzymes are extensive but most relate to studies *in vitro* in suckling rats. Many of the numerous enzymes inducible after birth are unresponsive before birth. Likewise, most studies in fetuses are performed *in vitro* in rats (Table 1) and there is a paucity of research *in vivo* in species with a longer gestation. The extent to which postnatal responses in rats can be extrapolated to prenatal responses in species such as primates, sheep and guinea-pigs is uncertain.

The fetus receives an inexhaustible supply of glucose by transplacental passage from the mother. At birth, the fetus is suddenly deprived of this source of glucose and an alternative source must become rapidly available; in this regard, the liver substitutes for the placenta in providing for the immediate needs for glucose from glycogen stores and the longer-term needs from gluconeogenesis and increased metabolism of fatty acids and amino acids.
Rising prepartum concentrations of cortisol play a part in promoting all these activities. The following discussion is drawn as far as possible from studies in species with a longer gestation.

**Glycogen Storage**

In all species investigated to date, including rats (Klepac 1985), mice (Tye and Burton 1980), monkeys and sheep (Barnes et al. 1978), glucocorticoid administration causes a marked increase in the accumulation of liver glycogen (Jones and Rolph 1981). The prenatal rise in liver glycogen in fetal sheep (Dawes and Shelley 1968) has a close temporal relationship with the prenatal rise in cortisol and it is prevented by fetal hypophysectomy or adrenalectomy (Barnes et al. 1978). Glycogen deposition in response to cortisol is largely the result of activation of glycogen synthetase (Schwartz and Rall 1973).

**Gluconeogenesis**

Villee (1953) first demonstrated gluconeogenesis in slices of human fetal liver. Increased incorporation of alanine into glucose and glycogen following exposure of human fetal liver to glucocorticoid was demonstrated subsequently by Schwartz and Rall (1975). However, experiments in vivo, particularly in rats, showed that increased gluconeogenesis, whether spontaneous or glucocorticoid-induced, apparently occurs only after birth and is activated by factors associated with the transition to extrauterine life. This was supported by a study of substrate fluxes across the liver during infusion of labelled lactate in chronically cannulated sheep fetuses at 124 days gestation; the cortisol-treated group showed no increase in glucose flux (Rudolph et al. 1989). However, when the experiments were repeated at 137–140 days gestation there was substantial gluconeogenesis (Townsend et al. 1991). Experiments are needed in other species to investigate the possibility that gluconeogenesis is responsive to glucocorticoids very close to term.

**Catecholamines**

Although the fetal adrenal medulla releases catecholamines in response to various stresses such as hypoxaemia and hypotension, its function becomes important only with birth. The catecholamines then play a major role in the adaptations to extrauterine life in several organs including lung (surfactant secretion, lung water resorption), vascular system (increase in cardiac output, peripheral resistance and blood pressure), brain (central control of breathing) and liver (mobilization of energy substrates) as well as the adaptation of brown fat for thermogenesis. These adrenergic responses occur partly as a result of a surge in the release of catecholamines during labour and delivery (Padbury et al. 1982) and the cutting of the umbilical cord (Padbury et al. 1981) and partly as the result of increased concentrations of β-adrenergic receptors; glucocorticoids contribute to both of these mechanisms.

**Phenylethanolamine N-methyltransferase (PNMT)**

The methylation of noradrenaline to form adrenaline is catalysed by PNMT which is stimulated by glucocorticoids (Wurtman and Axelrod 1966). Fetal adrenal medullary cells from sheep secrete increased amounts of adrenaline, but not noradrenaline or dopamine, when exposed to concentrations of cortisol similar to that in the plasma of the term fetus (Graham et al. 1986). It is possible that the medullary cells, through which the venous effluent is draining in the intact fetus, are exposed to high concentrations of cortisol and that the activation of PNMT and the secretion of adrenaline are paracrine events. An additional unidentified paracrine factor secreted by cortical cells which is synergistic with cortisol has been reported (Cheung 1984). Although the plasma concentration of catecholamines does not rise before parturition, the rising levels of cortisol prepare the adrenal medulla for the marked increase in activity observed during labour and after delivery (Eliot et al. 1981). As expected with enhanced PNMT activity, the predominant catecholamine released is adrenaline.

In the rat, the fetal lung contains PNMT the activity of which increases on exposure to glucocorticoid (Kennedy et al. 1990); this raises the possibility that adrenaline may have a paracrine function in promoting surfactant secretion and fluid reabsorption.
The activity of PNMT in the brain stem of the fetal rat is not enhanced by glucocorticoids (Bohn et al. 1986), but in the neonatal rat this treatment is followed by a sustained increase in activity (Turner et al. 1979).

**β-Adrenergic Receptors**

Mechanisms leading to increased secretion of surfactant and decreased secretion of lung fluid become more sensitive to adrenaline towards the end of gestation in fetal rabbits (Lawson et al. 1978). This heightened sensitivity appears to be the result of an increase in the concentration of pulmonary β-adrenergic receptors associated with rising levels of cortisol. Receptor concentrations are increased precociously by treatment with glucocorticoid (Cheng et al. 1980) and autoradiography demonstrates that the response is specific to the alveoli (Barnes et al. 1984).

**Adrenal**

The possibility that cortisol enhances the fetal adrenal response to adrenocorticotrophic hormone (ACTH) and thus contributes to the prepartum increase in cortisol secretion has been investigated in fetal sheep. The response in vivo to ACTH is enhanced by prior exposure to dexamethasone (Liggins et al. 1977). Similarly, cortisol restores the responsiveness to ACTH of dispersed adrenal cells in which production of cortisol is blocked by treatment in vivo with metyrapone (Challis et al. 1985). The mechanism of action of cortisol remains unknown but may involve enhanced production of cAMP rather than activation of 17α-hydroxylase (Challis et al. 1986).

**Kidney**

Maturation of fetal kidney function is accelerated by treatment with corticosteroids. Prenatal treatment of rats with dexamethasone stimulates the activity of Na⁺ K⁺-ATPase in the cortical tubules (Dobrovik-Jenik and Milkovic 1988). Hill et al. (1988) and Stonestreet et al. (1983) observed that the treatment of fetal sheep with cortisol increased the glomerular filtration rate and tubular reabsorption of sodium (Fig. 8). newborn infants whose mothers were treated with corticosteroids before preterm delivery showed no increase in creatinine clearance but sodium fractional excretion was reduced as expected with enhanced activity of Na⁺ K⁺-ATPase (Zanardo et al. 1990).

**Haemopoietic and Lymphatic Systems**

Progenitor cells of the erythropoietic system migrate from the yolk sac to the liver in early embryonic life. The liver remains the site of erythropoiesis throughout fetal life until shortly before birth when erythroid cells enter the bone marrow and the erythropoietic activity in the liver rapidly subsides. This late switch appears to be controlled by cortisol. However, in hypophysectomized sheep and rats erythropoiesis persists in the liver at and beyond term and treatment with glucocorticoids is associated with normal regression of erythroid tissue (Liggins and Kennedy 1968; Jacquot and Nagel 1976). The switch from fetal to adult haemoglobin is also weakly dependent on cortisol. In adrenalectomized fetal sheep, the onset of β-globin synthesis is normal but the rate of synthesis is decreased unless cortisol is infused (Wintour et al. 1985). However, infusion of ACTH in intact fetuses does not accelerate the rate of synthesis of adult haemoglobin (Jansen et al. 1982).

Lymphoid tissue in the spleen and thymus regresses late in fetal life and is dependent on rising levels of cortisol. In fetal rabbits, this regression is prevented by hypophysectomy and restored by treatment with ACTH (Bearn 1961; Bearn 1967).

The regression of erythroid and lymphoid tissue near term is a physiological response to cortisol and is distinct from the well-known effects of pharmacological doses of glucocorticoids that cause retardation of fetal growth by promoting differentiation at the expense of proliferation. Biphasic responses to glucocorticoids, in which doses below those causing growth retardation promote cortisol-sensitive systems and higher doses cause inhibition, are probably a common phenomenon; this emphasizes the need for care in selecting appropriate doses for studies of cortisol-related events in the fetus (Bian et al. 1991).

**Brain**

There are numerous reports on the effects of glucocorticoids on brain development (reviewed by Meyer 1985). However, almost invariably the experimental animal has been the suckling rat and the doses used are massive compared with those that induce enzyme activity in the fetus. As a consequence, the relevance of the results of these studies to the fetal rat or to the fetuses of any other species is questionable.
Conclusion

There is extensive evidence that the major role of cortisol in the fetus is in the preparation for the transition from intrauterine to extrauterine life. In prosocial species cortisol-induced maturation occurs very rapidly close to term and is tightly linked to the mechanism initiating parturition; in contrast, in altricial species it occurs over a greater proportion of gestation, extending into postnatal life in some species, and the relationship to parturition is ill-defined. In general, cortisol promotes cellular differentiation at the expense of proliferation. As a consequence, glucocorticoids in pharmacological doses are well known for their effects in retarding fetal body weight and organ growth. In physiological amounts, however, glucocorticoids precociously activate a very wide range of enzymes that are necessary after birth although having little or no function in the fetus. It is likely that a number of cortisol-sensitive enzymes remain to be identified, particularly in view of the recent demonstration that cortisol may be dependent on synergism with other hormones including T₃, prolactin and adrenaline.

Not surprisingly, because it is the organ on which postnatal survival most depends, the fetal lung is highly cortisol-dependent. This phenomenon has been effectively exploited to accelerate lung maturation in the human fetus before preterm delivery.

References


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