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Roles of glucocorticoids in human parturition: A controversial fact?

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ABSTRACT

The pivotal role of glucocorticoids in the initiation of parturition has been very well documented in several domestic mammalian animal species. However the role of glucocorticoids in human parturition remains controversial mainly because of the absence of effect of synthetic glucocorticoids, given to promote fetal organ maturation in pregnant women with threatened preterm delivery, on the length of gestation. This article will review studies of glucocorticoids in human parturition and provide evidence for an important role of glucocorticoids in human parturition as well but a simultaneous high concentration of estrogen within the intrauterine tissues may be necessary for GCs to initiate parturition.

The synthetic GCs dexamethasone and betamethasone pass through the placenta intact resulting in potent negative feedback on the fetal HPA axis and diminished production of DHEA from fetal adrenal glands for estrogen synthesis by the placenta. This may negate the effect of systemic administration of GCs on the induction of labor, especially in cases where the myometrium is not yet fully primed by estrogen. Endogenous glucocorticoids are inactivated by the placental 11β-HSD2 thus limiting the negative feedback of maternal cortisol on the fetal HPA axis and allowing the simultaneous rise of cortisol and estrogen levels towards the end of gestation. Therefore, endogenous glucocorticoids, particularly glucocorticoids produced locally in the intrauterine tissues may play an important role in parturition in humans by enhancing prostaglandin production in the fetal membranes and stimulating estrogen and CRH production in the placenta.

1. Introduction

The past 50 years has seen a tremendous amount of research aimed at understanding the mechanisms underlying the process of parturition in humans. In addition to our search for knowledge related to the normal physiologic process investigations have been spurred on by our desire to understand and prevent preterm birth which remains the major issue in clinical obstetrics. Preterm birth occurs in approximately 8–10% of all pregnancies, but accounts for more than 75% of perinatal mortality and morbidity [1,2]. Although the survival rates for very early preterm births have increased because of advances in neonatal care, neurodevelopmental, other disabilities and recurrent health problems are common into early childhood, and can persist into adolescence especially for cardiovascular and metabolic disorders [2]. The specific and effective diagnosis and treatment of preterm labor has been hampered both by incomplete understanding of the normal process of parturition in addition to the pathophysiologic changes of preterm birth. In most mammalian species, there is an increase in glucocorticoid concentration in maternal and fetal circulations as well as in amniotic fluid towards the end of gestation and at the onset of labor [3,4]. This surge of glucocorticoids is believed to be crucial to maturation of fetal organs as well as to be integral to the cascade of events in the initiation and maintenance of labor in most animal species [5]. The pivotal role of glucocorticoids in the initiation of parturition has been very well documented in several domestic mammalian animal species [5]. However the role of glucocorticoids in human parturition remains controversial mainly because of the absence of effect of synthetic glucocorticoids, given to promote fetal organ maturation in pregnant women with threatened preterm delivery, on the length of gestation. We believe that this absence of effect of exogenous glucocorticoids on the length of

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human gestation may be largely due to the potent negative feedback of synthetic glucocorticoids such as dexamethasone and betamethasone on the fetal hypothalamic–pituitary–adrenal (HPA) axis. In addition the unique role of human fetal adrenal glands in the production of estrogen by the placenta, which is the prerequisite for the transition of a quiescent to an active state of myometrium in initiation of parturition, may influence the effect. This article will review studies of the role of glucocorticoids in parturition and it is our intention to provide evidence for an important role of glucocorticoids produced locally in the intrauterine tissues in parturition in humans.

2. Pivotal role of glucocorticoids in triggering parturition in domestic animal species

Several converging lines of evidence indicate that glucocorticoids (GCs) derived from the fetal adrenal glands trigger parturition in domestic mammalian species including sheep [6–8], goat [9], cow [10] and pig [11]. In these species, either the corpus luteum in the maternal ovaries or the placenta serves as the primary sources of progesterone and estrogen during pregnancy. Regardless of the sources of progesterone and estrogen, GCs derived from the fetal adrenals evoke two major events that lead to parturition in these species. These are a shift from a progesterone-dominated quiescent myometrium to an estrogen-primed uterine activation phase towards the end of gestation [12], and stimulation of prostaglandin synthesis in the intrauterine tissues [7,8]. The mechanisms underlying these two events evoked by GCs in parturition have been studied most extensively in the sheep where the placenta is capable of de novo synthesis of progesterone and estrogen [6–8]. GCs induce the expression of the placental enzyme cytochrome P450 17αhydoxylase (P450c17) that converts C21 steroids (pregnenolone and progesterone) to C19 steroid aromatase precursors [6], leading to a fall in progesterone and a simultaneous rise in estrogen. Estrogen then primes the myometrium changing it from a quiescent to a contractile state by promoting expression of contraction associated proteins (CAPs) including connexin 43 (Cx43), oxytocin receptor (OTR) and prostaglandin (PG) receptor [12]. Once the myometrium is primed, synthesis of sufficient uterotonins is key to the successful fulfillment of the feed-forward cascade process of parturition. Prostaglandins (PGE2 and PGF2α) are among the most prominent uterotonins. In addition to initiating myometrial contraction, PGE2 and PGF2α are also involved in cervical ripening , rupture of membranes prior to parturition [13] and induction of placental P450c17 [13]. The conversion of arachidonic acid into PGH2 by prostaglandin H synthase (PGHS) is currently thought to be the rate-limiting step in prostaglandin synthesis. There are two isoforms of PGHS. PGHS-1 is constitutively expressed in many tissues, whereas PGHS-2 is the inducible isoform. The increase in prostaglandin synthesis at term and parturition is associated with increased PGHS-2 expression [8]. Glucocorticoids increase PGE2 and PGF2α synthesis via the induction of PGHS-2 expression in sheep placenta [7,14]. Therefore these two important events induced by GCs prepare the myometrium for contraction as well as supply it with uterotonins at parturition. Once parturition is initiated, distension of the cervix and uterus by the fetus during labor triggers the feed-forward oxytocin release from the posterior pituitary, which further stimulates contraction of the myometrium resulting in the birth of the fetus (Fig. 1). Consistent with the concept that glucocorticoids derived from the fetal adrenals play a central role in the onset of labor in domestic animals, early studies in the fetal sheep showed that ablation of the fetal pituitary gland, the fetal adrenal glands, pituitary stalk section, or lesioning of the fetal paraventricular nucleus (PVN) resulted in prolongation of gestation [15], whereas in utero infusion of the fetal lamb with adrenocorticotropic hormone (ACTH) or of a glucocorticoid resulted in premature parturition within 3–5 days of beginning the infusion [16].

3. The common and unique components of the onset of labor in primates

A number of components of the parturition pathway are common between domestic animals and primates including the myometrial transition from a quiescent to a contractile state under the influence of increasing estrogen production prior to parturition. In all species estrogen has a key role in priming myometrium for labor by inducing expression of contraction associated proteins including OTR, Cx43 and PG receptors in myometrium [12]. However, the pathway to estrogen production in the human placenta is unique as P450c17 is not induced in the placenta at term and therefore the conversion of progesterone to estrogen does not occur. Instead, the human placenta relies on dehydroepiandrosterone sulfate (DHEAS) from the fetal and maternal adrenal glands for the supply of precursor for estrogen synthesis, and bypasses the step catalyzed by P450c17 [17] (Fig. 2). Hence there is no reciprocal fall in plasma progesterone and rise in plasma estrogen in humans and other primates. Rather both estrogen and progesterone increase

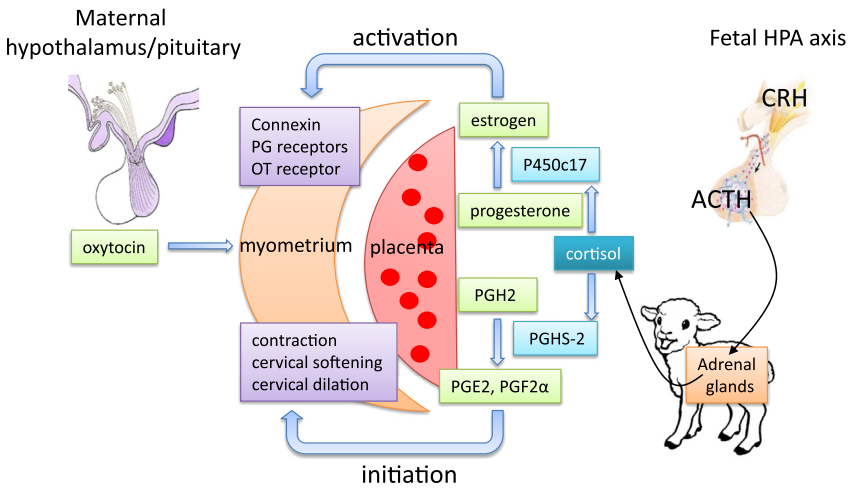

Fig. 1. The triggering role of glucocorticoids derived from fetal adrenal glands in parturition in the sheep. PG: prostaglandins, OT: oxytocin.