Maternal serum Dehydroepiandrosterone Sulfate level and success of labor induction in prolonged pregnancies

Thesis

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By

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Introduction

Dehydroepiandrosterone (DHEA) sulfate is a weak androgenic steroid produced by the adrenal cortexes of both the pregnant woman and her fetus. It acts as intermediary hormone in the fetoplacental production of androstenedione, testosterone, esterone and estradiol ***(Goolsby et al., 1996)***.

Dehydroepiandrosterone sulfate (DHEAS) is a measurable biochemical marker of cervical maturation. It stimulates collagenase and gelatinase production and increases the synthesis of PGE_2 by human cervical tissues which leads to an increased proportion of decorin (a proteoglycan is a component of connective tissue, binds to type I collagen fibrils, and plays a role in matrix assembly) to collagen and cervix maturation. It exerts its effect on the cervix through specific binding sites (receptors) in the cellular plasma membrane of the cervical fibroblasts ***(Maradny et al., 1996).***

Binding sites for DHEA sulfate have been identified on the plasma membranes of human cervical fibroblast, suggesting the hormone may play a role in cervical connective tissue function ***(Imai et al.,1992).***

Prolonged, post-term and post-dates' are different expressions used to signify a pregnancy that has extended beyond a certain duration accepted as the upper limit of normal. This definition varies from ٤١ to ٤٣ weeks of gestation. Many studies investigating management options include ٤١ completed weeks of gestation ***(Siozos and Stanley, ٢٠٠٧).***

Approximately ٥ to ١٠ percent of pregnancies are post-term. Studies have shown a reduction in the number of pregnancies considered post-term when early ultrasound dating is performed. Maternal and fetal risks increase with increase gestational age, but the management of otherwise

low-risk prolonged pregnancies is controversial. Antenatal surveillance with fetal kick counts, non stress testing, amniotic fluid index measurement, and biophysical profiles are used, although no data show that monitoring improves the outcome. Studies show a reduction in the rate of cesarean deliveries and possibly in neonatal mortality with a policy of routine labor induction at ٤١ weeks gestation ***(Briscoe et al., 2005).***

There's a need for an objective laboratory or clinical tool to assess the status of the cervix and predict the success of labor induction ***(Dogany et al., 2004).***

It was found that the ripe or mature cervix, as reflected by the Bishop score, is associated with high levels of dehydroepiandrosterone sulfate (DHEAS) in maternal plasma ***(Zuidema et al., 1986).***

Aim of The Work

The aim is to evaluate the relationship between pre-induction maternal plasma levels of DHEAS and the success of labor induction in prolonged pregnancy .

Dehydroepiandrosterone sulfate (DHEAS)

Introduction:

Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) are androgen precursors mainly secreted from the adrenal cortex in humans ***(Nieschlag et al., ١٩٧٣).***

The amount of DHEAS produced and the serum concentrations of DHEAS are higher than those of any other steroids in the body. DHEAS was suggested to be a reservoir and a precursor of DHEA, a precursor of sex steroids, which is released by the action of endogenous DHEAS sulfatase, found widely distributed in peripheral tissues ***(Miki et al., 2006).***

However, during pregnancy, DHEAS is a major source for estrogen formation in feto-placental unit. About one half of total estradiol produced in the placenta originates from maternal DHEAS. During pregnancy, maternal adrenal production rates of DHEA and DHEAS are increased twofold, but the maternal concentration of DHEAS is reduced to between one-third and one-half of the non-pregnancy levels ***(Braunstein, 2005) .***

The decrease of DHEAS was suggested to be associated with increasing estrogen levels due to enhanced estrogen biosynthesis in the placenta. There have been many studies on the changes of serum concentration of DHEAS during pregnancy. By ١٩٨٠, it was confirmed that maternal serum levels of DHEAS decrease with increasing gestational age and they are lower than those of non-pregnant women ***(Nieschlag et al., 1974) , (Schindler et al., 1975).***

On the other hand, although DHEA has been demonstrated to possess more biological activity than DHEAS, however, only a limited number of studies of DHEA in pregnancy have been reported. Moreover, the reported results were controversial ***(N. Tagawa et al., 2004) .***

The maternal immune system is altered both during and after pregnancy. It has been confirmed that postpartum onset of rheumatoid arthritis and autoimmune thyroid syndrome are caused by changes in the maternal immune system ***(Iijima et al., 2003) .***

While DHEA was reported to effect a variety biological activities in humans and experimental animals, its immuno-regulatory effect was also demonstrated. For example, DHEA administration to experimental animals or immunocompetent cell cultures affected cytokine production in vivo ***(Khalil et al., ٢٠٠٦)*** and in vitro ***(Du et al., ٢٠٠٦).***

Decreased DHEAS levels and a corresponding imbalance of cytokine production have been demonstrated in patients with systemic lupus erythematosus ***(Verthelyi and Klinman, 2005).***

Moreover, it was reported that DHEA administration reduced the severity of systemic lupus erythematosus ***(van Vollenhoven et al., 2000)*** and that the marked imbalance between DHEA and DHEAS in patients with autoimmune thyroid dysfunction potentially affects the pathogenesis of the disease ***(Tagawa et al., 2004).***

Taking these findings together, it would appear that DHEA and DHEAS during and after pregnancy may affect the maternal immune system. However, the effects of the changes of DHEAS and particularly of DHEA on maternal immunological regulation during and after pregnancy have not been fully elucidated to date.

Synthesis:

Dehydroepiandrosterone (DHEA) and its active metabolite, DHEA sulfate (DHEAS), are endogenous hormones synthesized and excreted primarily by the zona reticularis of the adrenal cortex, of the pregnant woman and her fetus, in response to adrenocorticotropic hormone. The exact mechanism of action and clinical role, if any, of DHEA and DHEAS remain unclear ***(Nippold and Nair, 1998)***.

It acts as an intermediary hormone in the fetoplacental production of androstenedione, testosterone, estrone and estradiol ***(Speroff et al., 1989)***.

In women, the synthesis of DHEA and DHEAS occurs almost exclusively in the adrenal cortex, whereas in men the testes secrete approximately ٥٪ of DHEAS and ١٠-٢٥٪ of DHEA ***(Kroboth et al., 1999)***. During gestation, large amounts of DHEA and DHEAS are secreted by the fetal adrenal glands. At birth, output drops to negligible amounts in both sexes and remains that way until five to seven years of age. At the onset of adrenarche, the adrenal glands gradually resume DHEA and DHEAS production, which accelerates through puberty. DHEA and DHEAS output is maximal between the ages of ٢٠ and ٣٠ years and then starts a decline of approximately ٢٪ per year leaving a residual of ١٠-٢٠٪ of the peak production by the eighth of ninth decade of life ***(Labrie et al., 1997)***.

DHEA and DHEAS serve as the precursors of approximately ٥٠٪ of androgens in men, ٧٥٪ of active estrogens in premenopausal women, and ١٠٠٪ of active estrogens after menopause ***(Labrie et al., 1997)***.

Maternal and neonatal DHEA sulfate levels were not linearly correlated, DHEA sulfate reaching the placental compartment from either the maternal or fetal steroid pool, is rapidly and irreversibly converted to estrogens. This large

placental capacity for C١٩ aromatization may be explain the lack of correlation between DHEA sulfate levels of the two pools ***(Peter et al., 1994)***.

The actions of DHEA sulfate have been attributed to estrogens derived from DHEAS ***(Gant et al., 1971)***.

The conversion of DHEAS to estradiol requires placental expression of four key enzymes. First, placenta expresses high levels of steroid sulfatase (STS), which converts the conjugated DHEAS to DHEA. DHEA is then acted upon by ٣β-hydroxysteroid dehydrogenase type ١ (٣βHSD) to produce androstenedione. Cytochrome P٤٥٠ aromatase (CYP ١٩) then converts androstenedione to esterone, which is converted to estradiol by the enzyme ١٧β-hydroxysteroid dehydrogenase type ١(١٧βHSD). The principal cellular location of STS, ٣βHSD, CYP ١٩, ١٧βHSD is in the syncytiotrophoplast ***(Bonenfant et al., 2000)***.

Concentration of DHEA and DHEA sulfate:

The major circulating androgens in women are testosterone, dehydroepiandrosterone (DHEA), and DHEA sulfate. The relative androgenic activity, serum concentration, and sources of these androgens are summarized in table (١). Testosterone is the principal circulating androgen in normal women. Both the ovaries and the adrenals normally secrete testosterone, approximately ٥٠٪ of the testosterone in serum however is derived from the peripheral conversion of steroid precursors principally androstenedione and to a lesser extent DHEA. ***(Speroff et al.,1989)*** .

Table (١): Circulating androgens and their relative androgenic activity. Serum concentration and site of formation in women

HORMONE	RELATIVE ANDROGENIC ACTIVITY	Serum Concentration		Sources of circulating Hormones		
		Ng/ml	N mol/L	Ovary	Adrenal	Peripheral Conversion
Testosterone	١٠٠	٠,٢-٠,٧	٠,٦٩-٢,٤٣	٥-٢٥	٥-٢٥	٥٠,٧٠
Dihydrotestosterone	٢٥٠	٠,٠٥-٠,٣	٠,١٧-١,٠٣	-	-	١٠٠
Anderost-enedione	١٠-٥٠	٠,٥-٢,٥	١,٧٢-٨,٦	٣٠-٤٥	٤٥-٦٠	١٠
DHEA	٥	١,٣-٩,٨	٤,٥-٣٤	٨٠	٢٠	-
DHEAS	Minimal	٤٠٠-٣٢٠٠	٧٩٠-٦٣١٨	>95	<5	-

(Speroff et al., 1989)

Metabolic clearance rate of DHEA sulfate:

Milewich et al., (1978) found that there is a ١٠ to ٢٠-fold increase in the metabolic clearance rate (MCR) of plasma DHEAS in normally pregnant women at term compared with that in men and non pregnant women. As a consequence, there is a progressive decrease in its plasma concentration. the increase in the MCR of plasma DHEAS in pregnant women appears to be due primarily to its removal through conversion to estradiol ١٧ beta in the syncytium. Also due to accelerated ١٦ alpha hydroxylation (probably in maternal liver) with ٣٠-٤٠ percent converted near term to ١٦ alpha hydroxy DHEAS ***(Kroboth et al., 1999)***.

The maternal adrenal glands do not produce sufficient amounts of DHEAS during pregnancy to account for more than a small fraction of placental estrogen biosynthesis. Fetal adrenal glands are quantitatively important source of placental estrogen precursors in human pregnancy ***(Cunningham et al., 2005)***.

The MCR of DHEAS and to a greater extent the placental

clearance of the maternal plasma DHEAS through E٢ formation, are influenced by role of uteroplacental perfusion. There are three factors alter the rate of DHEAS conversion to E٢ within the placenta.

These factors are:

١. Rate of delivery of DHEAS to the placenta i.e. uteroplacental blood flow.
٢. Uptake of DHEAS by the trophoblasts
٣. Activities of the enzymes catalyzing the conversion of DHEAS to E٢.

Placental uptake of DHEAS depends on simple diffusion and since deficiencies within the trophoblast of enzymes catalyzing the conversion of DHEAS to E٢ are rare ***(Tabre et al., 1976)***.

Effect of DHEAS in labor:

Among term women, maternal serum levels of DHEAS are significantly lower in those clinically requiring pharmacologic augmentation than in those progressing spontaneously through labor. DHEAS may be an important factor in efficient labor ***(Peter et al., 1994)***.

The largest part of pregnancy is characterized by a quiescent state of the uterus. The most important substrates responsible for uterine quiescence are progesterone and prostacyclin (PGI٢), both having an inhibitory effect on contractions ***(Mercer et al., 1997)***. next to this inhibition by progesterone and PGI٢, enzymes such as prostaglandin dehydrogenase (PGDH) which is produced by trophoblast cells, degrades prostaglandin E٢ (PGE٢) before labor ***(Van Meir et al., 1996)***.

Corticotrophin Releasing Hormone (CRH) is produced by the fetus and also in the placental syncytiotrophoblast

cells .

CRH production increases near term. Activation of the fetal Hypothalamic-Pituitary-Adrenal (HPA) axis as a result of maturation of the fetal organism induces CRH production and secretion of dehydroepiandrosterone sulphate (DHEAS) by increased activity of the fetal adrenals ***(Challis et al., 2003)***.

CRH induces PGE٢ synthesis and can augment the oxytocin-generated contraction by binding to CRH-receptors. Besides PGE٢, platelet activating factor (PAF) has potent contractile properties and is produced by the fetal lungs. Synthesis increases near term concomitant with fetal lung maturation. It reaches the myometrium through the membranes. Prior to term PAF is inactivated by PAF – acety١ hydrolase (PAF-AH) which is produced by decidual macrophages. Estrogens whose levels rise near term decrease the production of PAF-AH ***(Toyoshima et al., 1995)***.

Binding sites of DHEAS have been identified on the plasma membranes of human cervical fibroblasts suggesting the hormone may play a role in cervical connective tissue function ***(Imai et al., 1992)***.

In ***1991, Granström*** reported that insufficient remodeling of uterine connective tissue may contribute to protracted labor. Women with ineffective labor who required oxytocin administration and subsequent cesarean delivery due to arrest of labor had significantly higher uterine collagen concentrations and lower local collagenolytic activity than control women with normal labor progression. The underlying mechanisms responsible for such remodeling have not been elucidated fully.

Mochizuki and Tojo (1980) showed that collagenase activity in the uterine cervix increased significantly after repeated intravenous injections of DHEAS into pregnant

women at term.

The proposed mechanism of DHEAS action was an estrogen induced activation of collagenolytic activity mediated through placental conversion of DHEAS to ١٧ β-estradiol ***(Mochizuki and Tojo, 1980)***.

In contradiction to this theory of estrogen-mediated activation of collagenase activity, the addition of estradiol to rabbit uterine cervical cultures has been found to inhibit fibroblast collagenase activity, however addition of DHEAS to similar cultures resulted in an approximately ٦٠٪ increase in fibroblast collagenase action ***(Ito et al., 1984)***.

With the identification of DHEAS binding sites on the plasma membranes of human cervical fibroblasts ***(Imai et al., ١٩٩٢)*** there is now sufficient evidence to hypothesize a similar mechanism of direct DHEAS action on uterine collagenase activation ***(Goolsby et al., 1996)***.

The mechanisms of action of DHEAS have been attributed to its direct or indirect effect on the cervix**. *Imai et al., (1992)*** reported that DHEAS may induce its effect through specific membranes receptors in the cervical fibroblasts. This may stimulate the fibroblasts to produce collagenolytic enzymes. The indirect effect of DHEAS may involve the mobilization of the arachidonic acid from membrane phospholipids as DHEAS was found to stimulate the synthesis of the PGE٢ by cervical tissue ***(Takasaki et al., 1987)***.

It is well known that repeated administration of DHEAS to pregnant women accelerates cervical ripening, shown an increase in wet weight of the cervix and in enzymes such as collagenase and alkaline proteinase in cervical tissue ***(Zuidema et al., 1986)***.

The cervical collagenolytic effect of DHEAS may be mediated through PGE٢ because its synthesis is enhanced by

DHEAS in human cervical tissue ***(Liapis et al., 1993)***.

The animal studies have suggested that DHEAS acts synergistically with interleukin-٨ to increase collagenase, elastase, and gelatinase activity while decreasing the cervical collagen content. Interleukin-٨ (IL-٨) is a potent neutrophil chemotactic factor which plays a role in cervical ripening, vaginal application of DHEAS into rabbits promotes (IL-٨)-induced cervical ripening ***(Maradny et al., 1996)***.

DHEAS-treated cervical tissues and cervical fibroblasts showed an increase in IL-٨ concentration and IL-٨ receptor population. Thus, DHEAS may promote the expression of IL-٨ receptors in the cervix and increase the affinity of the tissues to bind IL-٨. The upregulation of the autocrine system of IL-٨ could markrdly affect the production and release of IL-٨ ***(Kanayama et al., 1998)***.

Evidence has also been presented that DHEAS enhances hyaluronic acid (HA) production and also acts as a stimulator of HA synthesis in human cervical fibroblasts ***(Tanaka et al., ١٩٩٧)***.

DHEAS stimulates neutrophil responses to HA-induced IL-٨ and plays a role in promoting an increase in neutrophil accumulation, water content, collagenase, elastase and gelatinase activities, and a decrease in collagen concentration in the cervix of rabbits. it was suggested that the DHEAS + HA-induced changes in cervical connective tissue may account for, at least in part, cervical maturation ***(Imai et al., 1992)***.

The level of pre-induction maternal serum DHEAS appears to influence the ultimate outcome success or failure of an induction attempt. Although the mechanism of this action of DHEAS remains to be clarified, available evidence implicates collagenase activation and a resultant remodeling of uterine connective tissue ***(Watson et al., 1996)***.

Rusen et al., (2003) presented a case of unsuccessful labor induction in association with placental sulfatase deficiency and contrasts this experience with the finding of an association between elevated maternal serum DHEAS levels and spontaneous labor. Amniotic fluid DHEAS levels are known to be significantly elevated in pregnancies complicated by placental sulfatase deficiency; however, this may not be true of maternal serum levels ***(Goolsby et al., 1996)***.

In fact, in a case report by ***Madden et al., (1976)*** described five possible metabolic pathways for DHEAS clearance from maternal plasma, only one of which is controlled by placental sulfatase activity. Because it is unclear whether maternal serum DHEAS values are elevated with placental sulfatase deficiency. Risk's failed induction attempt does not contradict the finding of an association between elevated maternal serum DHEAS levels and spontaneous labor ***(Goolsby et al., 1996)***.

The maternal serum DHEAS level is certainly not the sole factor determining the success or failure of an attempted vaginal delivery ***(Mursay et al., 1987)***.

Prolonged Pregnancy

Introduction :

The most famous post-term delivery in the past was the delivery of Princess Charlotte Augusta of Wales in ١٨١٧. She was the only eligible heir to the British throne, and when her pregnancy was announced, the entire nation was closely following the most important event of that time. At approximately ٤٣ weeks her water broke and labour soon began spontaneously. Contractions were weak and the first stage of labour lasted more than ٥٠ hours. Gradually, the fluid became meconium stained. After ٢٤ hours in the second stage of labour and after five hours of active pushing, she spontaneously delivered a stillborn boy. The baby appeared to have been dead for several hours. During the third stage, placenta was retained, and she had a post-partum hemorrhage from uterine atony. Princess Charlotte died approximately six hours after delivery. Three months later her obstetrician, Dr. Croft, committed suicide, unable to bear the burden of the responsibility for the death of the British heir to the throne. As this event resulted in the death of an infant, the mother and her physician, it has historically been referred to as the "*The Triple Obstetric Tragedy*." ***(Lancet, 1951)***

In ١٩٠٢, Ballantyne questioned the ability of the placenta to support the fetus that "has stayed too long in intrauterine surroundings". Ballantyne further stated that the post mature infant "has remained so long in utero that his difficulty is to be born with safety to himself and his mother" ***(Ballantyne, 1902)***. By the ١٩٥٠s, the syndrome was well recognized in the literature from Western Europe, where the condition was a frequent reason for induction of labor. In ١٩٥٤, Clifford recognized that prolonged pregnancy could