SYMPOSIUM

Hormones in pregnancy

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ABSTRACT

The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus. Progesterone and oestrogen have a great role along with other hormones. The controversies of use of progestogen and others are discussed in this chapter. Progesterone has been shown to stimulate the secretion of Th2 and reduces the secretion of Th1 cytokines which maintains pregnancy. Supportive care in early pregnancy is associated with a significant beneficial effect on pregnancy outcome. Prophylactic hormonal supplementation can be recommended for all assisted reproduction techniques cycles. Preterm labor can be prevented by the use of progestogen. The route of administration plays an important role in the drug's safety and efficacy profile in different trimesters of pregnancy. Thyroid disorders have a great impact on pregnancy outcome and needs to be monitored and treated accordingly. Method of locating review: Pubmed, scopus

Key words: Oestrogen, hormones, progesterone, thyroid

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INTRODUCTION

Steroid hormones like progesterone have been extensively studied in the literature with controversies in early pregnancy usage with varied literature. The role in preventing abortions, recurrent pregnancy loss and preterm labor has been the aim of the review. Role of supplementation of oestrogen and progesterone in assisted reproduction has been analysed. Factors may be connected to the alterations in the metabolic pathway. Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function

Steroid hormone production and uses

Progesterone

Progesterone is largely produced by the corpus luteum until about 10 weeks of gestation.[1] A study in ovarian failure and Assisted reproduction it was shown that one hundred mg of P were probably a supraphysiological dose to support pregnancy 6 to 8 weeks after conception. The fetoplacental unit was competent from 10 to 12 weeks' gestation.[2] When the pregnancy reaches term gestation, progesterone levels range from 100-200 ng/ml and the placenta produces about 250 mg/day. Almost all of the progesterone produced by the placenta enters the placenta, contrast to oestrogen. Progesterone production is independent of he precursor available, fetal status including the wellbeing.

In early pregnancy, the maternal levels of 17 a-hydroxyprogesterone rise, marking the activity of the corpus luteum. By the tenth week of gestation, this compound has returned to baseline levels, indicating that the placenta has little 17a hydroxylase activity. However, beginning about the 32nd week there is a second, more gradual rise in 17a-hydroxyprogesterone due to placental utilization of fetal precursors. This is relevant to understand prevention of preterm labor. Progesterone is also important in suppressing the maternal immunologic response to fetal antigens, thereby preventing maternal rejection of the trophoblast. And, of course, progesterone prepares and maintains the endometrium to allow implantation earlier. Studies have shown that the human corpus luteum makes significant amounts of estradiol, but it is progesterone and not oestrogen that is required for successful implantation.[3]

Oestrogen

The placenta does not have all the necessary enzymes to make oestrogens from cholesterol, or even progesterone. Human trophoblast lack 17-hydroxylase and therefore cannot convert C21-steroids to C19-steroids, the immediate precursors of oestrogen. To bypass this deficit, dehydroisoandrosterone sulfate (DHA) from the fetal adrenal is converted to estradiol-17ß by trophoblasts. In its key location as a way station between mother and fetus, placenta can use precursors from either mother or fetus

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to circumvent its own deficiencies in enzyme activities. Hormones act as catalysts for chemical changes at the cellular level that are necessary for growth, development and energy. Fetus lacks 3 B hydroxysteroid dehydrogenase-hence unable to produce progesterone-borrows from placenta. In return, fetus give placenta what it lacks (19 Carbon compounds)-precursor of oestrogen.

Protein hormones

Protein hormones are: Human placental lactogen (hPL), Human chorionic gonadotropin (hCG), Adrenocorticotropic (ACTH), Growth hormone variant (hGH-V), Parathyroid hormone-related protein (PTH-rP), Calcitonin, Relaxin, Inhibins Activins, Atrial natriuretic peptide, Hypothalamic-like releasing and inhibiting hormones, Thyrotropin releasing hormone (TRH), Gonadotropin releasing hormone (GnRH), Corticotropin-releasing hormone (CRH), Somatostatin, Growth hormone-releasing hormone (GHRH), alpha fetoprotein, prolactin, relaxin and other decidual proteins. Due to the comprehensiveness of the choices to describe hormones, clinical importance of hCG relevant for therapy is discussed in this chapter.

Human chorionic gonadotropin

The most widely studied trophoblast hormone product is hCG. In pregnancy this glycoprotein is critical since it rescues the corpus luteum from involution, and this maintains progesterone secretion by the ovarian granulosa cells. Its usefulness as a diagnostic marker of pregnancy stems from the fact that it may be one of the earliest secreted products of the conceptus. In pregnancy, placental production of hCG is at its peak between the eighth to the tenth week of gestation, and tends to plateau at a lower level for the remainder of pregnancy.

The only definitely known function for hCG is support of the corpus luteum (CL), taking over for LH on about the eighth day after ovulation, 1 day after implantation, when b-hCG first can be detected in maternal blood. At 8 cell stage, hCG has been detected in the embryo using molecular biology techniques.

Implantation occurs 5-6 days after ovulation and hCG must appear by 10 days of ovulation (4 days after ovulation) to rescue corpus luteum. Hence, Blastocyst should implant in a narrow window of time. The hCG stimulation of CL has a daily secretion of 25 mg of P and 0.5 mg of E2. hCG gene expression is present in both cytotrophoblast and syncytiotrophoblast, but it is synthesized mainly in the syncytiotrophoblast. The maternal circulating hCG concentration is approximately 100 IU/L at the time of the expected but missed menses. A maximal level of about 100,000 IU/L in the maternal circulation is reached at 8-10 weeks of gestation. There are two clinical conditions in which blood hCG titers are especially helpful: Trophoblastic disease and ectopic pregnancies. Trophoblastic disease is distinguished by very high b-hCG levels (3-100 times higher than normal pregnancy). Ectopic production of a-and b-hCG by non-trophoblastic tumours is rare, but does occur.

The Human placental lactogen (hPL) is secreted primarily into the maternal circulation, most of its functions occur at sites of action in maternal tissues. Human placental lactogen is thought to be responsible for the marked rise in maternal plasma insulin-like growth factor-1 (IGF-1) concentrations as the pregnancy approaches term. Human placental lactogen exerts metabolic effects during pregnancy, via IGF-I. It is associated with insulin resistance, enhances insulin secretion which stimulates lipolysis, increases circulating free fatty acids, and inhibits gluconeogenesis; in effect, it antagonizes insulin action, induces glucose intolerance, as well as lipolysis and proteolysis in the maternal system. Hence the role of universal screening for abnormal blood sugar in the beginning of the third trimester is emphasized in clinical practice.

In the fetus calcium concentrations, are regulated by the movement of calcium, across the placenta, from the maternal compartment. In order to maintain fetal bone growth, the maternal compartment undergoes adjustments that provide a net transfer of sufficient calcium to the fetus. Maternal compartment changes that permit calcium accumulation include increases in maternal dietary intake, increases in maternal D3 levels, and increases in parathyroid hormone levels.

Progesterone supplement in pregnancy: An immunologic therapy

There are several studies to understand the maintenance of pregnancy by progesterone. Progesterone has been shown to increase the cytokines produced by Th2 cells which predominate over those produced by Th1 cells, resulting in the maintenance of pregnancy. Th2 cells are dominant within the decidua in early pregnancy in humans. The Th2-derived cytokines, IL-4 and IL-6, induce the release of hCG from trophoblasts and the hCG stimulates progesterone production from corpus luteum in pregnancy. Progesterone has been shown to stimulate the secretion of Th2 and reduces the secretion of Th1 cytokines. Thus, maintenance of pregnancy has been attributed to Th2 type cytokine. This role in controlling the immune and endocrine system which promotes the function of the trophoblasts at the implantation site seems interesting.[4] Use of progestogen in threatened abortion is controversial.[5]

Progesterone for recurrent miscarriage

Progestogen has been used for several years even before there was knowledge of the immunomodulatory properties of progesterone. Since that time, studies of differing quality have been carried out to prove the benefits of progestogen supplementation in affected women. A study on 146 women who presented with mild or moderate vaginal bleeding during the first trimester of pregnancy was randomized to receive oral dydrogesterone (10 mg b.i.d.) (*n*=86) or no

treatment (n=60). Dydrogesterone was continued until 1 week after the bleeding had stopped. The incidence of miscarriage was significantly lower in the dydrogesterone group than in the untreated group (17.5% *vs.* 25%; P<0.05).[6] The majority of cited clinical trials revealed a trend to improved pregnancies and increased live birth rates in the progestogen treatment group, but unfortunately, many studies had poor designs and methodical weaknesses.[7] Several studies have shown that supportive care in early pregnancy is associated with a significant beneficial effect on pregnancy outcome. Women with otherwise unexplained recurrent pregnancy loss should be counselled regarding the potential for successful pregnancy without any treatment except supportive therapy such as folic acid or vitamin supplementation.[7,8] The route of Progestogen administration are in various formulations, but it is generally recommend the exclusive use of progestogen without any (anti-) androgenic or (anti-) oestrogenic effect. Progestogen supplementation is available as vaginal suppositories (0.4 g/day, preferably in the evening because natural progesterone can cause tiredness), intramuscular injection (250 mg hydroxyprogesterone weekly) or oral intake (e.g. 10 mg dydrogesterone, the stereo-isomer of natural progesterone.[9]

Progesterone supplementation following assisted reproductive technology

The use of the progesterone supplementation in ART cycles has better clarity.[10] The duration of progesterone supplementation following reproductive technology (ART) has been studied in a retrospective cohort study. One group had progesterone supplementation through the first trimester of pregnancy (first trimester protocol) till 12 weeks and the second group had the progesterone discontinued after a positive beta hCG test 2 weeks after retrieval (luteal protocol). A similar rate of clinical pregnancies occurred at 7 weeks (81.8% luteal protocol *vs.* 85.8% first trimester protocol) and for live birth rates (76.8% luteal protocol *vs.* 75.0% first trimester protocol). There was a trend toward a higher rate of pregnancy loss after 7 weeks in the first trimester protocol group occurred (15.5% *vs.* 4.4%), indicating that first trimester progesterone supplementation may support early pregnancy through 7 weeks by delaying miscarriage but does not improve live birth rates. There are randomized trials supporting the routine use of luteal support in ART cycles using GnRH agonists or antagonists. Fifty-nine studies were included in a review to evaluate the luteal phase support with hCG compared to placebo or no treatment, in terms of increased ongoing pregnancy rates. Luteal phase support with hCG or progesterone after assisted reproduction results in an increased pregnancy rate. HCG does not provide better results than progesterone, and is associated with a greater risk of OHSS when used with GnRHa. The optimal route of progesterone administration has not yet been established.[11] A review showed a significant effect in favour of progesterone for luteal phase support, favouring synthetic progesterone over micronized progesterone.[12]

Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate

Preterm delivery should be anticipated and prevented to decrease perinatal morbidity and mortality. Those women who have had a spontaneous preterm delivery earlier are at greatly increased risk for preterm delivery in subsequent pregnancies. The results of several small trials have suggested that 17 alpha-hydroxyprogesterone caproate (17P) may reduce the risk of preterm delivery. A double-blind, placebo-controlled trial involving pregnant women with a documented history of spontaneous preterm delivery was done.[13] A total of 19 clinical centers were taken for the study and pregnant women at 16 to 20 weeks of gestation were included and were randomly assigned by a central data center, in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks of gestation. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation which was 36.3 percent in the progesterone group *vs.* 54.9 percent in the placebo group; relative risk, delivery at less than 35 weeks of gestation was 20.6 percent *vs.* 30.7 percent; and delivery at less than 32 weeks of gestation was 11.4 percent *vs.* 19.6 percent. The incidence of necrotizing enterocolitis, intraventricular hemorrhage in infants of women treated with 17P had significantly lower rates of and need for supplemental oxygen. Hence, the study concluded that weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants. One double blind randomized placebo controlled trials reported lower preterm birth rate with the use of either intramuscular 17 alpha-hydroxyprogesterone caproate (17P) or intravaginal micronized progesterone suppositories in women at risk for preterm delivery.[14] The half-life of 17P was estimated to be approximately 7.8 days. The route of administration plays an important role in the drug's safety and efficacy profile. Oral progesterone has not been used for prevention of preterm labor because of its first-pass hepatic metabolism, and there is a lack of data on efficacy, high side-effect profile, and because of extreme variability in plasma concentrations. Vaginal administration of progesterone avoids first-pass hepatic metabolism and is associated with rapid absorption, high bioavailability, and local endometrial effects.[15] Vaginal route offers no local pain and few side effects, it is associated with variable blood concentrations.[16] To study the efficacy of progesterone for maintenance tocolytic therapy after threatened preterm labor was done in a randomized controlled trial.[17] The study was on 70 women who presented with symptoms of threatened preterm labor,

who after arrest of uterine activity were then randomized to progesterone therapy or no treatment and the purpose of this study was to determine whether supplementation of vaginal progesterone after inhibition of preterm labor is associated with an increased latency period and a decreased recurrent of preterm labor. Treatment group received progesterone suppository (400 mg) daily until delivery and control group received no treatment. The study concluded that the use of vaginal progesterone suppository after successful parenteral tocolysis associated with a longer latency preceding delivery but failed to reduce the incidence of readmission for preterm labor. Dydrogesterone supplementation in women with threatened had preterm delivery the impact on cytokine profile, hormone profile, and progesterone-induced blocking factor.[18]

A study on eighty-three women with symptoms of threatened preterm birth were either randomized to study groups receiving tocolytic treatment combined with intravaginal micronized natural progesterone (200 mg daily) or to a control group receiving only tocolysis. Micronized natural progesterone treatment resulted in a prolonged latency period of 32.1±17.8 versus 21.2±16.3 days in the control group and heavier birth weights of 2,982.8±697.8 g versus 2,585.3±746.6 g.[19]

Estradiol supplementation during the luteal phase of *in vitro* fertilization cycles

A prospective randomized study was done to find the optimal dosage of estradiol (E2) for luteal phase support through the addition of different doses of E2 to progesterone (P) luteal phase support in patients undergoing long GnRH agonist *in vitro* fertilization (IVF) treatments.[20] Two hundred and eighty-five women undergoing IVF treatment with a long GnRH agonist protocol were prospectively randomized into three groups. Group 1 (*n*=95) received P and 2 mg E2, group 2 (*n*=95) received P and 4 mg E2 and group 3 (*n*=95) received P and 6 mg E2 as luteal phase support. The primary outcome was the clinical pregnancy rate (PR). The secondary variables of interest were the implantation rate (IR), miscarriage rate and multiple PR. The clinical PR was 31.6%, 40% and 32% respectively in groups 1, 2 and 3 and the differences between groups were not statistically significant. However, the miscarriage rate was significantly lower in group 2 (2.6%) than in group 1 (20%) but was not significantly lower than in group 3 (9.6%). The study concluded that the in luteal phase adding 2, 4 or 6 mg of oral E2 to P creates no statistical difference in terms of pregnancy rates. However, a significantly higher miscarriage rate was found when 2 mg E2 was used. Therefore, in the luteal phase support, 4 mg of oral estradiol in addition to progesterone can be considered to reduce the miscarriage rate. More research is still required on identification of at risk group, the optimal gestational age at initiation, mode of administration, dose of progesterone and long-term safety.

Thyroid disorders

This has a great impact on fertility. Sex hormone-binding globulin (SHBG) is altered with hyperthyroidism and hypothyroidism. It also changes prolactin, gonadotropin-releasing hormone, and sex steroid serum levels. It may also have a direct effect on oocytes, because it is known that specific binding sites for thyroxin are found on mouse and human oocytes. There is also an association between thyroid dysfunction in women and morbidity and outcome in pregnancy. In males, hyperthyroidism causes a reduction in sperm motility. The numbers of morphologically abnormal sperm are increased by hypothyroidism. It has been found that when euthyroidism is restored, both abnormalities improve or normalize. In women, the alterations in fertility caused by thyroid disorders are more complex. Hyper- and hypothyroidism are the main thyroid diseases that have an adverse effect on female reproduction and cause menstrual disturbances-mainly hypomenorrhea and polymenorrhea in hyperthyroidism, and oligomenorrhea in hypothyroidism. All factors may be connected to the alterations in the metabolic pathway. Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function.[21]

Controlled ovarian hyperstimulation leads to increases in estradiol, which in turn may have an adverse effect on thyroid hormones and TSH. Ovarian hyperstimulation may become severe when autoimmune thyroid disease is present, depending on preexisting thyroid abnormalities. Autoimmune thyroid disease is present in 5-20% of unselected pregnant women. Isolated hypothyroxinemia has been described in approximately 2% of pregnancies, without serum TSH elevation and in the absence of thyroid auto antibodies. There is an association of increased rates of spontaneous abortion, premature delivery and/or low birth weight, fetal distress in labor, and perhaps gestation-induced hypertension and placental abruption in overt hypothyroidism. All antithyroid drugs cross the placenta and may potentially affect fetal thyroid function.[22]

Thyroid disorders are common in women during pregnancy. If left untreated, both hypothyroidism and hyperthyroidism are associated with adverse effects on pregnancy and fetal outcomes. It is important to correctly identify these disorders and treat them appropriately to prevent pregnancy-related complications. Indicated treatment is Levothyroxine for hypothyroidism, and thioamides are the treatment of choice for hyperthyroidism; thyroidectomy may be indicated in select cases.[23,24] Cochrane review of three RCTs involving 314 women showed in one trial of 115 women, levothyroxine therapy to treat pregnant euthyroid women with thyroid peroxidase antibodies was not shown to reduce pre-eclampsia but did significantly reduce preterm birth by 72%. One trial of 30 hypothyroid women compared levothyroxine doses, but only reported biochemical outcomes. A trial of 169 women compared

the trace element selenomethionine (selenium) with placebo and no significant differences were seen for either pre-eclampsia or preterm birth. None of the three trials reported on childhood neurodevelopmental delay.[25]

CONCLUSION

Sex steroids are the best known examples of hormones and hence the review is concentrating on these. Progesterone is indispensable in creating a suitable endometrial environment for implantation, and also for the maintenance of pregnancy. Successful pregnancy depends on an appropriate maternal immune response to the fetus. Progestogen supplementation should be used preferentially within the context of a clinical trial or, in selected cases, in a kind of pragmatic approach, because progestogen treatment seems to be without remarkable adverse effects and as no 'better' treatment exists to date. Adequate levels of circulating thyroid hormones are of primary importance for normal reproductive function

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