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Klotz Communications: Evolution of hormones during pregnancy

## Evolution of steroids during pregnancy: Maternal, placental and fetal synthesis

*Évolution des stéroïdes pendant la grossesse : origine maternelle, origine placentaire, origine fœtale ?*

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### Abstract

Progesterone, estrogens, androgens and glucocorticoids are involved in pregnancy from implantation to parturition. Their biosynthesis and their metabolism result from complex pathways involving the fetus, the placenta and the mother. The absence of expression of some steroidogenic enzymes as CYP17 in placenta and in adrenal fetal zone and the better determination of the onset and variation of others especially HSD3B2 during the pregnancy explain the production of the steroid hormones. Moreover the consequences of some disorders of steroidogenesis (especially aromatase, POR, CYP11A1 and 21-hydroxylase deficiencies) in fetus and mother during the pregnancy have permitted to elucidate these complex pathways. This better knowledge of steroid hormones production associated with their dosages in maternal plasma/urine or amniotic fluid using new specific assays as LC-MS MS could facilitate the follow-up of normal and pathological pregnancies. Moreover, these advances should be a basis to evaluate the impact of multiple pathologies of the pregnancy and pharmacologic and xenobiotic consequences on their metabolism.

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**Keywords:** Aromatase/deficiency; Androgens/metabolism; CYP11A1/deficiency; Estriol/metabolism; Estrogens/metabolism; Fetus/\*enzymology/metabolism; Glucocorticoids/metabolism; Gonadal steroid; Hormones/biosynthesis/\*metabolism; Humans; Placenta/\*enzymology/metabolism; Pregnancy; Progesterone/metabolism

### Résumé

Progestérone, estrogènes, androgènes et glucocorticoïdes interviennent lors de la grossesse de la nidation à l'accouchement. Leur biosynthèse et leur métabolisme impliquent de voies complexes dues à l'interaction entre le fœtus, le placenta et la mère. L'absence d'expression de quelques enzymes de la stéroïdogenèse comme CYP17 dans le placenta et la zone fœtale des surrénales et la meilleure détermination du début et des variations d'expression d'autres en particulier HSD3B2 lors de la grossesse expliquent la production de ces stéroïdes. De plus, les conséquences de quelques anomalies de leur biosynthèse (en particulier les déficits en aromatase, POR, CYP11A1 et 21-hydroxylase) chez le fœtus et la mère lors de la grossesse a permis d'élucider ces voies métaboliques complexes. Cette meilleure connaissance de la production des hormones stéroïdes associée à leurs dosages dans le plasma et les urines de la mère ou le liquide amniotique, en utilisant des méthodes plus spécifiques comme la LC-MS/MS, peut faciliter la surveillance des grossesses normales et pathologiques. De plus, ces avancées devraient être une base pour évaluer le retentissement des nombreuses pathologies de la grossesse et les conséquences de médicaments et xénobiotiques sur leur métabolisme.

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**Mots clés :** Aromatase/déficit ; Androgènes/métabolisme ; CYP11A1/déficit ; Oestriol/ métabolisme ; Oestrogènes/ métabolisme ; Foetus/\*enzymologie/ métabolisme ; Glucocorticoïdes/ métabolisme ; Hormones stéroïdes gonadiques/biosynthèse/\*métabolisme ; Homme ; Placenta/\*enzymologie/ métabolisme ; Grossesse ; Progesterone/ métabolisme

The initiation, maintenance and termination of pregnancy are dependent largely on the interaction of hormonal and neural factors. The fetal-placental endocrine system develops and functions independently of that of the mother. Most maternal

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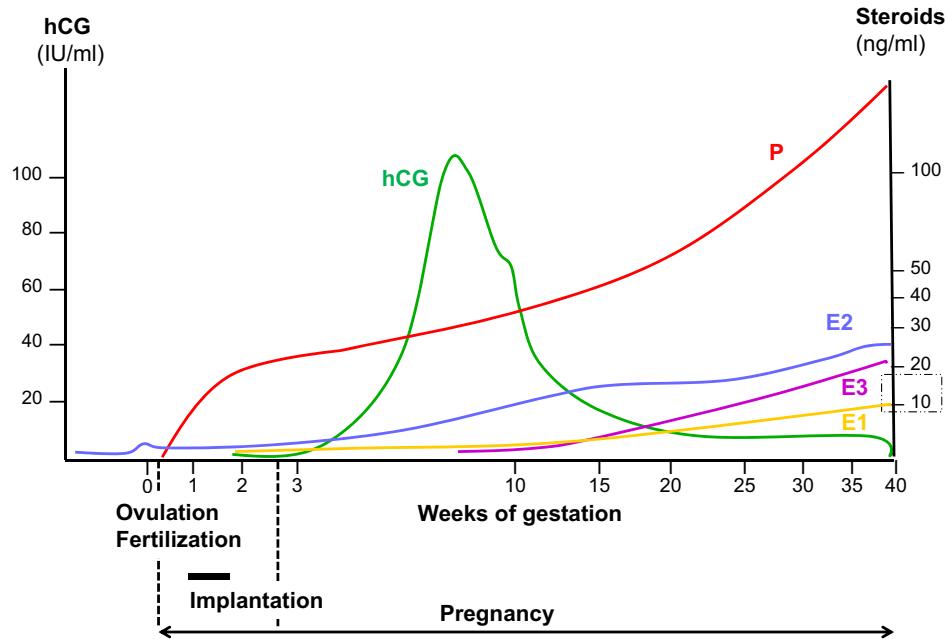


Fig. 1. Plasma steroids in the mother during the pregnancy.

hormones are prevented from entering the fetal compartment. The placenta functions as a hypothalamic-pituitary-end organ-like entity with stimulatory and inhibitory feedback mechanisms to dynamically regulate factors that affect fetal growth and development under a variety of conditions. The fetus and the placenta produce and secrete steroids and peptides into the maternal circulation as well as stimulate maternal hormone production [1,2]. Progesterone, estrogens, androgens and glucocorticoids are involved in pregnancy from implantation to parturition. They are synthesized and metabolized in complex pathways involving the fetus, the placenta and the mother. This review is focusing on the origin and the metabolism of steroids during the pregnancy except their modifications occurring during the preterm labor and delivery.

## 1. Progesterone

Progesterone is requiring for the maintenance of pregnancy by reducing myometrial contractility. Its maternal plasma concentration increase progressively during the pregnancy to reach a high concentration (in order of 130 ng/ml) in the third trimester (Fig. 1). Its production approximates 250 mg per day.

Following rupture of follicle, capillaries and fibroblasts from the theca proliferate and penetrate the basal lamina. The mural granulosa cells undergo morphologic changes referred as luteinization and secrete progesterone. After implantation, the hCG secreted by trophoblast appear in maternal circulation 9 days after LH peak of the conception cycle and rescue corpus luteum function that otherwise would regress. Hence, this progressive increase of maternal plasma progesterone and estrogens reflects the activity of the corpus luteum of pregnancy. It progressively involutes. The luteal-placental shift occurs between the 6th and 8th week of gestation. Human placental synthesis of progesterone requires two steps. The first step is

the conversion of cholesterol to pregnenolone by cytochrome P450ccc (CYP11A1) in mitochondria in a reaction requiring electrons delivered via adrenodoxin reductase and adrenodoxin. As the biosynthesis of cholesterol in placenta is very limited, the cholesterol comes essentially from LDL-cholesterol of the mother, but also from the fetus. Some authors suggest that pregnenolone sulfate originating in the adrenal fetal zone should bypass this step and is a key progesterone precursor [3]. Nevertheless, the progesterone levels and miscarriage do not differ in anencephalic fetuses [4,5] and during the pregnancy of mothers having an affected CAH fetus treated by dexamethasone [6]. The delivery of cholesterol to placental CYP11A1 is not dependent of StAR protein, but to MLN64, a placental constitutive protein containing a C-terminal START domain homologous to StAR protein and a number of other lipid transfer protein [7,8].

The second step is the conversion of Pregnenolone to progesterone by type 1 3 $\beta$ -hydroxysteroid dehydrogenase (HSD3B1). This HSD3B1 enzyme is bound to the membrane, but its intracellular localization remains unclear (see reviews [9,10]). Enzymatic activity has been located in microsomes but also in mitochondrial fractions [11,12]. Using immunogold labeling, 3 $\beta$ -HSD immunoreactivity is found in mitochondria and endoplasmic reticulum [13,14]. The 10-fold lower Km values of HSD3B1 for both pregnenolone and DHEA than that of HSD3B2 expressed in adrenals and gonads may facilitate the processing of low concentrations of pregnenolone in the placenta. Based on these data, it seems likely that HSD3B1 located in the inner mitochondrial membrane convert pregnenolone to progesterone and HSD3B1 located in the endoplasmic reticulum convert DHEA to androstenedione (Fig. 2).

The identification of the molecular defects of the first step of the steroidogenesis should confirm the essential role of progesterone to maintain pregnancy until term by suppressing uterine contractility. The majority of molecular defect is due to StAR

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