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Immune-endocrine crosstalk during pregnancy

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ABSTRACT

The success of pregnancy depends mostly on a synchronized immune-endocrine crosstalk at the maternal–fetal interface. Hormones are important in terms of maintaining the suitable environment and sufficient nutrition for the developing fetus. They also play a major role during the process of parturition and lactation. Maternal immunomodulation is important for the tolerance of semiallogeneic fetus. This is achieved in concert with a variety of endocrine stimulation. Estrogen, progesterone, and Human Chorionic Gonadotropin play a major role in immune modulation during pregnancy. Hormones modulate B cells, dendritic cells, uterine natural killer cells, macrophages, neutrophils to adopt fetal friendly immune phenotypes. Recently the use of hormones in assisted reproductive technology has been found to improve the pregnancy outcome. The present review focuses on the pregnancy-related hormones, their role in immunomodulation for successful pregnancy outcome. This also shed light on the immune-endocrine crosstalk at maternal–fetal interface during pregnancy.

1. Introduction

Pregnancy is the best example of the natural semiallogeneic model because half of the genes inherited from father and half from the mother. This semiallogeneic fetus is accepted and tolerated by maternal immune system throughout nine months gestation. The beauty of this phenomenon is that it defies common transplantation rules and accepts the fetus having 50% paternal contribution. Early pregnancy is marked by sequential events like implantation, decidualization followed by an invasion. Implantation and decidualization are tightly regulated by common endocrine changes. In women, menstrual cycle, early pregnancy, and parturition processes are marked by immune homeostasis and endocrine regulation (Nasar and Rahaman, 2006; Singh et al., 2011). Accommodation of semiallogeneic transplant as well as implantation, decidualization and parturition are supported by steroid hormones (Progesterone, estradiol, corticosteroids) and peptide hormones (human chronic gonadotropin, prolactin, relaxin, oxytocin) (Schumacher et al., 2014). Systemic and peripheral immunomodulation during pregnancy is for the acceptance of semiallogeneic fetus. Several mechanisms has been identified for establishment of pregnancy favorable milieu such as cell contact-independent (e.g. higher humoral immune response) and cell contact-dependent (e.g. active and balanced cell-mediated immune response), inhibition/attenuation of biosynthesis of essential amino acids/nitrogenous bases which are responsible for cell proliferation (e.g. inhibition of arginine synthesis) (Keogan et al., 2015). All these mechanisms are driven and regulated by endocrine system (Piccinni and Romagnani, 1996; Miyaura and Iwata, 2002; Matalka, 2003). In a nutshell; a balanced and tightly controlled immune-endocrine crosstalk is indispensable for a successful pregnancy.

The present review discusses in detail the role and importance of pregnancy-related hormones during pregnancy. We have also discussed the immune-endocrine cross talk and the effect of these hormones in innate and adaptive immunity during pregnancy.

2. Endocrine regulation of pregnancy

Pregnancy is marked by significant temporal changes of a variety of hormones during all three trimesters. Steroid hormone (progesterone; P4, estrogen) are normally involved in regulation of menstrual cycle and establishment and maintenance of pregnancy (Chambers and Clarke, 1979; Stewart et al., 1993). Progesterone (P4), estrogen (estrone; E1, estradiol; E2, estriol; E3) is produced during all the three trimesters of pregnancy at a different level. Early pregnancy primarily involves increased level of progesterone and estrogen that prepares the endometrium for implantation and also regulate the maternal immune cells against semiallogeneic fetus (Beagley and Gockel, 2003; Mendelson, 2009; Ramathal et al., 2010; Giannoni et al., 2011). In addition, there is a massive

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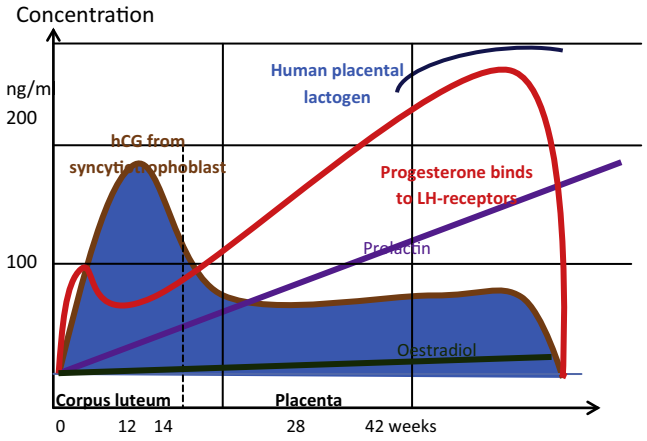

Fig. 1. Temporal changes of hormones throughout the different stages of pregnancy.

production of human chorionic somatomammotropin, human chorionic gonadotropin, as well as increased plasma levels of the oxytocin, rennin, and prostaglandin. Fig. 1 summarizes the temporal changes of different hormones throughout different stages of pregnancy.

Cytotrophoblast and syncytiotrophoblast are the morphological variants of the trophoblast cells of the chorionic villi. They have the distinctive capability to produce a wide variety of steroid, peptide, and protein hormones. The syncytiotrophoblast cells are in direct contact with the maternal blood and express chorionic gonadotropin (CG), chorionic somatomammotropin (CS), chorionic proopiomelanocortin and progesterone. However, these hormones do not readily gain access to the fetus due to the several barriers present between the maternal–fetal interface. We have discussed below the various hormones which are secreted during the period of pregnancy.

2.1. Peptide hormones

2.1.1. Chorionic gonadotropin

Human chorionic gonadotropin, hCG, a heterodimeric glycoprotein of 57 kDa synthesis takes place initially in the developing placenta after conception, and later by the placental component syncytiotrophoblast. Temporal fluctuations in the rate of production of hCG are marked by its maximal by the 10th week of pregnancy, and then it falls slowly to the lowest point at 17 weeks and remains at a low but readily measurable level for the remaining duration of the pregnancy (Cole, 2010). It function as a luteotropin by stimulating the production of progesterone by the corpus luteum (Niswender et al., 2000). A continual supply of ovarian progesterone is ensured by hCG up to 6–8 weeks of gestation and then placenta takes over the production of progesterone (Cole, 2010).

2.1.2. Chorionic somatomammotropin

Human chorionic somatomammotropin (hCS) also known as human placental lactogen (hPL) is an insulin antagonist and postulated to be involved in the regulation of maternal blood glucose levels (Alsat et al., 1998). It ensures optimal availability of blood glucose to meet the caloric requirements of the fetus. In addition, hCS has been suggested as being one of the contributory agents to the development of diabetic ketoacidosis in pregnant women who have no prior history of diabetes (Cohen et al., 1973; Chico et al., 2008). The function of the hCS function is more or less similar to pituitary growth hormone stimulating gluconeogenesis, lipolysis, and anabolism, thereby increasing nutrient availability for the fetoplacental unit (Alsat et al., 1998).

2.1.3. Relaxin

Relaxin (RLX) is a small 6-kDa peptide hormone produced within the corpus luteum during pregnancy but as the corpus luteum regress the level of relaxin goes down (Einspanier et al., 1997). In both pregnant and nonpregnant women, relaxin is secreted mainly by corpus luteum and reaches its peak around 14 days post ovulation (Einspanier et al., 1999). It mediates the hemodynamic changes that occur during pregnancy, such as increased cardiac output, increased renal blood flow, and increased arterial compliance (Conrad, 2011). Relaxin has a major role in pelvic girdle relaxation during parturition (MacLennan, 1991).

2.1.4. Oxytocin

Oxytocin is a nonapeptide secreted by the neurohypophysis. Milk letdown and milk ejection from the mammary tissue are the principal biological responses. There is also some preliminary evidence to support the action of oxytocin on the uterine endometrium at parturition to stimulate its contraction (Blanks and Thornton, 2003). High concentrations of oxytocin can be detected in the fetal blood which suggest that the fetus is a possible source of oxytocin for the mother during labor (Dawood et al., 1978).

2.2. Steroid hormones

2.2.1. Progesterone

Progesterone (17α-hydroxyprogesterone and 16α-Hydroxyprogesterone) is produced by the corpus luteum till 5–6 weeks of gestation and then after the 12th week of gestation, the placenta becomes the dominant site of its biosynthesis (Kumar and Magon, 2012). The placenta contains all the enzymes required for the conversion of maternally derived cholesterol into progesterone. During first 8–12 weeks of gestation the maternal corpus luteum is the principal site of 17α-hydroxyprogesterone (Tuckey, 2005). After the first trimester, the placenta uses the precursor 17-hydroxypregnenolone produced from 17-hydroxypregnenolone sulfates in the fetal adrenal cortex to produce 17-hydroxyprogesterone (Chung, 2014). The level of 17α-Hydroxyprogesterone in plasma rises gradually by 32 weeks of gestation (Kumar and Magon, 2012). The other least studied 16α-hydroxyprogesterone is also found to be produced from steroidogenic tissue and its detection in plasma and urine raises questions on the physiological relevance of this steroid (Storbeck et al., 2011).

Progesterone promotes endometrial decidualization for the healthy implantation of an embryo (Gellersen and Brosens, 2014). It inhibits smooth muscle contractility and help to maintain myometrial quiescence and prevent the onset of uterine contractions (Arrowsmith et al., 2010). Placental progesterone inhibit immune responses that might harm the placenta or fetus (Robinson and Klein, 2012).

2.2.2. Estrogens

Estrogens, or estrogen, are a group of compounds known for their importance in the estrous cycle of humans and other animals. There are three main common estrogens (estrone; E1, estradiol; E2, estriol; E3) present throughout the pregnancy. The placenta is the principal site of biosynthesis of estradiol and estrone. Placenta converts 16-hydroxydehydroepiandrosterone sulfate derived from the fetal liver and adrenals to estriol (Thomas and Potter, 2013). Estrogen (E2) trigger luteinizing hormone (LH) surge during menstrual cycle resulting in ovulation. Cooperatively both E2, P4 prepares the endometrium for implantation (Lee and DeMayo, 2004). It also promotes cervical softening (Stjernholm et al., 1996). Furthermore, E2 contribute in fetal tolerance regulating different immune cell

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