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Review

Steroids and insulin resistance in pregnancy

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ABSTRACT

Metabolism of glucose during pregnancy reflects the equilibrium between lactogenic hormones stimulating insulin production and counterregulatory hormones inducing insulin resistance. In physiological pregnancies, insulin-mediated glucose uptake is substantially decreased and insulin secretion increased to maintain euglycemia. This common state of peripheral insulin resistance arises also due to steroid spectra changes. In this review article, we have focused on the role of steroid hormones (androgens, estrogens, gestagens, mineralocorticoids, glucocorticoids, as well as secosteroid vitamin D) in the impairment of glucose tolerance in pregnancy and in the pathogenesis of gestational diabetes mellitus.

This article is part of a Special Issue entitled 'Pregnancy and Steroids'.

Contents

1. Insulin resistance in pregnancy, gestational diabetes mellitus

Pregnancy is characterized by a number of metabolic adaptations. In early gestation, adipose tissue accretion is promoted. Late pregnancy leads to insulin resistance (IR) and facilitated lipolysis coupled with increased free fatty acid (FFA) levels. Glucose metabolism during pregnancy reflects the equilibrium between

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lactogenic hormones prolactin and placental lactogens, which stimulate β-cell proliferation coupled with higher insulin production, and counterregulatory hormones, which induce IR. To sustain euglycemia in the mother, normal pregnancy is characterized by almost 50% decrease in insulin-mediated glucose disposal and more than 200% increase in insulin secretion [1–3]. The process involves lower ability of insulin to phosphorylate the insulin receptor, reduced IRS-1 (insulin receptor substrate 1) expression, and decreased PI3-kinase (phosphoinositide 3-kinase) response to insulin. The purpose of this obligatory adaptation in late gestation is to spare glucose, aminoacids, fatty acids, and ketones for the fetus, which is essential for the normal fetal development and growth.

Decrease in peripheral insulin sensitivity (IS) occurs due to substantial steroid spectra changes. Major change in the hypothalamo–pituitary–adrenal/–gonadal axis influences fetal growth and the timing of the delivery. Progressive is the increase in counterregulatory hormones including placental growth hormone (GH), glucocorticoid cortisol, progesterone and inflammatory cytokine TNFα (tumor necrosis factor-α). TNFα impairs insulin signaling by diminishing insulin receptor tyrosin kinase activity, by increasing serine phosphorylation of the IRS-1 [1,4], and also by suppression of adiponectin, the endogenous insulin-sensitizing hormone [5–7]. Number of risk factors such as visceral obesity, low energy expenditure, high carbohydrate consumption, sleep deprivation, ethnicity, and genetic background interact with IR and the mechanism behind is multifactorial [8].

Gestational diabetes mellitus (GDM) is a pathological state of glucose intolerance recognized for the first time during pregnancy. It develops in 1–8% of all pregnancies, depending on the ethnicity of the studied cohorts of patients [9–12] and is characterized by a relatively diminished insulin secretion coupled with a pregnancy-induced IR. The cellular background for this state is not yet fully understood. Women with GDM show signs of subclinical inflammation with increased TNFα. As mentioned above, TNFα and some other proinflammatory substances suppress the adiponectin transcription. As a consequence, its concentration

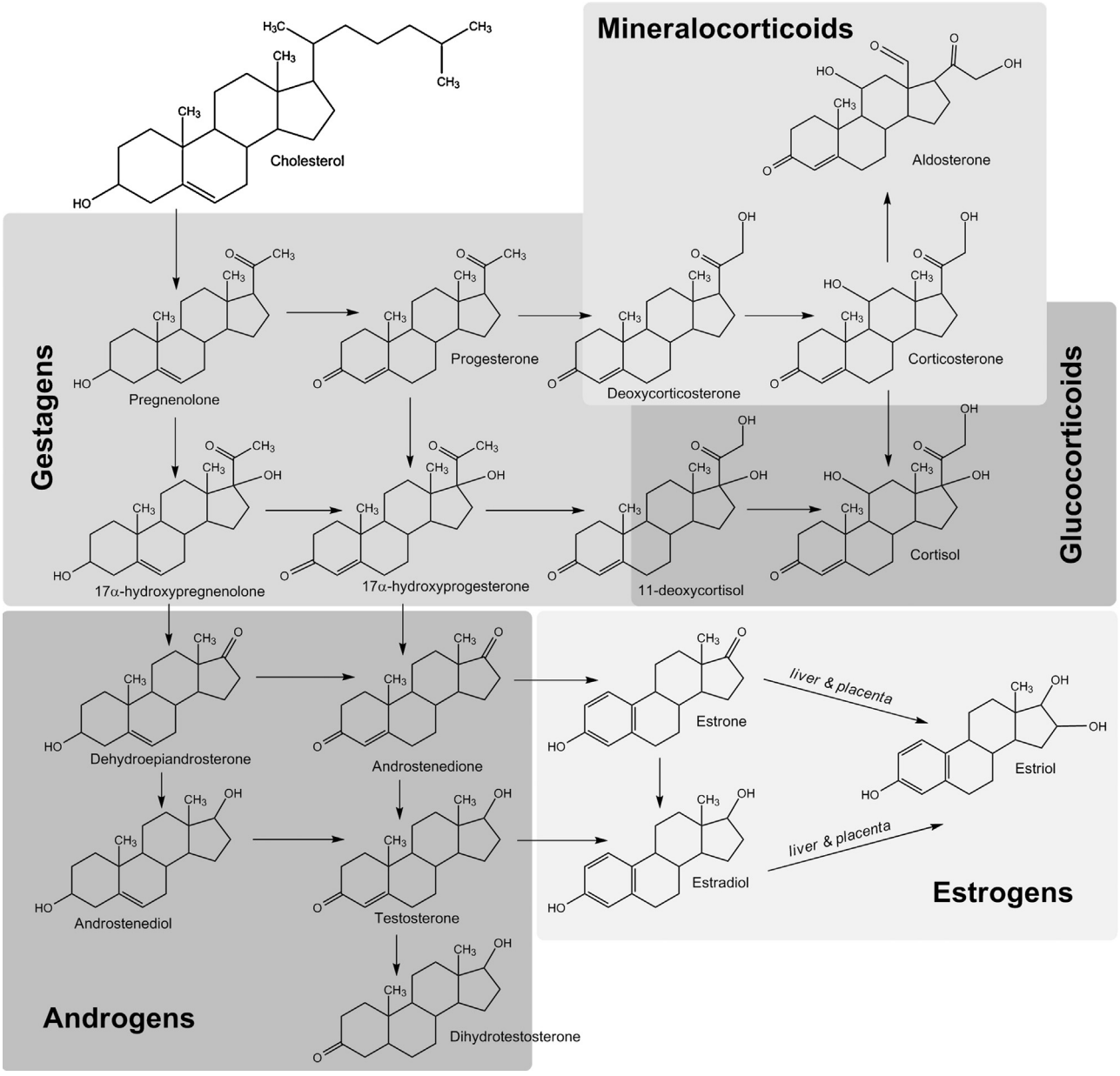

Fig. 1. Steroidogenesis.