# Pregnancy in Patients with Cushing's Syndrome

Marcio Carlos Machado, MD, PhD[a,b,c],
Maria Candida Barisson Vilares Fragoso, MD, PhD[a],
Marcello Delano Bronstein, MD, PhD[a,*]

**KEYWORDS**

• Cushing's syndrome • Pregnancy • Hypercortisolism

**KEY POINTS**

- Despite high prevalence of Cushing's syndrome in women of reproductive age, pregnancy rarely occurs due to hypogonadotrophic hypogonadism secondary to cortisol and androgens excess.
- Causes of Cushing's syndrome in pregnancy are adrenal disorders (in particular adenomas) in 60% cases, Cushing's disease in 33%, and 7% ectopic Cushing's syndrome.
- Although cortisol levels can be high, the circadian rhythm of cortisol secretion is preserved during normal pregnancy.
- Uncontrolled Cushing's syndrome during pregnancy is associated with a high rate of maternal and fetal complications. The rates of preeclampsia and premature delivery are increased even in patients with treated hypercortisolism.
- Surgery in the second trimester is the main treatment option in pregnant Cushing's syndrome patients.

## INTRODUCTION

Cushing's syndrome (CS) is one of the endocrine conditions that often impair ovulation and, consequently, fertility. De novo CS during pregnancy is challenging to diagnose due to shared clinical features and impact on normal gestation on testing. Untreated CS during pregnancy significantly increases the risk for complications for mother and fetus. This review intends to bring insights both in diagnosis and treatment of CS in pregnancy.

Disclosure Statement: The authors have nothing to disclose.
[a] Neuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clínicas, University of São Paulo Medical School, Avenida Enéas de Carvalho Aguiar, n° 155, 8° andar, bloco 03, São Paulo, São Paulo 05403-000, Brazil; [b] Endocrinology Service, AC Camargo Cancer Center, Rua Prof. Antonio Prudente n° 211, São Paulo, SP 01509-010, Brazil; [c] Laboratory for Endocrinology Cellular and Molecular – LIM25, University of São Paulo Medical School, Av. Dr. Arnaldo, 455, 4° andar, São Paulo, SP 01246-903, Brazil
* Corresponding author.
*E-mail address:* mdbronstein@uol.com.br

Endocrinol Metab Clin N Am 47 (2018) 441–449
https://doi.org/10.1016/j.ecl.2018.02.004
0889-8529/18/

## HYPOTHALAMIC-PITUITARY-ADRENAL AXIS CHANGES DURING PREGNANCY

Pregnancy is considered a physiologic state of hypercortisolism due to an activation of the hypothalamic-pituitary-adrenal axis (HPA) (Fig. 1). Nevertheless, albeit sharing some clinical features with CS, normal pregnancy usually is not accompanied by specific clinical manifestations of CS, such as large purple striae, proximal muscle weakness, and cutaneous atrophy/easy bruising.

The corticotropin-releasing hormone (CRH) is synthetized in the hypothalamus but has also been detected in thecal and in stromal cells as well as in cells of the ovarian corpora luteum.[1] The epithelial cells of the endometrium have shown CRH receptors,[2,3] which mediate CRH effects on maturation of the fetal adrenal, fetal-placental unit circulation, and placenta itself. The placental CRH has an identical molecular structure to the hypothalamic form.[4]

During pregnancy, CRH and corticotropin levels increase in the first trimester due to CRH and corticotropin secretion by the placenta. CRH-binding protein levels also increase.[5] Due to corticotropin stimulation, maternal adrenal glands gradually become hypertrophic during pregnancy. The result is a small rise of cortisol levels (serum,

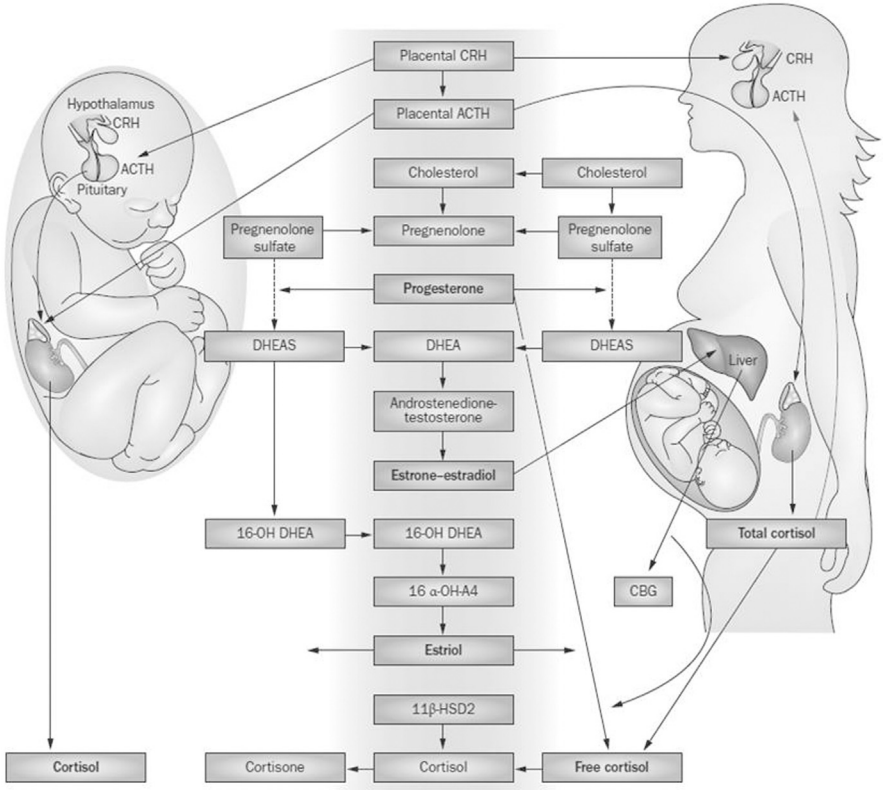


**Fig. 1.** The physiologic activation of the HPA axis during pregnancy. The production of cortisol linked to CBG is increased, as is the free fraction. The concentration of corticotropin is high, and the adrenal cortex is responsible for stimulus. 16 a-OH-4A, 16α-hydroxyandrostenedione. 16'OH, 16α-Hydroxydehydroepiandrosterone; 16α-OH-A4, 16α-hydroxyandrostenedione; DHEA, dehydroepiandrosterone; HSD2, 11β-hydroxysteroid dehydrogenase type 2. (*From* Bronstein MD, Paraiba DB, Jallad RS. Management of pituitary tumors in pregnancy. Nat Rev Endocrinol 2011;7:306; with permission.)