WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 4, 110-119. Review Article ISSN 2277– 7105

# PITUITARY DISORDERS IN PREGNANCY

**Rajiha Majid Abdulateef* and Lamyaa Abdullah Mohammed**

Ministry of Health, Baghdad, Iraq.

Article Received on
21 Jan. 2019,

Revised on 11 Feb. 2019,
Accepted on 04 March 2019

DOI: 10.20959/wjpr20194-14444

***Corresponding Author**
**Rajiha Majid Abdulateef**
Ministry of Health, Baghdad, Iraq.

## ABSTRACT

Major hormonal changes emerge during pregnancy. The pituitary gland is one of the most affected organs with altered anatomy and physiology. The pituitary gland is enlarged as a result of lactotroph hyperplasia. Due to physiological changes in the pituitary and target hormone levels, binding globulins, and placental hormones, hormonal evaluation becomes more complex in pregnant women. As a consequence of physiological hormonal changes, the evaluation of pituitary functions in pregnant women is quite different from that done in the prepregnant state. Pituitary adenomas may cause problems by their hormone secretion that affects the mother and the fetus besides causing an increased risk of tumor growth. Furthermore, diagnosis, course, and treatment of pituitary diseases point out differences. The changes in anatomy and physiology of the pituitary gland during pregnancy are reviewed. Being aware of all this information will prevent any serious problems which mother and child will be exposed to.

**KEYWORDS:** Pituitary Disorders, Pregnancy.

## INTRODUCTION

Anterior pituitary gland and pregnancy Pituitary adenomas are common in women, constituting 5.7% of intracranial (malignant and nonmalignant) neoplasms, with an age-adjusted incidence rate of 0.82 cases/100,000 person-years[1]. These adenomas may cause problems in women because of oversecretion of hormones by the tumor and hypopituitarism. Hormonal dysfunction caused by pituitary adenomas may affect fertility and pregnancy outcome if pregnancy does ensue. In addition, the pregnancy itself alters hormone secretion and pituitary function, complicating the evaluation of patients with pituitary neoplasms.

The need for preventing harm to the developing fetus influences therapeutic decisions for the mother. During pregnancy, the normal pituitary gland enlarges considerably as a result of the estrogen-stimulated hyperplasia and hypertrophy of the prolactin-producing lactotrophs[2]. Concomitantly, prolactin levels increase gradually throughout gestation[3]. The elevated prolactin levels found at term prepare the breast for lactation. The finding of amenorrhea associated with hyperprolactinemia could be due to pregnancy and not due to pathologic hyperprolactinemia. MRI scans of the pituitary during pregnancy show a size increase secondary to the lactotroph hyperplasia, with the peak size occurring in the first 3 days postpartum when gland heights of 12 mm may be seen[4]. After delivery, there is a rapid involution of the gland so that normal pituitary size is found by 6 months postpartum. This stimulatory effect of pregnancy on the pituitary has important implications for a patient with a prolactinoma who desires pregnancy.

Beginning in the second half of pregnancy, pituitary growth hormone (GH) secretion decreases, and the circulating level of a GH variant made by the syncytiotrophoblastic epithelium of the placenta increases to 10 to 20 ng/mL[5]. The decreased production of normal pituitary GH likely is caused by negative feedback effects of insulin-like growth factor type 1, which is stimulated by the placentally produced GH variant[6]. In patients with acromegaly who have autonomous GH secretion and become pregnant, both forms of GH persist in the blood throughout pregnancy[7]. During gestation, cortisol levels progressively increase, resulting in a 2 to 3-fold increase by the term[8]. Most of the elevation of cortisol levels is due to the estrogen-induced increase in cortisol-binding globulin levels[9]. The bioactive ‘‘free’’ fraction also is elevated 3-fold, and the cortisol production rate is increased so that there is a 2 to 3-fold elevation in urinary free cortisol level. Adrenocorticotropic hormone (ACTH) levels have been variously reported as being normal, suppressed, or elevated early in gestation[10].

Later in the pregnancy, however, there is a progressive increase, followed by a final surge of ACTH and cortisol levels during labor. ACTH does not cross the placenta, but it is manufactured by the placenta[11]. The amounts of ACTH in serum that are of placental compared with pituitary origin at various stages of gestation are unknown. Corticotropin-releasing hormone (CRH) also is produced by the placenta and is released into the maternal plasma[12].

The CRH is bioactive and may release ACTH from the placenta, in a paracrine fashion, and from the maternal pituitary[13]. The role of placental CRH in regulating ACTH and cortisol

secretion during pregnancy in humans is unclear. Thyroid-stimulating hormone (TSH) levels decrease in the first trimester, in response to the increased thyroid hormone levels that are stimulated by human chorionic gonadotropin, but return to the normal range by the third trimester[14]. In response to placental sex steroid production, hypothalamic gonadotropin releasing hormone (GnRH) and pituitary gonadotropin (follicle-stimulating hormone and luteinizing hormone) levels decline in the first trimester of pregnancy, with a blunted gonadotropin response to GnRH.

## BACK GROUND

Anatomical changes in the pituitary gland during pregnancy

The size and shape of the pituitary depend on the sella turcica; therefore, there is considerable variability in its contour[15]. During the first two decades of life, it grows rapidly and, in adults, the size of the pituitary gland measures ~10 mm in length, 5–10 mm in height, and 10–15 mm in width. After the fourth decade, considerable interstitial fibrosis occurs and the gland loses weight throughout the rest of life.[16] Women of childbearing age tend to have larger glands, and upward convexity of the pituitary gland is also seen more frequently in this age and sex group.

There is considerable evidence regarding the enlargement of the pituitary gland during pregnancy. Comte first showed the enlargement of the pituitary gland in pregnant women in the 19th century[17], which was confirmed by other autopsy studies. *In vivo* studies also demonstrated increased pituitary volume. The pituitary gland size was found to be increased in three dimensions with an overall increase of 136% when compared to the control group. This increment was 45% in the first trimester[18]. Pituitary volumes during pregnancy were found to be increased by 120% compared to the control in another study.[19]

The highest pituitary volumes and widths of the infundibulum were observed during the first three *postpartum* days. The mean height of the pituitary glands during the *postpartum* period was found to be 9.3 mm, which was significantly higher than that during the last half of pregnancy. The upper limit for the height of the normal pituitary gland was suggested as 9.6–10 mm for the gestational period and as 10.2–12 mm for the immediate *postpartum*period. The height of the gland correlated best with the gestational age, and the mean height of the gland was 8.8 mm in the third trimester. The pituitary glands were demonstrated to gain their

normal size, shape, and volume within 6 months *postpartum*[20]. The height of the pituitary gland seems to be a good measure for the demonstration of the increased size.

The differential diagnosis of pituitary gland enlargement is difficult in pregnant women since magnetic resonance imaging (MRI) is not specific enough. Previous pituitary adenoma, pituitary apoplexy or hemorrhagic necrosis of an adenoma, acute Sheehan's syndrome (SS), and lymphocytic hypophysitis (LyH) should be kept in mind in a differential diagnosis. Asymmetrical enlargement and deviation of the stalk, which is not seen during physiological enlargement of the pituitary gland, may indicate the presence of an adenoma. The pituitary height that is higher than 9–10 mm during pregnancy may arouse suspicion of a pathological reason[21]. Compression of optic chiasma and visual field loss was reported in a few cases in the literature[22]. Thus, pituitary gland lesions should be evaluated carefully in pregnant women with headaches and visual problems. Surgical intervention is usually not required unless there is a suspicion of pituitary adenoma or apoplexy on MRI causing compressive signs.

MRI without i.v. contrast injection seems to be safe during pregnancy, but all FDA-approved Gd chelates belong to 'Pregnancy Category C'. Although the diverse effects of these contrast agents with increased dosage and exposure time were reported in animals, the effect of a single clinical dose of Gd in humans is not well known.[23] Studies with magnevist (gadopentetic dimeglumine) and omniscan (gadodiamide) for the evaluation of nonpregnancy-related pathologies carried out on pregnant women did not reveal any adverse effects.[24] The rational approach for pregnant patients is to consider postponing MRI after birth. If not possible, MRI without a contrast agent should be the choice. MRI with a contrast agent after the first trimester of pregnancy should be reserved for cases which require definitive diagnosis that may have serious outcomes for the fetus or the mother.

**Physiological changes of pituitary hormone axes during pregnancy**

Although the corticotroph number is unaltered, normal gestation is associated with increased maternal hypothalamic–pituitary–adrenal axis (HPA) axis activity. Urinary free cortisol (UFC), plasma 17-hydroxycorticosteroids, total and free plasma cortisol, and corticosteroid-binding globulin (CBG) levels are all elevated.[25] As hepatic CBG production increases under the effect of placental estrogen, free cortisol levels drop transiently and increase ACTH stimulation to maintain a normal free cortisol level. But it is also shown that free cortisol levels start to increase by the 11th week of gestation, and higher levels are observed in the

second trimester and they reach a plateau in the third trimester of pregnancy.[26] There are different explanations for the increased free cortisol levels in pregnancy: resistance to cortisol action, antiglucocorticoid effects of elevated progesterone, altered set point for pituitary ACTH, and autonomic secretion of ACTH from the placenta, The circadian rhythm of cortisol are usually preserved, but it may also be partially blunted.[27]

Hyperprolactinemia is responsible for about one third of all cases of female infertility.[28] Hyperprolactinemia impairs the hypothalamic-pituitaryovarian axis at several levels, the primary site of inhibition being at the hypothalamus, where it inhibits the pulsatile secretion of GnRH.[29] The differential diagnosis of hyperprolactinemia is extensive[30]. For patients with prolactinomas, the choice of therapy may have important consequences for decisions regarding pregnancy. Transsphenoidal surgery is curative in 50% to 60% of cases and rarely causes hypopituitarism when it is performed on women with microadenomas.

**Effects of pregnancy on prolactinoma growth**

In women with prolactinomas, the stimulatory effect of the hormonal milieu of pregnancy may result in significant tumor enlargement during gestation. A review summarized 16 series reported during the years 1979–1985 totaling 246 women with microadenomas and 91 women with macroadenomas who became pregnant[31]. Subsequently, three series totaling an additional 130 women with microadenomas and 60 women with macroadenomas have been reported[32]. When these data are combined[33], only 6 of the 376 women (1.3%) with microadenomas had symptoms of tumor enlargement (headaches or visual disturbances or both).

In no case was surgical intervention necessary. These series included 86 patients with macroadenomas who had not had prior surgery or irradiation. Of these, 20 (23.2%) had symptomatic tumor enlargement. During pregnancy, surgery was required in 4 patients, and bromocriptine was required in.[34] Seventy-one women with macroadenomas had been treated with irradiation or surgery before pregnancy; only 2 of the 71 (2.8%) had symptomatic tumor enlargement, If tumor enlargement occurs, reinstitution of bromocriptine and cabergoline usually is successful in reducing the size of the tumor, but transsphenoidal surgery may be necessary.[35]

**Table 1 Summary of changes in anterior pituitary hormones during pregnancy.**

| Number of pituitary cells | Pituitary hormones | Pituitary hormones | Hypothalamic and placental factors affecting the pituitary | Target hormone | Binding proteins/metabolites |
|---|---|---|---|---|---|
| Corticotrophs unaltered | ACTH ↑ | Pituitary | Hypothal mic CRH | Free cortisol ↑ | CBG ↑ |
| Somatotrophs ↓ | GH ↓ | Pituitary GH suppressed GH-V ↑ | Hypothalamic GHRH Placental GHRH (stimulate pituitary GH/no effect on GH-V) | IGF1 slightly ↑IGF1 also produced from the placenta | GHBP ↑ |
| Lactotrophs ↑ | PRL ↑ | PituitaryDecidua | Hypothalamic dopamine (inhibits pituitary PRL/no effect on decidual PRL) | | |
| Gonadotrophs ↓ | FSH, LH ↓ | Decreased due to increased sex steroids | GnRH (gonadotropin response to GnRH is decreased) | Estrogen ↑Progesterone ↑ (from placenta) | SHBG ↑ |
| Thyrotrophs unaltered | TSH decreased in the first trimester | Decreased due to the similarity of TSH with hCG | TRH (response is preserved) | $T_4$ (total and free $T_4$) ↑ in the first trimester | TBG ↑ |

## DISCUSSION

Pergolide has been shown to cross the placenta in mice, but no teratogenicity was seen in doses of 60 mg/kg/d.[36] Detailed data are available on the safety during early gestation for only one patient treated with pergolide for Parkinson's disease[37]. In this pregnancy, no teratogenicity or developmental abnormalities were found in the child, but the authors stated in this report that, ''in premarketing studies of pergolide for endocrine disorders, two major and three minor congenital abnormalities were described among 38 pregnancies, but a causal relationship has not been established'[38]. Other information from the manufacturer (Eli Lilly & Co) stated that they had only limited data on pregnancies in which the fetus was exposed to pergolide, finding that 7.2% of pregnancy outcomes resulted in spontaneous abortions, 7.2% in minor malformations, 14.3% in intentional abortions, and 28.6% in healthy infants; for 43.4%, no information was available.[39]

This limited information is sufficient to recommend against using pergolide when a woman wishes to get pregnant. Some early publications reported no detrimental effects on pregnancy or fetal development in women who became pregnant during treatment with Table 1 Effect of bromocriptine on pregnancies Bromocriptine Criteria No. % Normal population (%) Pregnancies 6239 100.0 100.0 Spontaneous abortion 620 9.9 10.0–15.0 Termination 75 1.2 d Ectopic 31 0.5 0.5–1.0 Hydatidiform moles 11 0.2 0.05–0.7 Deliveries (known duration) 4139 100.0 100.0 At term (O 38 wk) 3620 87.5 85.0 Preterm (38 wk) 519 12.5 15.0 Deliveries (known outcome) 5120 100.0 100.0 Single births 5031 9.3 8.7 Multiple births 89 1.7 1.7 Infants (known details) 5213 100.0 100.0 Normal 5030 96.5 95.0 Who have malformations 93 1.8 3.0–4.0 Who have perinatal disorders 90 1.7 O2.0 Data from Krupp P, Monka C, Richter K. The safety aspects of infertility treatments.

A more recent review of 176 pregnancies, in which quinagolide was maintained for a median duration of 37 days, reported 24 spontaneous abortions, 1 ectopic pregnancy, and 1 stillbirth at 31 weeks' gestation.[40] Nine fetal malformations were reported in this group: spina bifida, trisomy 13, Down syndrome, talipes, cleft lip, arrhinencephaly, and Zellweger syndrome.[41] Quinagolide also should not be used if pregnancy is desired. Cabergoline has been shown to cross the placenta in animal studies, but such data are lacking in humans. Data on exposure of the fetus or embryo during the first several weeks of pregnancy have been reported in more than 350 cases, and such use has not shown an increased percentage of spontaneous abortion, premature delivery, multiple gestation, or congenital abnormalities.[42]

No alterations in newborn weights were observed. Available data from 107 infants followed for 1 to 72 months showed normal physical and mental development. With respect to using a dopamine agonist to facilitate ovulation and fertility, bromocriptine has the largest safety database and has a proven safety record for pregnancy.

Although the database for cabergoline use in pregnancy is much smaller, it does not seem to exert any deleterious effects on pregnant women, and the incidence of malformation in their offspring is not greater than in the general population. For a woman who is intolerant to bromocriptine and who is doing well with cabergoline, a continuation of cabergoline for facilitating pregnancy seems reasonable. The safety databases for pergolide and quinagolide are limited, but they seem to raise considerable concerns, so these drugs should not be used when fertility is desired. The effects of transsphenoidal surgery during gestation are not known specifically, but would not be expected to be significantly different from the effects of other types of surgery (unless hypopituitarism should ensue).[43]

Pregnancy induces long-term changes in PRL secretion. Pregnancy suppresses the secretion of PRL by the maternal pituitary permanently.[44]

Big big PRL is reported in a range of 8–38% of total PRL during pregnancy, Frequency of macroprolactinemia during pregnancy is reported as 2.9–3.8% due to anti-PRL autoantibodies.[45] Macroprolactinemia persists during pregnancy, and the PRL increment in macroprolactinemic women is less than that in normal pregnant women.

Although the appearance and distribution of thyrotropic cells are preserved, thyrotropin (TSH) secretion is altered during pregnancy. The biochemical similarity of TSH and human chorionic gonadotropin (hCG) results in decreased maternal TSH levels, particularly in 9–13 weeks of gestation, when hCG production by the placenta is highest.[46] Additionally, increased estrogen levels lead to a significant increase in thyroxine (T4)-binding globulin (TBG) levels that reach a plateau after 12–14 weeks of gestation, and total thyroid hormone levels are concomitantly increased.[47] There is a slight increase in serum concentrations of free T4 during the first trimester, and they then decrease, but these changes are minimal and serum levels of free T4 usually remain within the normal ranges for nonpregnant women.[48] There is also a study which measured free tri-iodothyronine and free T4 levels in women at term using ten different commercially available kits, which revealed that free thyroid

hormones are always significantly lower than those in nonpregnant women. The negative-feedback control of TSH is intact during pregnancy, and TSH concentrations are usually similar to those in nonpregnant women.

**REFERENCE**

1. Central Brain Tumor Registry of the United States (CTBRUS). Statistical report: primary brain tumors in the US 1997–2001.Available at: http://www.cbtrus.org/. Accessed April 8, 2005.
2. Goluboff LG, Ezrin C. Effect of pregnancy on the somatotroph and the prolactin cell of the human adenohypophysis. J Clin Endocrinol Metab, 1969; 29: 1533–8.
3. Scheithauer BW, Sano T, Kovacs KT, et al. The pituitary gland in pregnancy: a clinicopathologic and immunohistochemical study of 69 cases. Mayo Clin Proc, 1990; 65: 461–74.
4. Rigg LA, Lein A, Yen SSC. Pattern of increase in circulating prolactin levels during human gestation. Am J Obstet Gynecol, 1977; 129: 454–6.
5. Gonzalez JG, Elizondo G, Saldivar D, et al. Pituitary gland growth during normal pregnancy: an in vivo study using magnetic resonance imaging. Am J Med., 1988; 85: 217.
6. Elster AD, Sanders TG, Vines FS, Chen MYM. Size and shape of the pituitary gland during pregnancy and post-partum: measurement with MR imaging. Radiology, 1991; 181: 531–5.
7. Dinc¸ H, Esen F, Demirci A, et al. Pituitary dimensions and volume measurements in pregnancy and post-partum: MR assessment. Acta Radiol, 1998; 39: 64–9.
8. Frankenne F, Closset J, Gomez F, et al. The physiology of growth hormones (GHs) in pregnant women and partial characterization of the placental GH variant. J Clin Endocrinol Metab, 1988; 66: 1171–80.
9. Eriksson L, Frankenne F, Eden S, et al. Growth hormone 24-h serum profiles during pregnancy lack of pulsatility for the secretion of the placental variant. Br J Obstet Gynaecol, 1989; 106: 949–53.
10. Beckers A, Stevenaert A, Foidart J-M, et al. Placental and pituitary growth hormone secretion during pregnancy in acromegalic women. J Clin Endocrinol Metab, 1990; 71: 725.
11. Carr BR, Parker CR Jr, Madden JD, et al. Maternal plasma adrenocorticotropin and cortisol relationships throughout human pregnancy. Am J Obstet Gynecol, 1981; 139: 41.

12. Nolten WE, Lindheimer MD, Rueckert PA, et al. Diurnal patterns and regulation of cortisol secretion in pregnancy. J Clin Endocrinol Metab, 1980; 51: 466–72.
13. Rees LH, Burke CW, Chard T, et al. Possible placental origin of ACTH in normal human pregnancy. Nature, 1975; 254: 620–2.
14. Sasaki A, Shinkawa O, Yoshinaga K. Placental corticotropin-releasing hormone may be a stimulator of maternal pituitary adrenocorticotropic hormone secretion in humans. J Clin Invest, 1989; 84: 1997–2001.
15. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev., 1997; 18: 404–33.
16. Jeppsson S, Rannevik G, Liedholm P, Thorell JI. Basal and LHRH stimulated secretion of FSH during pregnancy. Am J Obstet Gynecol, 1977; 127: 32–6.
17. Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. N Engl J Med., 1994; 331: 904–9.
18. Molitch ME. Dopamine resistance of prolactinomas. Pituitary, 2003; 6: 19–27.
19. Bevan JS, Webster J, Burke CW, Scanlon MF. Dopamine agonist and pituitary tumor shrinkage. Endocr Rev., 1992; 13: 220–40.
20. Biller BMK, Molitch ME, Vance ML, et al. Treatment of prolactin-secreting macroadenomas with the once-weekly dopamine agonist cabergoline. J Clin Endocrinol Metab, 1996; 81: 2338–43.
21. Colao A, DiSarno A, Landi ML, et al. Macroprolactinoma shrinkage during cabergoline treatment is greater in naı¨ve patients than in patients pretreated with other dopamine agonists: a prospective study of 110 patients. J Clin Endocrinol Metab, 2000; 85: 2247–52.
22. Molitch ME. Pregnancy and the hyperprolactinemic woman. N Engl J Med., 1985; 312: 1364–70.