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REVIEW

Pregnancy and pituitary disorders

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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. Pituitary disorders namely Cushing's disease; acromegaly; prolactinoma; TSH-secreting, gonadotropin-producing, and clinically nonfunctioning adenomas; craniopharyngioma; and Sheehan's syndrome, which is one of the most common causes of hypopituitarism, lymphocytic hypophysitis, and hypopituitarism, in relation to pregnancy are discussed. Being aware of all this information will prevent any serious problems which mother and child will be exposed to.

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Introduction

Pregnancy might be accepted as a new physiological state for the pituitary gland with altered anatomy, modified courses, diagnosis, and treatment of pituitary diseases. This review summarizes the changes in the pituitary gland during normal pregnancy, the placenta as a source of new hormones, and pituitary disorders during pregnancy.

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 (1). 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 (2, 3). 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 (4), which was confirmed by other autopsy studies (5, 6). *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 (7). Pituitary volumes during pregnancy were found to be increased 120% compared to the control in another study (8). 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* (8, 9). 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.

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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 are not seen during physiological enlargement of the pituitary gland, may indicate the presence of an adenoma. Pituitary height that is higher than 9–10 mm during pregnancy may arouse suspicion of a pathological reason (10). Compression of optic chiasma and visual field loss were reported in a few cases in the literature (11–13). 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 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 (14, 15). 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 (16–19). 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

Hypothalamic–pituitary–adrenal axis

Although the corticotroph number is unaltered, normal gestation is associated with increased maternal hypothalamic–pituitary–adrenal axis (HPA) axis activity (Table 1 and Fig. 1). Urinary free cortisol (UFC), plasma 17-hydroxycorticosteroids, total and free plasma cortisol, and corticosteroid-binding globulin (CBG) levels are all elevated (20–22). 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 (21, 23). 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 (21, 24, 25). The circadian rhythm of cortisol is usually preserved, but it may also be partially blunted (20, 26, 27).

The placental 11β-hydroxysteroid dehydrogenase (11β-HSD 2), which is located in syncytial trophoblastic cells, inactivates active glucocorticoids, cortisol, and corticosterone, which protects the fetus from maternal hypercortisolism (28). Dexamethasone can cross the placenta, which is a poor substrate for 11β-HSD 2 (29). In normal subjects, conversion of cortisol to cortisone predominates, but in late gestation, the enzyme activity favors the production of the active

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

Number of pituitary cells	Pituitary hormones	Source of hormones	Hypothalamic and placental factors affecting pituitary	Target hormone	Binding proteins/ metabolites
Corticotrophs unaltered	ACTH ↑	Pituitary Fetoplacental unit	Hypothalamic CRH Placental CRH (stimulate maternal pituitary (?) ACTH/ fetoplacental unit ACTH)	Free cortisol ↑ Bound cortisol ↑	CBG ↑ CRH-BG ↑ Urinary cortisol metabolites ↑
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 placenta	GHBP ↑
Lactotrophs ↑	PRL ↑	Pituitary Decidua	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 similarity of TSH with hCG	TRH (response is preserved)	T_4 (total and free T_4) ↑ in the first trimester	TBG ↑

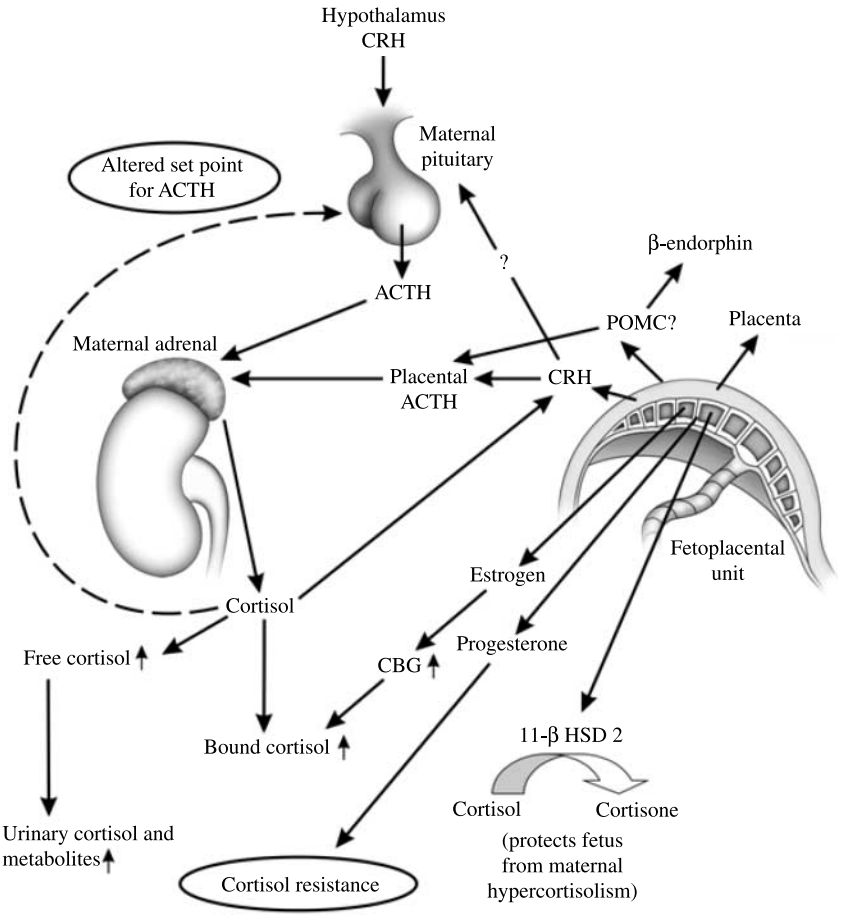

Figure 1 HPA axis during pregnancy: hypothalamic CRH stimulates maternal ACTH secretion, which in turn stimulates adrenal cortisol secretion. Placental CRH is an important stimulator of fetoplacental unit ACTH which contributes to increased adrenal cortisol secretion. The effect of placental CRH on maternal pituitary is unclear. There is a positive feed-forward effect between CRH and cortisol. Estrogen increases CBG, though total cortisol is increased, but free cortisol secretion is also increased during pregnancy. Progesterone has antiglucocorticoid effects in the mother and 11β-HSD 2 protects the fetus from maternal hypercortisolism (—, stimulation; – – –, inhibition; CRH, corticotropin-releasing hormone; ACTH; POMC, proopiomelanocortin; CBG, corticosteroid-binding globulin; 11β-HSD 2, 11β-hydroxysteroid dehydrogenase 2).

hormone which is important for fetal lung maturation (30). Corticosterone and immunoreactive ACTH were found to have circadian variation throughout and during early pregnancy respectively in pregnant rats (31).

Plasma ACTH levels increase throughout pregnancy reaching maximum levels during labor. Demura *et al.* showed the presence of ACTH and β-endorphin in trophoblastic tissues, suggesting a common origin, probably proopiomelanocortin (32). The elevation of ACTH in late pregnancy suggests a source which is not subject to normal feedback control (20). Placental ACTH is shown to be regulated by corticotropin-releasing hormone (CRH) (33).

The placenta is the source of elevated CRH during gestation (34). Placental CRH is similar to hypothalamic CRH in structure, immunoreactivity, bioactivity, and transcriptional sites. Although the circadian rhythms of ACTH and cortisol are preserved, the circadian rhythm of CRH could not be demonstrated; therefore, a noncircadian, nonpulsatile stimulation of maternal HPA axis by placental CRH is assumed (26). There seems to be a positive feed-forward effect of CRH and glucocorticoids. Placental CRH is stimulated by glucocorticoids, which explains the rise in CRH preceding parturition (35, 36). CRH stimulates ACTH release from the placenta in a paracrine fashion besides stimulating the maternal pituitary, although the latter source is not exactly proven (37). Systemic maternal effects of CRH are thought to be limited due to CRH-binding globulin (CRH-BG). CRH-BG levels decrease in the last few weeks of pregnancy, which normally inactivates CRH. Thus, biologically active CRH is increased (38).

Although maternal corticotrophs are desensitized, HPA axis function remains intact in normal pregnancy. Placental CRH appears to be the major stimulus for the HPA axis in the third trimester (28, 38). CRH receptors are present in reproductive tissues such as the placenta and endometrium besides CNS, heart, lung, skeletal muscles, and lymphatic organs (39). CRH is important for decidualization, implantation, and ovarian function. Placental CRH is important for fetal adrenal steroidogenesis, maintenance of fetoplacental circulation, and determination of the onset of parturition (40).

GH–insulin-like growth factor 1 axis

Pregnancy is a state of mild physiological acromegaly (41). During early gestation, maternal GH is secreted from the pituitary, which is suppressed in later weeks (Table 1 and Fig. 2). In rat pregnancy, baseline circulating GH level is not affected by ghrelin; therefore, direct alteration of somatotroph function without an increased number of somatotrophs is assumed (42). Placental GH (GH-V) is detectable by the fifth week of pregnancy, and levels increase exponentially and peak at 35–37 weeks. Individual GH-V levels vary widely with peak levels that range between 4.6 and 69.2 ng/ml (43). GH-V is secreted continuously, and it is regulated neither by GH-releasing factor nor by ghrelin (44). It binds to hepatic GH receptor with an affinity that is similar to the affinity with which the receptor binds to GH, and it is not detected by routine RIA and IRMA methods (45). GH-V decreases pituitary GH secretion by stimulating insulin-like growth factor 1 (IGF1) (46, 47). GH-V and IGFs have growth-promoting effects on the fetus and placenta (41). Most of the GH-V is cleared from plasma 30 min after delivery and is not detectable in the fetal circulation (48). Decreased GH response to insulin-induced hypoglycemia or arginine suggests decreased reserve of GH secretion by the maternal pituitary (49, 50).

Prolactin axis

The enlargement of the pituitary gland is explained by massive hyperplasia of lactotrophs and their transformation to pregnancy cells. The pregnancy cells are morphologically modified prolactin (PRL)-producing cells derived from the preexisting mature lactotrophs (6) (Table 1). During pregnancy, maternal PRL levels increase by tenfold parallel to estrogen increases (51) (Fig. 3). Progesterone also stimulates PRL secretion (52). Maternal PRL originates from the maternal pituitary with small contributions from the decidua and fetal pituitary. Maternal decidua is responsible for increased PRL levels in the amniotic fluid (53). Maternal pituitary PRL secretion is stimulated by thyrotropin-releasing hormone (TRH), arginine, meals, and sleep as in nonpregnant women (54). Increased PRL secretion during pregnancy is important for the preparation of breast tissue for lactation, but the role of PRL in amniotic fluid is unknown.

Pregnancy induces long-term changes in PRL secretion. Pregnancy suppresses the secretion of PRL by the maternal pituitary permanently (55, 56).

Big big PRL is reported in a range of 8–38% of total PRL during pregnancy (57–59). Frequency of macroprolactinemia during pregnancy is reported as 2.9–3.8% due to anti-PRL autoantibodies (60, 61). Macroprolactinemia persists during pregnancy, and the PRL increment in macroprolactinemic women is less than that in normal pregnant women (62).

TRH–TSH axis

Although the appearance and distribution of thyrotropic cells are preserved, thyrotropin (TSH) secretion is altered during pregnancy (Table 1). 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 (63) (Fig. 4).

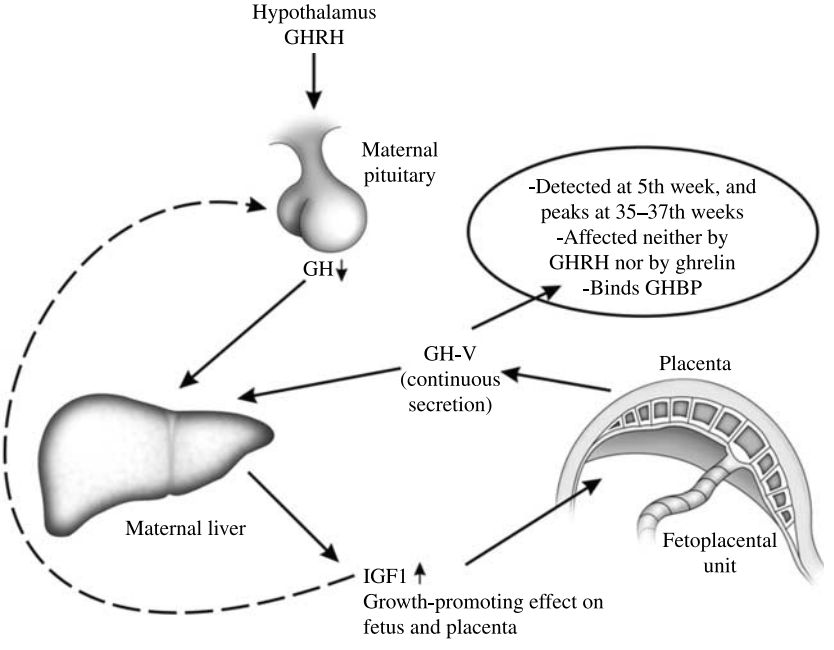

Figure 2 GH–IGF1 axis during pregnancy: the placenta secretes a variant of GH, which replaces pituitary GH for stimulating IGF1 production from the liver. Increased IGF1 inhibits pituitary GH secretion. (—, stimulation; – – –, inhibition; GH; GH-V, GH variant; IGF1; insulin-like growth factor 1).

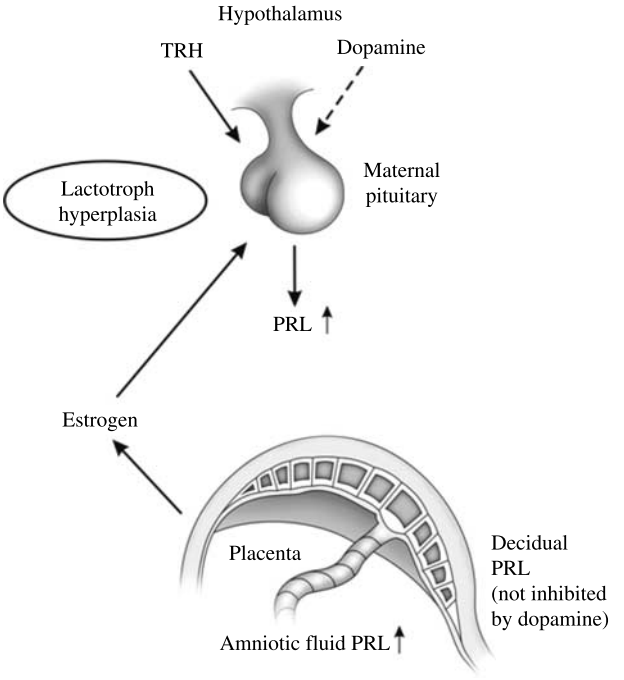

Figure 3 PRL axis during pregnancy: maternal PRL is increased during pregnancy due to estrogen-stimulated lactotroph hyperplasia with small contributions from decidual PRL. Maternal decidua is responsible for increased PRL in amniotic fluid. Unlike pituitary PRL, decidual PRL is not affected by TRH and dopamine. (—, stimulation; – – –, inhibition; TRH, thyrotropin-releasing hormone; T_4, thyroxine; TBG, thyroxine-binding globulin; hCG, human chorionic gonadotropin; PRL, prolactin).

Additionally, increased estrogen levels lead to a significant increase in thyroxine (T_4)-binding globulin (TBG) levels that reach a plateau after 12–14 weeks of gestation, and total thyroid hormone levels are concomitantly increased (64). There is a slight increase in serum concentrations of free T_4 during the first trimester, and they then decrease, but these changes are minimal and serum levels of free T_4 usually remain within the normal ranges for nonpregnant women (65). There is also a study which measured free tri-iodothyronine and free T_4 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 (66). The negative-feedback control of TSH is intact during pregnancy, and TSH concentrations are usually similar to those in nonpregnant women (63, 67, 68).

There is an increased requirement of T_4 during pregnancy, which is sustained until delivery (69). Therefore, the increased serum TBG cannot be the sole explanation for the increased demand for T_4. The increased requirement is also attributed to the placental degradation of T_4, transfer of T_4 from mother to fetus, and increased maternal clearance of T_4 (64).

Gonadotropin axis

Gonadotropic cells show decreased immunoreactivity for LH during pregnancy, which is fully established at 6 months and returns to normal at *postpartum* 11th month (6) (Table 1). Maternal serum gonadotropins start to decrease by 6–7 weeks of pregnancy and become undetectable in the second trimester. Pituitary FSH and LH synthesis are suppressed due to elevated sex steroids (17-β-estradiol and progesterone) and regulatory peptides (inhibin) during pregnancy (54). FSH and LH responses to GnRH stimulation are also decreased (70).

Posterior pituitary

Pregnancy is associated with a lowering of the set point for serum osmolality by about 10 mOsm/kg. The decrease starts by the first missed menstrual period and gradually decreases until the tenth week of gestation, which does not change later on (71). Serum sodium is decreased by about 4–5 mEq/ml due to this reset osmostat. On the other hand, placental vasopressinase is associated with increased vasopressin (AVP) degradation, which may unmask borderline diabetes insipidus (DI) or worsen DI during pregnancy (72).

The majority of DI cases (58%) deteriorate, 20% improve, and 15% remain the same during pregnancy. The increased glomerular filtration rate, which increases the requirement of AVP; changes in tubular sensitivity to AVP; degradation by the enzyme

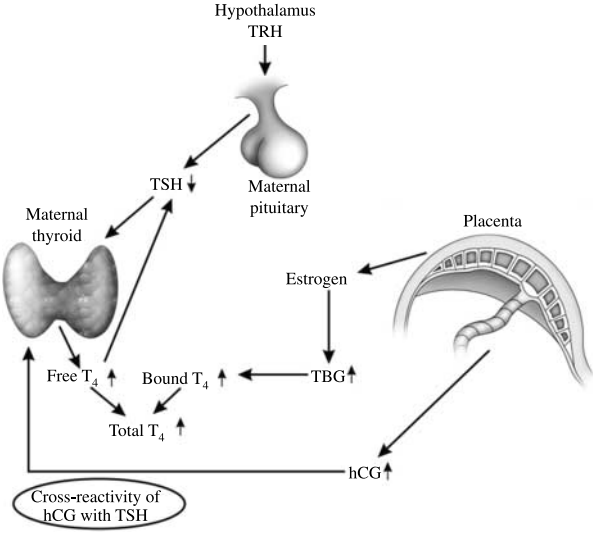

Figure 4 TRH–thyrotropin axis during pregnancy: due to the similarity of hCG with TSH, TSH level is decreased in the first trimester of pregnancy with a slight increase in free T_4, but after the first trimester, free thyroid hormones usually remain within the normal ranges. Estrogen increases TBG levels, which leads to an elevation in total T_4 levels. (—, stimulation; – – –, inhibition; TRH, thyrotropin-releasing hormone; T_4, thyroxine; TBG, thyroxine-binding globulin; hCG, human chorionic gonadotropin; PRL, prolactin).

vasopressinase; effects of increased glucocorticoids, progesterone, and T_4 on AVP; and the possible compression of posterior pituitary were thought to be responsible for the different effects of pregnancy on the progression of DI. In clinical practice, lactation may improve or may not change the course of DI (73).

Pituitary disorders and pregnancy

Cushing's disease and pregnancy

Pregnancy is rare in patients with Cushing's syndrome (CS) because of hypercortisolemia, hyperandrogenemia, and/or hyperprolactinemia, leading to impaired fertility (74, 75). The etiologies of CS are similar to those found in nonpregnant women in pregnancy, but benign adrenal tumors are the most frequent cause in contrast to nonpregnant patients. It is probably because of aberrant adrenal receptors for LH and hCG. Half of the reported gestational CS cases have adrenal causes, and about 40% are Cushing's disease (CD) (28, 76, 77). Cyclical CD due to an ACTH-producing pituitary adenoma with fluctuating ACTH levels was also reported (78).

Maternal and fetal morbidities are increased in pregnant women with CS. Gestational diabetes, hypertension, preeclampsia, eclampsia, congestive heart failure, and pulmonary edema are all related to these morbidities. Fetal loss such as spontaneous abortions, stillbirths, and early neonatal deaths are increased (79) besides premature birth in almost half of the cases (76, 80).

Diagnosis of Cushing's syndrome during pregnancy CS may be detected before or during pregnancy. The cases which are diagnosed during gestation have similarities to normal pregnancy such as weight gain, hypertension, glucose intolerance, and striae. In normal pregnancy, the striae are usually white in contrast to large purple striae in CS. Hirsutism and acne may indicate excessive androgen production during pregnancy. The presence of hypokalemia, muscle weakness, pathological fractures, and large purple abdominal striae are important clues for CS (81, 82). Diagnostic tests for CS become less reliable during gestation. Low-dose dexamethasone administration usually fails to suppress cortisol secretion during pregnancy, suggesting a reset of maternal feedback set point. Mean cortisol levels ranging from 4 μg/dl in the first trimester to more than 20 μg/dl in the second and third trimesters after low-dose dexamethasone administration are reported in the literature (83). According to the guidelines of diagnosis of CS, the use of a dexamethasone suppression test should not be preferred because of false positive results during pregnancy due to blunted response to dexamethasone (84).

Late-night cortisol <7.5 or 5 μg/dl or 50% of morning levels are considered to be normal, which can also be applied to pregnant patients. Since serum cortisol circadian variation is preserved during pregnancy, loss of circadian rhythm might be a clue for CS, but the nadir level for late-midnight cortisol is higher than that in the nonpregnant state. UFC has been suggested as the best choice for screening of CS during pregnancy (84). UFC levels are unchanged during the first trimester, but levels may be increased up to threefold in the second and third trimesters (20). UFC greater than three times the upper limit should be taken into consideration in the last two trimesters (84). The role of salivary cortisol for the diagnosis of CS during pregnancy needs to be determined.

Plasma ACTH levels can be used for differential diagnosis of ACTH- and nonACTH-dependent CS, taking into account the predominance of adrenal etiology and the physiological increase of ACTH during gestation (85). ACTH levels may not be suppressed in pregnant patients with adrenal CS, unlike in nonpregnant ones. This may be attributed to the production of ACTH by the placenta or stimulation of ACTH by placental CRH. Detectable ACTH levels may not exclude adrenal etiology.

A high-dose dexamethasone suppression test for distinction of CD and ectopic ACTH may be helpful. The HPA axis becomes resistant in the third trimester of pregnancy, and higher doses of CRH (2 μg/kg) are needed to evoke sufficient ACTH and cortisol response (28, 86, 87). CRH stimulation by 100 μg causes an increase in ACTH and cortisol in pregnant patients with CD (88).

Inferior petrosal sinus sampling should not be a routine investigation method because of radiation exposure and increased thrombotic events, although it has been used in a few pregnant patients with suspected CD. The direct jugular approach should be preferred to minimize radiation to the fetus (28, 88–90).

If CD is suspected, imaging studies can be used to localize the adenoma, but unfortunately CD is usually caused by a microadenoma, and the growth of the pituitary gland during normal pregnancy can mask the visualization of the microadenomas. Adrenal computerized tomography (CT) scans should be avoided, and pituitary MRI should be reserved for patients for whom pituitary surgery is planned (85).

Treatment of Cushing's disease during pregnancy Pregnancy may influence the course of CS in different ways, either exacerbating or ameliorating the disease (76, 79, 80, 91, 92). Unregulated placental CRH may be the cause of exacerbating hypercortisolemia during pregnancy, and it improves after parturition.

Due to the small number of reported pregnant women with CD, available data are not enough to compare the outcome of treated and untreated patients. While making a decision about treatment, the severity of hypercortisolemia and the stage of gestation are important factors. Treatment of CS may be considered if the increased fetal loss rates and premature labor are taken into account (91, 93). Early diagnosis and treatment of the disease are important to improve the outcome of both the fetus and the mother. Treatment of

choice for ACTH-secreting adenomas is transsphenoidal surgery, which has been performed successfully during the second trimester of pregnancy (28, 88, 92, 94). Radiotherapy is normally contraindicated during gestation, but pregnancy shortly after treatment by gamma-knife for CD with normal gestational course, despite high disease activity, is reported (95).

In severe CS, when surgery cannot be performed and the term is not close, medical treatment can be considered. Ketoconazole, metyrapone, and mitotane are the agents used in medical treatment of CS. Ketoconazole has been used in CS during pregnancy without untoward effects (28, 81, 96–98). Although metyrapone may cause adrenal insufficiency in the neonate, it has been used during pregnancy but not always with symptom control (99–104). Lindsay *et al.* reported 20 women receiving medical therapy (11 patients metyrapone; 3, ketoconazole; 3, cyproheptadine; 1, aminoglutethimide; and 2, mitotane) for CS usually starting in the second or third trimester (28). Eighteen of the patients had live births, and two infants whose mothers were treated with metyrapone died (99, 101). Intrauterine growth retardation, fetal hypoadrenalism and coarctation of aorta with metyrapone, and transient neonatal hypoglycemia with ketoconazole were reported in individual cases (28, 81, 100, 104). Mitotane during pregnancy is teratogenic and requires therapeutic abortion (105). If medical treatment is considered, metyrapone is recommended instead of ketoconazole due to its inhibitory effects on androgen synthesis (106).

There are limited data regarding the long-term outcome of CD following pregnancy, but management of CD during pregnancy by surgery usually results in remission, and sometimes, subsequent uneventful pregnancies may also occur (28).

Conclusion If CD is diagnosed during the first trimester, medical therapy should be considered according to the severity of hypercortisolemia until the removal of the tumor in the second trimester. Surgery is the treatment of choice for pregnant women with CD during the second trimester. For cases with delayed diagnosis late in the third trimester, medical treatment may be preferred, and the surgery may be postponed to the *postpartum* period. Metyrapone is the drug of choice for medical therapy. Patients treated for CD during pregnancy either by surgery or by medical therapy should be monitored and treated for possible adrenal insufficiency when necessary.

Acromegaly and pregnancy

Fertility is usually impaired in acromegaly due to altered gonadotropin secretion, which is caused by the destruction of gonadotroph cells or hyperprolactinemia, which occurs in about 40% acromegalic patients (107), and hyperandrogenemia (108, 109). The role of increased GH and IGF1 on gonadal impairment is less clear.

Diagnosis of acromegaly during pregnancy In pregnant acromegalic patients, pituitary GH secretion is not diminished, and IGF1 increases in the second trimester as in normal pregnancy. To diagnose acromegaly in pregnancy, specific RIAs for GH-V are required to differentiate pituitary and placental secretion of GH (108). IGF1 levels are less useful in diagnosis and the follow-up of acromegaly during pregnancy since its occurrence is also increased by GH-V in normal pregnancy (110). If acromegaly is suspected during pregnancy, definitive diagnosis is difficult, and treatment may be postponed to the *postpartum* period. The use of an oral glucose tolerance test for suppression of GH during pregnancy is not well established, although it has been used in some of the reports (108, 111, 112). Increased GH in response to TRH stimulation may also be observed during the course of gestation in acromegalic patients, whereas placental GH does not respond to TRH (110, 113). The increased, but highly pulsatile GH levels might be a clue for the diagnosis of acromegaly during pregnancy (110, 114).

Limited data are available about pregnancy in acromegaly. The series about acromegaly are summarized in Table 2.

Treatment of acromegaly during pregnancy The major concern about acromegaly during pregnancy is the potential tumor expansion leading to neurological and/or visual complications probably due to the growth-promoting effect of estrogens. Dopamine agonists can control the disease in 10% of acromegaly cases (115). Bromocriptine has been used in previously treated or untreated acromegalic patients during pregnancy (116–118). The drug will be more effective on tumors with GH and PRL cosecretion. There are no data regarding the use of cabergoline for acromegaly during pregnancy at least according to our knowledge.

Octreotide treatment used throughout pregnancy for different problems, such as nesidioblastosis, TSH-secreting pituitary adenoma, or acromegaly, seems to be feasible and safe (119–122), but octreotide is not registered during pregnancy. Octreotide can cross the placenta, and the receptors demonstrated on the placental membranes of octreotide-treated and untreated pregnant women displayed low affinity for octreotide, which may explain the lack of changes in GH-V and IGF1 concentrations during octreotide treatment (123). Octreotide has been used successfully in acromegalic pregnant patients until confirmation of pregnancy without any deleterious effect on the fetus (112, 124). Maternal–fetal transfer of octreotide has been detected in patients with acromegaly, and TSH-secreting adenoma without any effect on TSH, thyroid hormone, or IGF1 in the newborn (121, 125). Lanreotide has also been used in a pregnant woman without any side effects, but it was discontinued after confirmation of pregnancy (126).

Table 2 Summary of the series reported about acromegaly during pregnancy.

Series	Number of patients/pregn.	Time of diagnosis	Treatment during pregnancy	Acromegaly course during pregnancy	Gestational outcome	Fetal outcome
Colao *et al.* (1997) (132)	Six pts, ten pregn.	Four of six patients were diagnosed during pregn.	Two patients discontinued OCT after confirmation of pregnancy One of them continued OCT during whole pregnancy Others did not receive any treatment during pregnancy	GH and IGF1 were normalized only in the patient who continued OCT during whole pregnancy None of the patients had tumor growth	One abortion One was ongoing at the time of report	Seven infants were overweight One normal full-term infant whose mother was on OCT
Herman-Bonert *et al.* (1998) (108)	Four pts, seven pregn.	All patients were diagnosed before pregn.	One patient discontinued OCT after confirmation of pregnancy Others did not receive any treatment during pregnancy	Tumor enlargement was noted in one of the patients with previous history of two surgeries and gamma-knife	One was ongoing at the time of report One conception occured following ovulation induction	Six normal full-term infants
Cozzi *et al.* (2006) (133)	Six pts, seven pregn.	All patients were diagnosed before pregn.	Two patients discontinued OCT after confirmation of pregnancy One of them continued OCT during whole pregnancy Others did not receive any treatment during pregnancy	GH increased in one of the patients, remained stable in three, and increased in three of them IGF1 remained stable, close to the normal range in all patients Tumor enlargement was noted in one of the patients who refused surgery before pregnancy and was on OCT, but no compression signs were noted	No problems regarding gestation were noted	Seven normal full-term infants
Atmaca *et al.* (2006) (131)	Seven pts, nine pregn.	One of the patients was diagnosed at 29 weeks of gestation with PA	Two patients discontinued bromocriptine use after confirmation of pregnancy One patient underwent surgery Others did not receive any treatment during pregnancy	One of the patients was diagnosed at 33 weeks of gestation with visual loss and was operated for PA besides CS	Two IU fetal losses at 8 and 8.5 months One elective abortus (patient's will) and one therapeutic abortus in the patient who was on OCT Two gestational diabetes	Four normal full-term infants One transient neonatal jaundice

Pts, patients; pregn., pregnancy; OCT, octreotide; PA, pituitary apoplexy; IU, intrauterine.

Pegvisomant has been used in two pregnant patients with acromegaly until confirmation of pregnancy without untoward effects. Maternal IGF1 was controlled well, and transplacental passage of the drug was absent or minimal. So the effect on the fetal GH axis is unlikely, and there is no evidence of substantial secretion into breast milk (127, 128).

Since acromegaly itself has metabolic and cardiovascular complications, it may affect the mother and the fetus by causing diabetes mellitus, hypertension, and coronary artery disease (129). Pregnancy may lead to improvement of acromegaly as reported in three pregnancies of an acromegalic woman with uncontrolled disease probably due to the blocking effects of estrogen on IGF1 production in the liver. Despite increasing placental GH, IGF1 levels were lower than those in the nonpregnant state close to the normal range (130).

Follow-up of patients with acromegaly after parturition was reported by some authors. Six patients had recurrence shortly after parturition, and two of them were managed with octreotide and radiotherapy, three of them with octreotide, and one with cabergoline only (108, 131). Pituitary imaging studies performed after parturition did not reveal any tumor growth (128, 132, 133).

Conclusion Pregnancy should be considered in acromegalic women with amenorrhea before starting any treatment. If conception is planned, acromegaly should be treated first to prevent the potential growth of a tumor. If acromegaly is diagnosed during pregnancy, octreotide may be used in cases with compressive signs. Interruption of medical therapy during pregnancy is unlikely to affect the long-term outcome of acromegaly if the prolonged course of the disease is considered. Breastfeeding is not contraindicated for acromegalic women with uneventful pregnancies.

Prolactinomas and pregnancy

Prolactinomas are the most common cause of persistent hyperprolactinemia and account for 50% of the functioning pituitary tumors (134). After the use of bromocriptine as the first-line treatment in prolactinomas since the 1970s, pregnancies in patients lacking a previous history of surgery and growth of prolactinoma during gestation have been described. Women with prolactinomas who are on dopamine agonist therapy should be warned about the rapid restoration of fertility, sometimes before resuming the first menses. So when a woman with a PRL-secreting macroadenoma wishes to become pregnant, normalization of serum PRL and significant reduction in tumor volume are necessary in order to prevent the compression of vital structures during pregnancy (135).

In pregnant women with microprolactinomas, dopamine agonists can be stopped safely due to the low risk of clinically relevant tumor expansion (136, 137) (Table 3). So patients should be followed up monthly according to clinical symptoms such as headache and visual disturbance. Visual field examinations should be done each trimester. There is no need for periodical imaging of the prolactinoma during pregnancy, and PRL measurement is of little help.

Maximal pituitary proliferation, pituitary tumor-transforming gene mRNA, fibroblast and vascular endothelial growth factor expression are found to be increased under the effect of estrogen, and PRL levels and the size of prolactinomas are found to be decreased under the effect of antiestrogen treatment in rats (138). So pregnancy may lead to an increase in prolactinoma size. The risk of tumor growth in pregnant patients with macroprolactinomas is higher than that in those with microprolactinomas. Pregnancy should be avoided in these patients by nonhormonal contraceptive methods until tumor shrinkage occurs. Although the use of

Table 3 Summary of growth of prolactinomas during pregnancy.

Series	Patient number and characteristics	Symptomatic tumor growth (%)	Asymptomatic tumor growth (%)
Molitch (1985) (136)	Two hundred and forty-six patients with microprolactinoma without previous history of surgery or irradiation	1.6	4.5
Molitch (1985) (136)	Forty-five patients with macroprolactinoma with previous history of bromocriptine use before gestation	15.5	8.9
	Forty-six patients with macroprolactinoma with previous history of surgery or irradiation before gestation	4.3	
Musolino *et al.* (2001) (137)	Seventy-one patients with microprolactinoma with previous history of bromocriptine use before gestation	2.4	2.4
Musolino *et al.* (2001) (137)	Twenty-one patients with macroprolactinoma with previous history of bromocriptine use before gestation	37	17.7 (all macroprolactinomas)
	Thirty patients with macroprolactinoma with previous history of surgery before gestation	33	

bromocriptine and cabergoline during gestation does not cause problems, exposure of the fetus to these drugs should be minimized. The first trimester is the period in which teratogenicity from any drug is found most often, and the growth of a macroadenoma is the least. Therefore, it is recommended to stop the drug when pregnancy is confirmed (135). There is an advantage of cabergoline due to its prolonged action, and PRL levels may be suppressed up to 120 days after its withdrawal (139), but it may also be considered as a problem since the intrauterine exposure time of the fetus is increased for an additional one week or more weeks. Quinagolide can be used in hyperprolactinemic patients willing pregnancy until confirmation of pregnancy due to its short life (22 h) (140). Surgery before pregnancy is indicated in patients whose tumor does not respond to dopamine agonists or in those who developed tumor growth in previous gestations (141). The increased duration of treatment with dopamine agonists before conception might be a good prognostic factor for pregnancy (142).

There are two options for pregnant patients with macroprolactinoma. The first is to discontinue the dopamine agonist after confirmation of pregnancy with close follow-up. Monitoring should include screening for symptoms such as headache and visual problems, visual field examination every 2 months, and pituitary MRI without a contrast agent after the first trimester, which can be individualized for each patient. PRL assays may be useful if the levels are decreased in spite of the increasing tumor size, which may indicate apoplexy rather than tumor expansion. Monitorization may be preferable in patients with relatively small macroadenomas away from the optic chiasma. The second option is continuing dopamine agonist therapy throughout pregnancy. The second option may be preferred when the duration of dopamine agonist therapy before conception is short or when the tumor is outside intrasellar boundaries. If clinical signs of progression such as severe headache and visual field defects occur, an MRI without Gd should be performed, and then a dopamine agonist should be restarted if there is an increase in tumor size (143). If there is no response to dopamine agonist therapy, delivery may be the treatment of choice when the term is close. Transsphenoidal surgery can be performed on patients whose term is not close (144). Although good results have been reported with surgery, increased risk of spontaneous abortions should be kept in mind (145).

There is much experience of bromocriptine use during pregnancy. The incidence of abortions, ectopic pregnancies, or congenital malformations is similar in bromocriptine-using mothers and the general population (136, 146–149). One undescended testis and one talipes deformity were reported with the use of bromocriptine throughout gestation (147). Although most of the reported cases received bromocriptine during the first 4 weeks of pregnancy, no teratogenic effects have been demonstrated. Long-term follow-up of 64 children between 6 months and 9 years whose mothers had been treated with bromocriptine showed no adverse effects (150). Bromocriptine is the preferred dopamine agonist for prolactinoma during pregnancy, but since it crosses the placenta, it should not be continued if not necessary (151). Although the number of pregnancies is smaller in the studies, similar results are obtained with cabergoline (139, 152–158). Cabergoline may be an effective and safe alternative to bromocriptine during pregnancy with a good tolerance (159). Since the data regarding pergolide and quinagolide are limited, they should not be used in this setting during pregnancy. Ectopic pregnancy, miscarriages, and fetal malformations were reported during quinagolide usage (160). Morange *et al.* reported better tolerability and efficacy of quinagolide in pregnant patients with prolactinoma without any congenital abnormalities (161). For medical therapy of prolactinomas, vomiting may be a problem during the first trimester. If vomiting occurs within 2 h after bromocriptine use, patients may be advised to retake their medication.

The main goal of treatment during pregnancy is to maintain the adenoma away from the optic chiasma. There is no universally accepted target level for PRL. Low levels or levels within the normal range for physiological pregnancy may be the target (162). Despite the evidence that hypoprolactinemia may impair progesterone secretion from corpus luteum, marked hypoprolactinemia which may be caused by dopaminergic agents does not affect the spontaneous abortion rate. The women who are treated continuously with bromocriptine throughout pregnancy did not reveal any adverse influences on the course of pregnancy, breastfeeding, or development of their children (163).

Patients should be reassessed 2 months following delivery or cessation of lactation. After delivery, PRL levels may decrease or normalize (164, 165). Musolino and Bronstein reported *postpartum* decreases in PRL levels than in pregestational levels in 60% of microprolactinoma and 72% of macroprolactinoma patients (137). Similarly Bergh *et al.* reported a decrease in serum PRL in 50% and normalization of PRL in 8% of patients (166). Whether the improvement of hyperprolactinemia is due to autoinfarction of the adenoma or other mechanisms may be involved is not clarified yet. Pituitary imaging 2 months after the end of lactation is recommended in order to reevaluate the adenoma (162). Reduction in adenoma size after pregnancy in prolactinoma patients is also possible (141).

Patients who wish to breastfeed their infants should not be started on dopamine agonists since they will impair lactation. But patients who have to maintain dopamine agonists to prevent tumor growth should continue their treatment although lactation may be impaired (141). There are no data regarding increased tumor size due to lactation at least to our knowledge.

Conclusion Prolactinomas are common in females during reproductive age. Treatment of prolactinomas usually restores fertility and results in pregnancies. In microadenomas, due to the low risk of tumor growth, follow-up without treatment according to clinical symptoms can be considered. In macroadenomas, pregnancy should be planned after the control of tumor growth. Close follow-up or dopamine agonist treatment throughout pregnancy may be preferred depending on the patient. To minimize fetal risks, dopamine agonists should be commenced after the first trimester. Pregestational treatment length should be taken into consideration while making a decision about treatment. There is no need for periodical imaging of the prolactinoma during pregnancy, and PRL measurement is of little help. Breastfeeding may be allowed since the data are not enough to be against it. Patients who have to maintain dopamine agonists to prevent tumor growth should continue their treatment although lactation may be impaired.

TSH-secreting adenomas and pregnancy

There are case reports of TSH-secreting adenomas during pregnancy. Transsphenoidal surgery was performed in a 39-year-old female who developed visual loss at 27 weeks of gestation under bromocriptine and antithyroid treatment (167). Octreotide has also been used in pregnant women with TSH-oma for different periods of time (119, 168). As with other pituitary tumors, patients with TSH-omas also need close follow-up for mass-related symptoms of tumor.

Sometimes thyroid hormone resistance may lead to a diagnostic dilemma due to tumor-like enlargement of the pituitary gland during pregnancy (169).

Gonadotropin-producing pituitary adenomas and pregnancy

Gonadotropin-producing pituitary adenomas are very rare in women of reproductive age, and there are only a few case reports regarding pregnancy since it causes hypogonadism. It may lead to ovarian hyperstimulation syndrome (170, 171). These tumors may be sensitive to bromocriptine via D2R which was demonstrated in the adenoma. Ovarian size can be normalized, and spontaneous conception may be possible following treatment with bromocriptine (171).

Nonfunctioning pituitary adenomas and pregnancy

Nonfunctioning adenomas are not common during pregnancy since fertility is usually impaired. Tumor debulking is indicated in patients who wish to become pregnant (141). Pregnancy rarely increases the size of clinically nonfunctioning pituitary adenomas. Enlargement of the pituitary adenoma may be due to tumor growth, infarction, or hemorrhage of the tumor during pregnancy. Sometimes apoplexy of pituitary adenoma with visual field loss may be the first sign during pregnancy (172). The risk of visual field defect is increased in patients whose tumor is more than 1.2 cm in size (143). Increased pituitary gland size due to lactotroph hyperplasia may contribute to the mass effect of pituitary adenomas during pregnancy with a rapid response to bromocriptine (173). Surgery might be considered during the second trimester if needed. Dopamine agonists or conservative management may be preferred in the third trimester.

Craniopharyngiomas and pregnancy

Craniopharyngiomas usually result in panhypopituitarism due to the tumors themselves or the treatment, so pregnancy is rarely reported with these tumors. Fertility may be achieved with gonadotropin treatment (174). The tumors may increase in size during pregnancy causing visual problems, which usually require surgical intervention (175–177). DI, which is a common symptom of these tumors, can be seen during pregnancy. Hypopituitarism and DI may be the presenting features, but visual deterioration is common with these tumors. Surgery is the treatment of choice if mass effects occur (178, 179). Preservation of fertility following excision of craniopharyngioma during pregnancy is also reported (180).

Sheehan's syndrome

SS is described as *postpartum* hypopituitarism due to pituitary necrosis caused by severe hypotension or shock secondary to massive bleeding during or just after delivery. The exact pathogenesis and natural history are not understood well (Fig. 5). The clinically significant SS is not very common due to the developed clinical care today (181). But it is found to be the sixth leading cause of GH deficiency among 1034 GH-deficient patients (182). So it seems that it is not as rare as it is thought to be.

The role of autoimmunity needs to be established in the pathogenesis of SS. Patients with SS do not show increased prevalence of anti-thyroid peroxidase (TPO) positivity compared to controls, but pituitary autoantibody positivity is significantly higher (183–186), although not proven by other studies (187). Recently, antihypothalamus antibodies were found in 40% and antipituitary antibodies in 35% of SS patients. So an autoimmune process involving both the hypothalamus and pituitary gland may contribute to delayed pituitary dysfunction in SS patients (188). Although most of the patients with SS reveal an empty or a partially empty sella with a normal sella size (189, 190), a relatively small sella may also be a risk factor for the development of SS (189, 191, 192).

The criteria suggested for the diagnosis of SS are as follows: i) typical obstetric history of severe *postpartum*

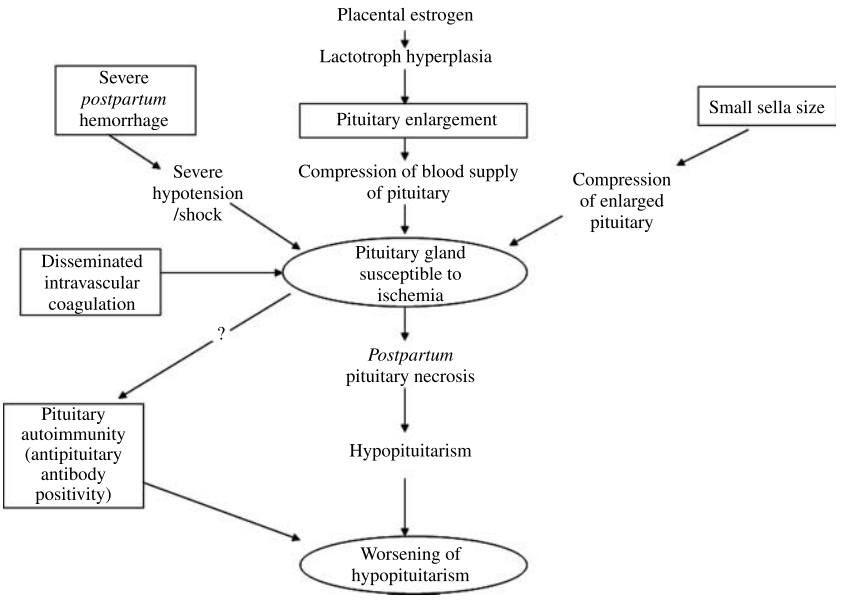

Figure 5 Pathogenesis of Sheehan's syndrome.

vaginal bleeding; ii) severe hypotension or shock for which blood transfusion or fluid replacement is necessary; iii) failure of *postpartum* lactation; iv) failure to resume regular menses after delivery; v) varying degrees of anterior pituitary failure and partial or panhypopituitarism; vi) empty sella on CT scan or MRI (193).

The symptoms of anterior pituitary dysfunction are usually nonspecific such as weakness, fatigue, and anemia, but severe pituitary insufficiency resulting in coma and death may also be seen (193, 194). *Postpartum* pituitary apoplexy should be kept in mind in patients with hypotension and shock who have a bleeding history during the peripartum period. The mean duration between *postpartum* hemorrhage and clinical manifestations varies from 1 to 33 or 2 to 40 years without a correlation between severity of hypopituitarism and degree of empty sella (195, 196). SS detected in the acute phase is rare (197–199), but most of the SS cases are diagnosed during the early *postpartum* period in the western countries.

Hypopituitarism due to SS may be of different degrees. Panhypopituitarism is reported in SS in between 55 and 86% of patients in different studies (196, 200–202). GH deficiency is reported in all patients with SS (196, 202–204). It is characterized by more severe GH deficiency than other types of hypopituitarism (205). Although failure of *postpartum* lactation is a classical symptom of SS, hyperprolactinemia is also reported (206, 207). Adrenocortical insufficiency due to SS results in hypotension, orthostatic hypotension, tiredness, hypopigmentation, and sometimes adrenal crisis under stressful conditions. Secondary hypothyroidism is also very common in SS, and is usually less severe than primary hypothyroidism. Facial edema and periorbital puffiness are usually not seen in SS. Skin is hypopigmented due to ACTH deficiency, and fine wrinkling, which is a remarkable finding of SS, can be seen due to long-term GH and estrogen deficiency. Although atrophy of posterior hypophysis is reported in over 90% of patients with SS, DI is very rare (208–210). Partial DI is reported to be more frequent than expected (211). The thirst center may be affected by ischemic damage and the osmotic threshold for thirst is increased in patients with SS (212).

Basal hormone levels may be enough in patients with typical histories, but most of the patients need more detailed investigation including dynamic pituitary function tests. Pituitary MRI is the most sensitive method of imaging, but CT may also be helpful. In the early stages, the pituitary gland shows nonhemorrhagic enlargement. Subsequently, the gland atrophies, and an empty sella develops. There is no correlation between the degree of *postpartum* pituitary necrosis and the severity of clinical expression (213).

Subsequent pregnancies are reported following SS (195, 214–220). Pregnancy might improve hypopituitarism by stimulating the pituitary remnant (221). Recovery of thyrotropic functions after spontaneous pregnancy in SS is reported in a case (222).

Differential diagnosis of SS should be made from spontaneous infarction of pituitary adenoma due to hypotension during or after delivery. Both are characterized by an enlarged pituitary gland in the early stage and varying degrees of hypopituitarism, but decompressive surgery may be necessary for apoplexy of a pituitary adenoma, which is contraindicated in SS. LyH should also be ruled out.

Treatment of SS includes replacement of deficient hormone(s). Glucocorticoid replacement may be lifesaving in severe pituitary insufficiency. During

maintenance treatment, the minimum dose of glucocorticoid that corrects the clinical symptoms should be given. L-T_4 is the treatment of choice for TSH deficiency. Serum levels of free T_4 and clinical findings help to adjust the drug dosage. Hypogonadism should also be treated with estrogen and progesterone in premenopausal women. For women who wish to become pregnant, ovulation induction might be a choice. GH replacement may be useful for improvement of the lipid profile, waist circumference, visceral fat, body composition, carotid artery intima-media thickness, and quality of life (201, 223, 224). GH replacement also has modulatory effects on sebum content of the skin in SS patients (225). GH deficiency has been shown to induce sleep-disturbing effects in SS, but GH replacement was ineffective to reduce these abnormalities (226).

Lymphocytic hypophysitis

LyH is an autoimmune disorder characterized by lymphocytic infiltration and destruction of the pituitary gland leading to various degrees of pituitary dysfunction and is associated with other autoimmune disorders. Lymphocytic adenohypophysitis (LAH) is more common in females and is characterized by anterior pituitary dysfunction. Lymphocytic infundibuloneurohypophysitis is characterized clinically by DI and characteristic MRI findings. Lymphocytic panhypophysitis involves both anterior and posterior pituitary (227).

LyH affects females more frequently than males (228). About 55–57% of females with LAH presented during pregnancy or *postpartum* with a predilection to the last month of gestation and the first 2 months *postpartum* (229–232). Earlier presentations in the first or second trimester of pregnancy are also reported (233, 234). LyH does not have adverse effects on the fetus or gestational outcome. Maternal mortality during labor is reported in a case (235). The striking temporal association of pregnancy and LyH is not clarified yet, but there are possible explanations, which are as follows: i) pregnancy may unmask a latent pituitary insufficiency and lactotroph hyperplasia may contribute to compression signs caused by LyH, both resulting in earlier diagnosis during gestation (236, 237). ii) The increased size of pituitary gland, which may lead to the release of pituitary antigens, may be one of the reasons for autoimmune hypophysitis. iii) The pituitary gland may become more accessible to the immune system during pregnancy due to hyperestrogenemia, which changes the pattern of pituitary blood flow and derives more from systemic blood and less from portal circulation (238). iv) Pituitary antibodies are shown to target a 49 kDa cytosolic autoantigen, α-enolase, and react with both pituitary and human placental tissue, explaining the relationship between LyH and pregnancy (239, 240). Experimental LyH in rats has shown that the major antigens are GH, TSH, and LH (241).

Women presenting during pregnancy or the *postpartum* period usually manifest with symptoms of hypopituitarism and/or symptoms of mass lesion such as headache and visual field defects. Mild hyperprolactinemia and DI may also be found (129). They can also be misdiagnosed as SS when they occur in the *postpartum* period. The diagnosis of LyH should be considered, especially in the absence of a history of obstetric hemorrhage, but LyH diagnosed clinically during gestation, which is complicated by *postpartum* hemorrhage, is also reported (242). In contrast to SS, ACTH is the first hormone to be lost, and hyperprolactinemia is not as uncommon as SS. Hyperprolactinemia affects about one-third of the patients with LyH. Several causes have been suggested for hyperprolactinemia: stalk compression or the inflammatory process itself altering the inhibitory effect of dopamine on PRL or the release of hormones into the bloodstream from destructed tissue or PRL-stimulating antibodies (243–245). Hypoprolactinemia manifested by the inability to lactate after pregnancy may also be seen with LyH (186, 237, 246).

Diagnosis of LyH is pathological, but imaging studies, especially pituitary MRI, are also very helpful. Diffuse thickening of the pituitary stalk, enhanced contrast enhancement of the gland, and loss of the neurohypophyseal 'bright spot' can be seen on MRI (247, 248). LyH can easily be mistaken for a pituitary adenoma and referred for surgery (249). Symmetrical pituitary enlargement, thickened stalk without deviation, uniformly flat sellar floor, appearance of dural tail, which represents the contrast enhancement of dura adjacent to the pituitary, and loss of the 'bright spot' of neurohypophysis are the clues for differentiation from pituitary adenoma (228). The radiological findings of LyH and SS early in the *postpartum* period may be confusing, and the appearance of an empty sella in the later period can also be seen in LyH, which is typical for SS (250–253) (Fig. 6). Pituitary antibodies may be helpful for suspected cases of LyH presenting with an empty sella. But it has also been reported that autoimmunity *per se* may not be significantly linked to the occurrence of a primary empty sella (254).

History of previous pregnancies does not increase the risk of developing LyH in subsequent pregnancies. Pregnancies may occur following a history of LyH either spontaneously or following ovulation induction (237, 255–258).

Treatment of LyH consists of replacement of deficient pituitary hormones; surgery is preserved for cases with visual impairment or neurological impairment. Bromocriptine has been used in hyperprolactinemic patients with various results with improvement in visual fields (231). Corticosteroids can be used since LyH is an autoimmune disease. Reusch *et al*. tried a short course of dexamethasone in a pregnant woman because of visual field defects due to a pituitary mass. The patient underwent partial hypophysectomy for decompression since there was a rapid progression of visual field defects

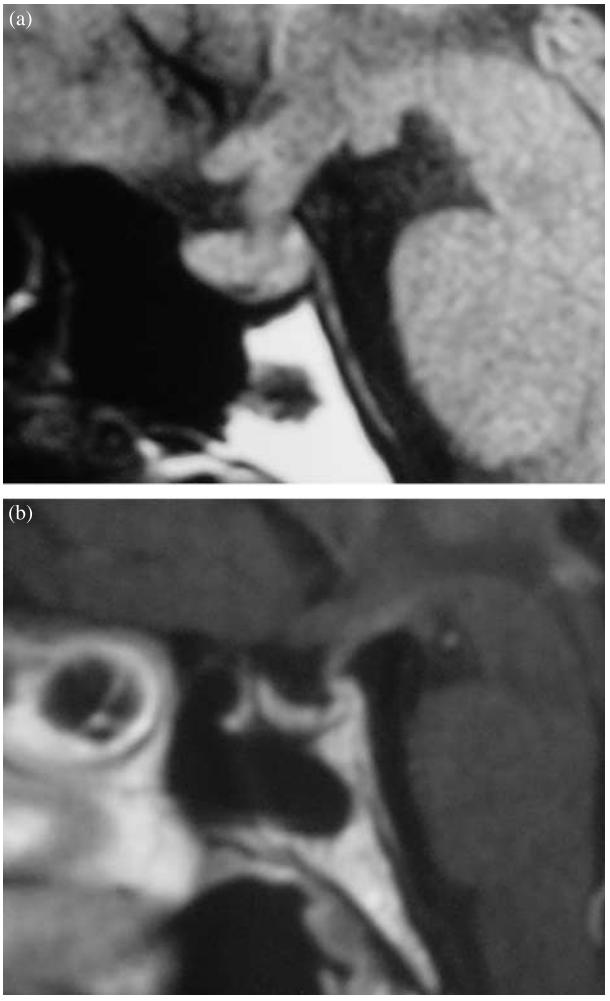

Figure 6 (a) The precontrast sagittal section of pituitary MRI demonstrates thickened pituitary stalk and loss of 'bright spot' of the neurohypophysis in a case of lymphocytic hypophysitis, and (b) the postcontrast sagittal section of pituitary MRI demonstrates empty sella 9 years after the diagnosis of lymphocytic hypophysitis (reproduced from Karaca *et al.* 2009) (251).

while the patient was on glucocorticoid therapy, and the pathology confirmed the diagnosis of LyH. The authors suggested that the dosage and duration of steroids were ineffective (259). There is no consensus for the dose and length of treatment with corticosteroids, but high doses are usually preferred. The management of LyH during pregnancy should be conservative unless progressive visual deterioration or other mass effects occur. The data are limited regarding surgery or therapeutic doses of steroids for LyH during pregnancy (233, 257).

Hypopituitarism and pregnancy

The introduction of ovulation induction after the 1960s led to normal fecundity in women with hypopituitarism. In the earlier reports, a high rate of spontaneous abortion and maternal mortality was recorded with little information regarding fetal outcome of pregnancies (218, 260, 261). More detailed studies were carried out later. Twin pregnancies had poorer outcomes, which is attributed to incomplete preparation of the uterus before pregnancy leading to poor placental function. Twin pregnancies should be avoided in this particular group of patients despite increased cost, and more attention should be paid to the preparation of the uterus with estrogen and growth hormone for gestation (262). In hypopituitary patients, the pregnancy rate is reported as 47% and birth rate as 42% (263). The ovulation and conception rates are higher, and spontaneous miscarriage rates are lower in isolated hypogonadotropic hypogonadism (HH) cases (264). Uterine size is reported to be similar in HH and hypopituitarism (265). Therefore, uterine size alone cannot explain the poorer outcome of patients with hypopituitarism. Probably, associated pituitary hormone deficiencies might play a role.

There are much more data regarding isolated GH deficiency than those regarding isolated ACTH and TSH deficiencies. An intact GH–IGF1 axis is not always essential for normal fertility, but it has been established that GH deficiency leads to difficulties in conception and subfertility (266). The use of GH in GH-deficient patients increases ovarian sensitivity to endogenous gonadotropins (267), but the use of GH has not proven to be useful in patients with intact pituitary function (268). GH treatment has been used successfully in a GH-deficient patient during pregnancy (269). Although GH deficiency is reported to result in uneventful pregnancies (266, 270–272), its use during pregnancy is not approved. GH therapy during pregnancy in GH-deficient women might be important for placental function and fetal growth, especially before and during conception and in the early weeks of gestation. It becomes less important in the later stages of pregnancy because there is a progressive rise of GH after the 20th week of pregnancy with decrement in pituitary GH in maternal serum (47). GH was suggested to improve gonadotropin hormonal action in follicular development, which could be necessary in eugonadal patients with GH deficiency (273). Gestational GH therapy in the first two trimesters of pregnancy was reported to be safe for the mother and the fetus without important adverse events and obstetric complications (274). So fertilization problems and early gestational complications such as abortions and miscarriages can be prevented by use of GH in GH-deficient women either in isolated deficiencies or accompanied by other hormone deficiencies.

Adrenal insufficiency is associated with increased morbidity and mortality during pregnancy if undiagnosed or left untreated (275). However, it may be difficult to recognize adrenal insufficiency during pregnancy. Signs and symptoms such as emesis, fatigue, and mild hyponatremia may be ignored since they can also be seen in a normal pregnancy. Pregnancy is a state of physiological hypercortisolism where CBG and

cortisol levels increase. An insulin tolerance test and metyrapone tests are contraindicated during pregnancy, and the CRH test is useless due to its placental production (86). Standard ACTH stimulation test should be preferred during pregnancy, although cut-off values are not determined to diagnose adrenal insufficiency in pregnant women. Suri *et al*. demonstrated nearly twofold elevations in total serum cortisol and salivary cortisol and eightfold elevations in serum aldosterone in the late gestation than in the non-pregnant stage. Increased adrenal response to ACTH despite increasing basal cortisol and aldosterone was observed as the pregnancy progressed. They suggested salivary cortisol to be more consistent and generalizable than total serum cortisol (276). Hydrocortisone or prednisolone may be preferred to dexamethasone for the treatment of maternal adrenal insufficiency (277, 278). Patients on glucocorticoid replacement may need to increase their hydrocortisone dose by 50% during the last trimester of pregnancy. By the start of the labor, the hydrocortisone dose should be increased to stress doses till 48 h *postpartum* (279, 280). Glucocorticoids may pass to breast milk, but the amounts are insufficient to affect neonatal adrenal functions (281).

Central hypothyroidism is characterized by low levels of serum free T_4 and TSH, but in most of the young patients, TSH may be normal, which is explained by reduced bioactivity of TSH, perhaps due to increased glycosylation of the molecule. Replacement with L-T_4 by adjusting the dose to keep free T_4 in the upper half of the normal range for the age is recommended (282). There are no reliable trimester-specific ranges for TSH, but levels of 0.2–2.5 mU/l are considered to be the normal range for pregnant women. Women with known hypothyroidism before pregnancy should increase the L-T_4 dose by 25–50% as early as possible, ideally by the fourth week of gestation (69). Approximately one-third of the maternal thyroid hormone crosses to the fetus, and it plays an important role in fetal neurodevelopment in the first half of pregnancy prior to fetal pituitary–thyroid axis development (283).

Mild DI may worsen in pregnant patients, and asymptomatic women may become symptomatic during pregnancy. Patients treated with pitressin tannate oil and lysine AVP spray may also experience such worsening, but not with desmopressin since it is not degraded by vasopressinase (284–286). Desmopressin seems safe during pregnancy, except for a small risk of increased uterine contractility due to its oxytocin-like structure and activity. However, this effect is more prominent during i.v. use rather than during nasal use (287). Since desmopressin is transferred to breast milk in little amounts and gastrointestinal absorption is poor, breastfeeding does not affect water metabolism of the infant (284–286).

Gestational DI is a rare endocrinopathy due to excessive vasopressinase activity. It is categorized into three groups: AVP resistant and dDAVP sensitive, AVP and dDAVP resistant (nephrogenic), and AVP and dDAVP sensitive (central). Besides placental vasopressinase activity, transient liver dysfunction may decrease the degradation of vasopressinase in the liver. This may explain the association of acute fatty liver of pregnancy and HELLP syndrome (288–291). Therefore, women developing DI late in gestation should be screened for liver function abnormalities.

Primary empty sella is reported rarely during pregnancy since it is associated with infertility due to hypogonadism or pituitary hormone deficiencies. There are case reports of women treated for HH or GH deficiency in eugonadism resulting in successful pregnancies (273, 292, 293).

Conclusion Hypopituitarism during pregnancy should be managed carefully. Patients treated for hypoadrenalism and hypothyroidism may need to increase their replacement doses during gestation. The growth hormone is not replaced routinely during pregnancy, but for planned pregnancies, GH may be used until confirmation of pregnancy, which helps preparation of the uterus for conception and results in better fertilization results. Asymptomatic DI may become symptomatic during pregnancy, and dDAVP dose may need to be increased.

Conclusion

The anatomy and physiology of the pituitary gland are almost completely altered during pregnancy. For better understanding the mechanisms of both the anatomical and the physiological changes of the pituitary and pituitary diseases during pregnancy, *in vivo* studies with larger numbers are required. Multicenter studies and databases recording pregnant patients with pituitary disorders might help to make consensus statements.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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