

## Review Article

# Hypopituitarism and successful pregnancy

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**Abstract:** Hypopituitarism is a disorder characterized by the deficiency of one or more of the hormones secreted by the pituitary gland. Hypopituitarism patients may present the symptoms of amenorrhea, poor pregnancy potential, infertility, and no production of milk after delivery. Successful pregnancy in hypopituitarism patient is rare because hypopituitarism is associated with an increased risk of pregnancy complications, such as abortion, anemia, pregnancy-induced hypertension, placental abruption, premature birth, and postpartum hemorrhage. Hypopituitarism during pregnancy and perinatal period should be managed carefully. The hormone levels should be restored to normal before pregnancy. GH and HMG-hCG are combined to improve follicular growth and the success rate of pregnancy. Hypopituitary patients must be closely monitored as changes may need to be made to their medications, and serial ultrasound measurements are also necessary for fetal growth assessment.

**Keywords:** Hypopituitarism, assisted reproductive techniques, pregnancy, hormone replacement

### Introduction

Pituitary gland is the most important endocrine gland in the body, and composed of adenohypophysis (anterior pituitary) that secretes gonadotropins (FSH and LH), TSH, ACTH, GH, and prolactin (PRL), and neurohypophysis (posterior pituitary) that stores antidiuretic hormone (ADH) and oxytocin released in the hypothalamus. These hormones play important roles in a wide variety of physiological processes, including metabolism, growth and development, and reproduction. Hypopituitarism is a disorder characterized by the deficiency of one or more of the hormones secreted by the pituitary gland. It has been suggested that damage to > 50% of pituitary gland may inhibit the secretion of anterior pituitary hormones, which in turn may affect a variety of target organs, including ovary, thyroid gland, and adrenal gland. The deficiencies of growth hormone (GH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are the most commonly encountered [1], whereas the deficiencies of adrenocorticotropic hormone (ACTH) and/or thyroid-stimulating hormone (TSH) are the least [2]. Therefore, it is still possible for patients with partial necrosis of anterior pituitary to have a normal ovulatory function, and even to achieve

pregnancy. Hypopituitarism is associated with an increased risk of pregnancy complications, such as abortion, anemia, pregnancy-induced hypertension, placental abruption, premature birth, and postpartum hemorrhage [3-5]. The advance of assisted reproductive techniques makes it possible to improve the pregnancy rate in hypopituitary patients. This highlights the need for an accurate assessment and treatment of this disease during pregnancy and perinatal period. The common types of hypopituitarism include Simmonds' syndrome, also referred to as Sheehan's syndrome that occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage, and pituitary dwarfism which is characterized by small stature but normal body proportions due to growth hormone deficiency in childhood.

Dökmetaş et al. [6] investigated the clinical characteristics of Sheehan's syndrome in 20 patients, and found that hypopituitarism due to Sheehan's syndrome could be of different degrees of severity, ranging from partial failure to panhypopituitarism. Panhypopituitarism has been reported to occur in between 55% and 86% of patients with Sheehan's syndrome, and almost all of these patients have GH deficiency. The most common causes of hypopituitarism

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are pituitary adenomas and postpartum hemorrhage, the clinical manifestations of which vary considerably, depending on the severity of hormone deficiency and the atrophy of target glands. Patients may have isolated or combined pituitary hormone deficiencies, and impairment of hormone secretion usually occurs in the order of gonadotropin, thyroid hormone, and adrenocorticotrophic hormone. Patients with hypogonadism may present symptoms of atrophic breast, amenorrhea, infertility, and no production of milk after delivery. In recent years, the rapid development of endocrinology and imaging techniques contributes significantly to the detection and treatment of pituitary tumors. However, due to the increasing incidence of hypopituitarism in young adults who want children, the preparation and perinatal treatment of hypopituitarism have become a topic of interest.

### **Effects of hypopituitarism during pregestational, gestational, and postnatal period**

Hypopituitary patients may present the symptoms of amenorrhea, poor pregnancy potential, and infertility. In addition, hypopituitarism has been reported to be associated with an increased risk of pregnancy complications, including high rate of abortion during early gestation and postpartum uterine inertia, thus leading to postpartum hemorrhage and poor pregnancy outcomes. Idris et al. [7] retrospectively studied 167 pregnancies managed in the antenatal endocrine clinic, and showed that the cesarean section rate was significantly higher in hypopituitary patients (28.7%) than in normal local women (18%).

Breastfeeding in the postpartum period depends to a great extent on the PRL level of the mother. Although failure of milk production is a typical symptom of Sheehan's syndrome, hyperprolactinemia has also been reported in patients with Sheehan's syndrome [1]. PRL deficiency is common in panhypopituitary patients [8]. Hyposecretion of PRL can lead to failure of milk production in the postpartum period; on the other hand, hypersecretion of PRL can lead to galactorrhea and nipple tenderness, neither of which is suitable for breastfeeding. Thus, hypopituitary patients generally do not have sufficient milk production to breastfeed their babies. In a retrospective study of 18 pregnancies in 9 hypopituitary patients, Overton et al.

[4] found that only one patient could breastfeed her baby.

Maternal thyroid deficiency may be detrimental to fetal brain development [9], and the infants could develop respiratory distress syndrome and have a high risk of cognitive disorders. Lazarus et al. [10] showed that perinatal thyroid dysfunction caused a significant reduction in body weight and height, delayed neurodevelopment, and depression-like behaviors of the infants. This is because that approximately one third of maternal thyroid hormone is delivered 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 [1]. Alexander et al. [11] showed an association between gestational hypopituitarism and impaired intellectual and cognitive development in offspring, and Wada et al. [12] also showed irreversible damage to the auditory system functions caused by perinatal hypothyroidism in rats.

### **Treatment of hypopituitarism**

#### *General treatment*

Replacement of deficient hormones remains the main treatment modality for hypopituitarism, and the order of treatment is glucocorticoid, thyroid hormone, sex hormone, and growth hormone. In general, thyroid hormone replacement should be initiated two weeks after glucocorticoid replacement, and it is advisable to begin with low dosage to prevent Addisonian crisis.

#### *Preparation before pregnancy*

Adult hypopituitary patients with hypogonadism should also receive hormones to maintain the secondary sex characteristics and uterine reproductive function. Artificial cycle treatment could stimulate the proliferation of endometrium and vaginal epithelium. It also allows the vaginal superficial cells to be epithelialized, and leads to increase in intracellular glycogen. The breakdown of glycogen to lactic acid is expected to be beneficial for vaginal self-cleaning and maintenance of secondary sex characteristics. Thus, sequential replacement of estrogen and progesterone is a viable method to promote uterine development and prepare for pregnancy. The hormone levels should be restored to

normal before pregnancy. High-dose estrogen and GH could improve the prognosis of hypopituitarism, and GH is helpful for the preparation of uterus and conception [1]. However, in hypopituitary patients with hyperprolactinemia, it is desirable to reduce the prolactin level to normal prior to the artificial cycle treatment to induce ovulation. Patients can be treated with human menopausal gonadotropin (HMG) and human chorionic gonadotropin (hCG) during preparation for pregnancy. Thomas et al. [8] showed that the combination of GH and HMG-hCG promoted follicular growth and improved the success rate of pregnancy.

### *Assisted reproductive technique*

Gonadotropin treatment can successfully induce follicle formation in most hypopituitary patients, but higher doses of gonadotropins are required for stimulation of follicular growth in these patients as compared with other causes of anovulation [13]. Some patients respond poorly to HMG-hCG protocol, probably due to the diminished ovarian reserve in these patients [14]. Pulsatile gonadotropin releasing hormone (GnRH) appears to be ineffective in the treatment of pituitary gland diseases [4], thus patients with hypopituitarism and gonadotropin deficiency can be treated with hormones with LH activities to allow for an adequate response to estrogen. Thomas et al. [8] also proposed to use HMG and recombinant FSH (including FSH and LH) to induce ovulation. If the hypopituitary patients respond poorly to traditional ovulation induction treatment, GH replacement can be applied prior to the ovulation induction [5]. A panhypopituitary female with poor response to gonadotropin took GH replacement for 4 months until the serum level of insulin-like growth factor-I (IGF-I) was normalized, then she began ovulation induction with gonadotropins and transdermal estradiol and become pregnant [14]. Another 31-year-old nulliparous woman with hypopituitarism and GH deficiency took GH replacement for 5 months prior to ovulation induction with HMG, ultimately resulting in normalization of IGF-I levels and successful pregnancy [15]. It has also been reported that a woman with adult growth hormone deficiency (AGHD) became pregnant after GH treatment [8]. Kitajima et al. [16] reported that the application of HMG-hCG successfully induced ovulation and pregnancy in a patient with normal serum GH and IGF-1.

The mechanisms of GH responsible for the improved pregnancy outcomes may be that: (1) GH can stimulate follicular growth and maturation, and it may also facilitate ovulation by increasing the sensitivity of ovarian response to gonadotropins, such as LH and FSH, and by reducing the rate of apoptosis in preovulatory ovarian follicles, which is thought to be IGF-I mediated, while GH has no such effect in pregnant women with normal pituitary function [17]; (2) GH/IGF-1 has a role in fertility disorders caused by pituitary hormone and gonadotropin deficiencies. GH/IGF-1 signaling transmission is important in patients with infertility or difficulty in conception caused by GH deficiency; and (3) GH/IGF-1 can improve egg fertilization, and thus helps to improve infertility due to fertilization problems [1, 13, 17]. Thus, GH should be used to normalize the IGF-1 and/or GH level to improve the success of pregnancy prior to ovulation induction.

### **Treatment during pregnancy**

The symptoms can be improved or even eliminated in some hypopituitary patients after pregnancy due to the partial or complete compensation of the function of pituitary gland, and thus it does not necessarily need hormone replacement therapy. This can be attributed to the fact that the physiological changes during pregnancy stimulate the proliferation of residual pituitary gland and abundant blood supply, leading to the improvement of pituitary function and eventually disappearance of clinical symptoms. It has been suggested that placenta could compensate for the endocrine function of pituitary gland, thus the symptoms may reappear after delivery. Hypopituitary patient with LH deficiency could receive luteal support with micronised progesterone administered intravenously, orally, or vaginally until the 12th week of gestation to avoid early pregnancy loss (placenta can produce sufficient amount of progesterone to maintain early pregnancy) [8].

A patient with Sheehan's syndrome and anterior pituitary insufficiency became pregnant spontaneously, and her thyrotropic function recovered after delivery [18]. A large amount of thyroid hormone and adrenaline are needed to maintain maternal and fetal endocrine function, thus hypopituitary patients should be closely monitored for hormone levels during pregnancy, and it is crucial to adjust the dose of

hormone replacement accordingly. Kitajima et al. [16] reported that a hypopituitary woman with hyperprolactinemia was treated with mes-tranol and dihydroprogesterone for luteal support until the 8th week of gestation. Thus, close monitoring during pregnancy appears to be mandatory in hypothyroid women.

A great amount of thyroid hormone is needed to meet maternal and fetal need during pregnancy, thus serum TSH and free thyroxine (FT<sub>4</sub>) measurements are mandatory in pregnant patients, and an increase in daily doses of L-T4 is necessary to maintain FT<sub>4</sub> at a high level (> 19.3 pmol/L; normal range, 10.3-25.8 pmol/L) [8, 19]. Wang et al. [20] retrospectively studied the perinatal care, treatment, and pregnancy outcomes in 31 hypopituitary women, and the results showed that there was no significant difference in LT<sub>4</sub> dosage between early pregnancy (51 ± 36 µg/d) or postpartum (38 ± 34 µg/d) and pre-gestation (33 ± 35 µg/d) (*P* > 0.05). However, the required dose of LT<sub>4</sub> at the second (68 ± 42 µg/d) and third trimester (76 ± 42 µg/d) was increased by about 35% on average as compared to the pre-gestational period (*P* < 0.05). It has also been shown that LT<sub>4</sub> requirements increased during early pregnancy in most women with primary hypothyroidism, reaching a plateau after 16 to 20 weeks of gestation at a value about 47% higher than the pre-pregnancy value and persisting throughout pregnancy [21].

Glucocorticoid therapy in pregnancy should take into account that adrenal reserve increases as pregnancy progresses, and salivary free cortisol (SaFC) is a more consistent, corticosteroid-binding globulin independent, and physiologically rational measure of adrenal function in pregnancy rather than serum total cortisol [22]. Patients on glucocorticoid replacement may need to increase their hydrocortisone dose by 50% during the last trimester of pregnancy, and by the start of the labor, the hydrocortisone dose should be increased to stress doses until 48 h postpartum [1]. Wiren et al. [23] followed 8 hypopituitary women during their 12 distinct pregnancies, and found that GH replacement was maintained at the same pregestational dose during the first trimester, with a gradual decrease of the dose during the second trimester and discontinuing the treatment at the beginning of the third trimester, and all of the 12 pregnancies were successful.

Considerable evidence has accumulated that pregnancies in women with hypopituitarism are at increased risk of pregnancy complications, thus it is crucial to monitor maternal and fetal hormone levels, and serial ultrasound measurements are also necessary for fetal growth assessment. Although twin pregnancy carries a particularly poor outcome and thus should be avoided at all costs [4], Kitajima et al. [16] reported successful twin pregnancy in a woman with hypopituitarism caused by a suprasellar germinoma, and then pointed out that hormone replacement after ovulation induction was necessary for these patients to achieve pregnancy.

Uterine size is reported to be similar in hypopituitary patients [1], thus uterine size alone could not explain the poor pregnancy outcomes of hypopituitarism. For this reason, the poor pregnancy outcomes are more likely to be related to pituitary hormone deficiencies. Overton et al. [4] showed that patients with only GH deficiency had more favorable outcome than those with panhypopituitarism. However, GH deficiency is unlikely to be the main contributor to the poor pregnancy outcomes because placental GH can compensate for its action during gestation. GH replacement is effective during early pregnancy [13, 20]. Muller et al. [24] showed that GH treatment reduced the abortion rate in patients with GH deficiency [13]. Davis et al. [5] showed that maternal implications were more impressive in 14 overtly hypothyroid patients than in 12 subclinical hypothyroid patients, and that overt thyroid deficiency was associated with adverse pregnancy outcomes, which could be improved by thyroxine replacement. Kübler et al. [3] analyzed 31 pregnancies in 27 hypopituitary women, and found that oxytocin supplementation helped establish the physiologic conditions and prevent postpartum uterine inertia. It may have contributed to correct fetal presentation, but could not prevent postpartum hemorrhage in patients with severe hypopituitarism. Hypopituitarism may not be an absolute indication for cesarean delivery, but it is associated with an increased risk of pregnancy complications, thus a more liberal indication for cesarean delivery is preferred in these patients.

### Treatment of infants

Maternal hormone deficiencies and replacement may have adverse effects on their infants,

and close follow up is thus mandatory. However, a number of studies have shown that GH treatment during early pregnancy had no long-term adverse effect on mothers and their babies, and patients who received GH therapy for 6-12 months until pregnancy had uneventful pregnancies, full-term deliveries, and healthy babies with normal stature in length and weight [13]. However, as the glucocorticoid can pass to breast milk, whether it has a detrimental effect on the infants needs to be further studied. It is believed that the amount of glucocorticoid in breast milk is insufficient to affect neonatal adrenal functions.

### Conclusions

Hypopituitarism during pregnancy and perinatal period should be managed carefully. The hormone levels should be restored to normal before pregnancy. GH and HMG-hCG are combined to improve follicular growth and the success rate of pregnancy. Hypopituitary patients must be closely monitored as changes may need to be made to their medications, and serial ultrasound measurements are also necessary for fetal growth assessment.

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### Disclosure of conflict of interest

None.

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