

# Luteal phase deficiency during the early trimester in a case with secondary hypopituitarism following craniopharyngioma resection

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## Abstract

A 31-year-old woman, who had been diagnosed with craniopharyngioma (CP) at the age of 13, suffered secondary hypopituitarism after two surgical resections of CP, receiving supplement of levothyroxine, cortisone, and sequential estrogen and progesterone because of primary amenorrhea. She managed to conceive after ovulation induction with human menopausal gonadotropin. Luteal phase deficiency (LPD) was found during the first trimester, as the progesterone stayed at a low level between 0.07 and 1.63 ng/ml within seven gestational weeks, followed by a gradual rise from 4.01 up to 34.70 ng/ml in the 11th week, which was mainly secreted by the placenta. Estrogen and progesterone were administered to the patient as luteal support until the 12th week, who succeeded in delivering a healthy baby at term. In conclusion, the patient with hypopituitarism who develops severe LPD during the early pregnancy may need luteal support until 12th week.

**Key words:** craniopharyngioma, dydrogesterone, hypopituitarism, infertility, luteal phase deficiency.

## Introduction

Craniopharyngioma (CP) is one of the rare embryonic malformations in the sellar and parasellar area, in which the quality of life is frequently impaired in the long-term survivors due to the sequelae caused by the anatomical proximity of the tumor to the optic nerve/chiasma and hypothalamic-pituitary axes.<sup>1</sup> The endocrine dysfunction of pituitary impairment or loss and subsequent hypopituitarism usually occurs, especially after CP resection, with an incidence up to 78%–100%.<sup>2</sup> Gonadotropin-releasing hormone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and adrenocorticotrophic hormone all decrease significantly in hypopituitarism; therefore, a diagnose of any hor-

mone deficiency and an appropriate replacement are within the disease-specific considerations for CP.<sup>3</sup> True, secondary hypogonadotropic hypogonadism (HH) always leads to amenorrhea and infertility. A few cases of successful pregnancy following CP resection have been reported.<sup>4</sup> As the German cross-sectional study reported in 2018, 79 patients were followed up for 15 years with regard to growth hormone substitution therapy, and only 11 (13.9%) got married and 2 (2.5%) conceived or had children.<sup>5</sup> A recent review summarized six successful pregnancies after CP resection.<sup>6</sup> However, there have been few reports on luteal phase deficiency (LPD) and luteal support during pregnancy after the ovulation induction in the CP patients.<sup>6</sup> LPD is a condition of progesterone not sufficient enough to maintain a normal

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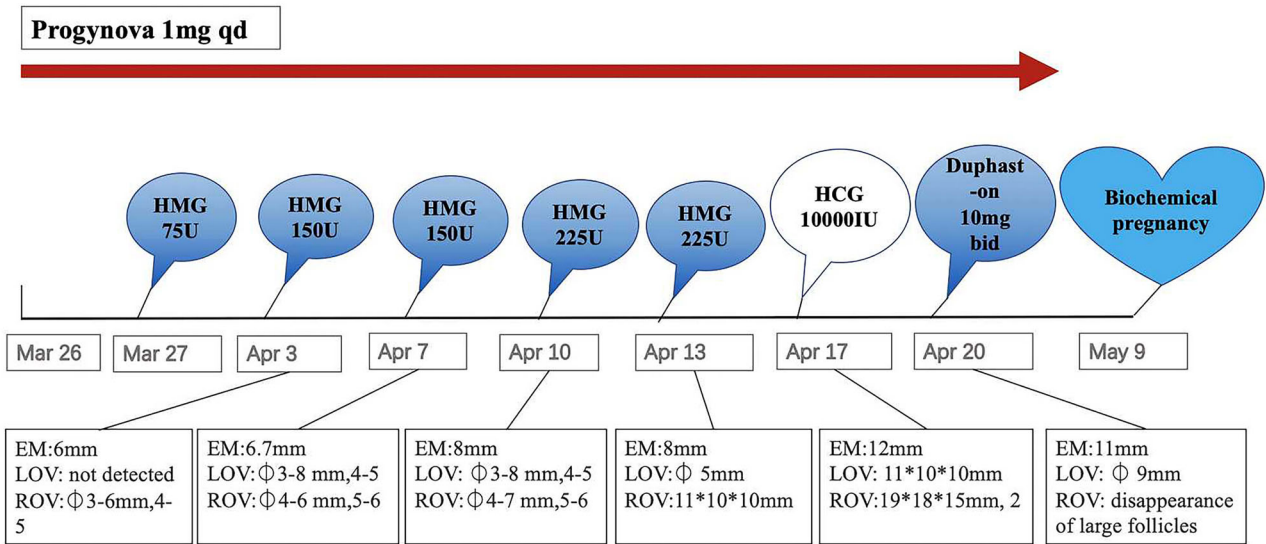
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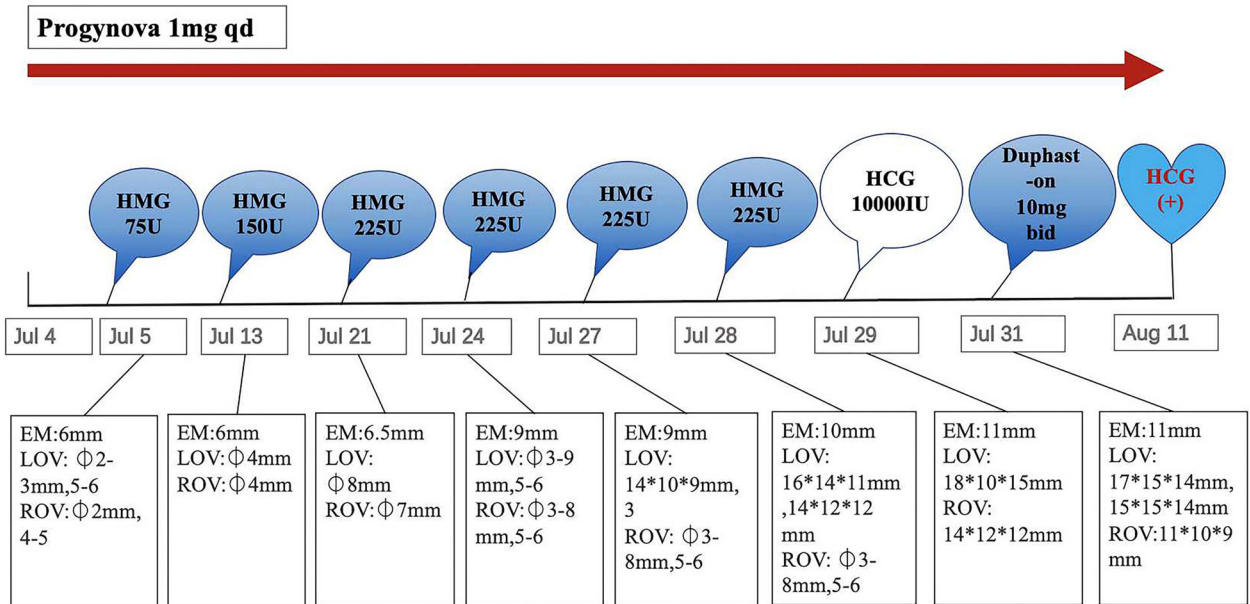
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**Figure 1** The dynamic ultrasonic image during the two cycles of ovulation induction with progynova and HMG injection; (a) Luteal support was withdrawn in the late luteal phase, with the first cycle ending in biochemical pregnancy; (b) Luteal support continued during the early pregnancy, with the second cycle ending in a delivery of a healthy baby. HMG, human menopausal gonadotropin

secretory endometrium and to allow for normal embryo implantation and growth.

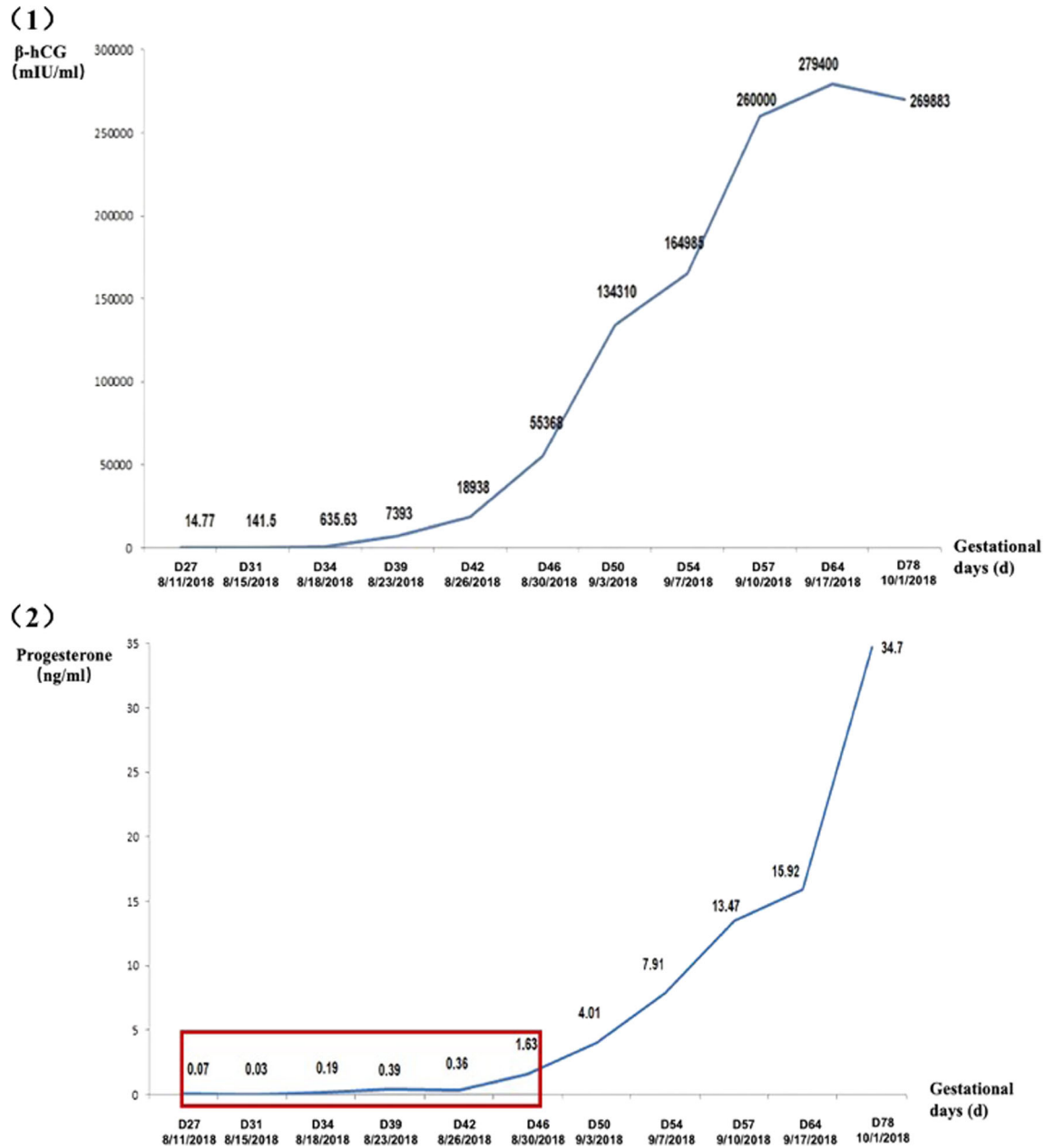
In the current study, we presented a case of severe LPD during the first trimester in a female patient, who successfully conceived after ovulation

induction at our hospital in 2018, and who, because of secondary HH following CP resection, succeeded in delivering a healthy term baby, thanks to the continuous luteal support beginning in the 12th gestational week.

## Case presentation

A 31-year-old female, who complained of primary amenorrhea and 2-year infertility after marriage, had been diagnosed with CP at the age of 13, for which she underwent surgical resection of CP in the

department of neurosurgery before receiving supplement of levothyroxine and cortisone because of post-operative hypopituitarism. When she was 16 years old, she had a CP recurrence so that she underwent the second resection. She continued her postoperative treatment with levothyroxine and cortisone. She



**Figure 2** The dynamic serum  $\beta$ - human chorionic gonadotropin ( $\beta$ -hCG) and progesterone levels during the early trimester; (a) During the first 8 weeks of gestation, the  $\beta$ -hCG levels doubled every 3–4 days, maintaining a peak of more than 260 000 mIU/ml after that; (b) The serum progesterone level was as low as 0.07 ng/mg in the early pregnancy, which began to increase from about 7 weeks of gestation, reaching a peak around the 11th week

developed primary amenorrhea, initiating estrogen and progesterone supplement intermittently, from her age of 18 on. In 2016 when she was 29 years old, she got married. As recommended, she was put on sequential estrogen and progesterone supplement, withdrawing vaginal bleeding periodically.

The patient came to our hospital on January 16, 2018, complaining of 2-year infertility. She was prescribed another laboratory test for sex hormone concentrations after treatment, its results showing FSH to be 1.21 mIU/ml; LH, 0.57 mIU/ml; estradiol (E<sub>2</sub>), 14 pg/ml; testosterone (T), 0.01 ng/ml; TSH, 0.06 ng/ml; progesterone (P), 0.56 ng/ml; and anti-müller hormone, 2.4 ng/ml. The image of Mode-B ultrasonography (Aloka SSD 5500 ultrasonoscope, Aloka Inc.) demonstrated bilateral shrunken ovaries and normal uterus. Her karyotype was 46, XX, and her husband's semen examination was normal.

The patient signed the written consent, permitting us to use her medical records and results without mentioning her name in the current case report.

The patient was initially treated with Climen<sup>®</sup> (Complex packing Estradiol Valerate Tablets, Estradiol Valerate and Cyproterone Acetate Tablets, Climen<sup>®</sup>, Bayer, German), besides levothyroxine and cortisone. Because of her infertility, she accepted ovulation induction through a routine human menopausal gonadotropin (HMG) increasing program. She experienced two cycles of ovulation induction. In the first cycle, the dominant follicles developed when the total amount of HMG was up to 75 IU\*45, from 75 to 150 IU/day, and then up to 225 IU/day, which was associated with Progynova<sup>®</sup> (Estradiol Valerate Tablets, Progynova<sup>®</sup>, Bayer, German) 1 mg/day. On April 17, 2018, human chorionic gonadotropin (hCG) at 10 000 IU was injected when two mature follicles (diameter: 18 mm) were observed in the ultrasonic image. Three days later after the injection of hCG, the luteal support started with combined Progynova<sup>®</sup> (1 mg/day) and Duphaston<sup>®</sup> (20 mg/day), which lasted only 10 days. Fourteen days later, serum β-hCG was detected, which indicated pregnancy. Two days later, however, the patient suspended the luteal support, complaining of vaginal bleeding. Thus she ended with a biochemical pregnancy (Figure 1(a)).

In the second cycle, a mature follicle appeared when the total amount of HMG reached 75 IU\*45. The luteal support started from the third day after an injection of hCG as before. Thirteen days later, serum β-hCG was detected to be 14.77 mIU/ml. Then

Duphaston<sup>®</sup> was adjusted to be 30 mg/day, and Progynova<sup>®</sup> was added to 20 mg/day for the continuous luteal support until the 12th gestational week (Figure 1(b)). As a result, the patient succeeded in delivering a term healthy baby girl. In this case, the gestational age was recalculated according to the ovulation date of July 31, 2018; therefore, August 11, 2018 must have been the 27th day of the gestation.

As indicated in Figure 2, the levels of serum progesterone and β-hCG were monitored regularly. During the first 8 weeks of gestation, the level of β-hCG doubled every 3–4 days, until a peak was maintained at over 260 000 mIU/ml, which was consistent with the level of the normal dynamic β-hCG during the gestation (Figure 2(a)). However, the level of serum progesterone was as low as 0.07–1.63 ng/ml in early pregnancy, which began to increase in the seventh gestational week, and reached a peak at 4.01–34.70 ng/ml around the 11th week (Figure 2(b)). Since Duffton<sup>®</sup>, an isomer of progesterone, having a strong affinity with the progesterone receptor, cannot be measured from serum, the level of progesterone truly indicated the ovarian luteal function in the early trimester. However, the level of the patient's serum progesterone was significantly low within 7 weeks of pregnancy, indicating that the patient had a deficient luteal function. Therefore, the supplementation of estrogen and progesterone was performed as luteal support until the 12th gestational week.

After all this, the patient entered a routine obstetric checkup before delivering a healthy baby girl.

## Discussion

In the current case, we presented the fluctuating levels of serum estrogen, progesterone, and β-hCG during the first trimester in a female patient, who successfully conceived after ovulation induction because of secondary HH following CP resection, which indicated severe LPD in the early pregnancy.

It was reported that the luteal and placental function switched in the seventh week of gestation, after which the placenta began secreting progesterone, and that the placenta completely replaced the corpus luteum between the 10th and 12th gestational week.<sup>7</sup> In the current case, the level of the patient's serum progesterone elevated gradually, reaching a peak in the 11th gestational week, exactly the time when the placenta started to produce progesterone. Progesterone is known to be essential for embryo implantation and pregnancy maintenance. With the LH surge

following ovulation, the luteal granulocytes were reported to secrete a large amount of estrogen and progesterone, thus regulating the endometrial receptivity and embryo implantation.<sup>8</sup> The increasing amount of estrogen and progesterone is well known to be secreted by pregnant corpus luteum to maintain pregnancy. Clinically, LPD has been associated with abnormal estradiol (E2) and progesterone production, shortening the luteal phase,<sup>9,10</sup> and with pregnancy-related disorders such as infertility and early pregnancy loss.<sup>11</sup> It was reported that LPD with a short luteal phase duration, defined as less than 10 days, or with suboptimal luteal progesterone, defined as less than 5 ng/ml maximum progesterone, affected 8.9% and 8.4% of the ovulatory cycles, as the primary clinical and biochemical diagnostic criteria,<sup>12</sup> thus leading to a decreased implantation rate or miscarriage.<sup>13</sup> Both pilot cohorts of 119 and 360 women showed that serum progesterone <35 nmol/L (11 ng/ml) between 6 and 10 gestational weeks was prognostic of spontaneous miscarriage by the 16th week in women with threatened miscarriage in early pregnancy.<sup>14,15</sup> In the current case, therefore, the patient's biochemical pregnancy might have been related to the lack of timely luteal support. From the continuous dynamic monitoring of hormones in the second pregnancy, we learned that the patient had severe LPD. Thanks to the estrogen and progesterone therapy as luteal support during the early trimester, followed by a healthy placental function, the pregnancy was successfully maintained until the full term childbirth.

The relevant guidelines and consensuses have recommended that since LPD exists in ovulation-induced pregnancy, routine luteal support should be administered in these patients, including progesterone supplementation and hCG injection.<sup>16,17</sup> Most of progesterone preparations, such as progesterone injection, progesterone capsules, and vaginal progesterone gel pills, can be measured from serum; consequently, the level of serum progesterone cannot accurately indicate the changes of endogenous progesterone. Therefore, it is difficult to measure the severity of LPD. However, dydrogesterone, an isomer of natural progesterone, can specifically be combined with the progesterone receptor, but cannot be detected from serum.<sup>18</sup> Therefore we examined the level of endogenous progesterone while the patient was on estradiol and progesterone supplement, which could uncover the severe LPD in this patient, thus developing a clinical therapy accordingly.

It is a complicated process to treat female infertility following hypogonadotropic amenorrhea, which includes the promotion of reproductive-organ development through estrogen and progesterone replacement, and a HMG injection to induce ovulation. In the current case, we found that the patient developed a significantly low level of progesterone between 0.07 and 1.63 ng/ml within seven gestational weeks. After ovulation, luteum formation and progesterone secretion were achieved by regulating FSH and LH, especially pulsatile LH secretion. Long-term LH deficiency due to impaired pituitary function could lead to loss of LH receptors on the granulocytes, abnormal secretion of granulocytes, and consequently complete loss of luteal function in early pregnancy; moreover, exogenous gonadotropins directly stimulated the ovaries to produce and secrete E2, thus resulting in negative feedback at the levels of the hypothalamus and pituitary.<sup>19</sup> This could impair progesterone secretion from the corpus luteum.<sup>20</sup> As previously reported, a shortened luteal phase could occur after ovulation induction with gonadotropins, which could be explained in terms of a low level of serum progesterone in luteal phase.<sup>22</sup> Therefore, there exists biologic plausibility for the benefit of exogenous progesterone to luteal phase support in ovulation induction cycles with gonadotropin.

In summary, for the first time we reported the dynamic LH and progesterone level of severe LPD during the first trimester in a patient, who conceived successfully through hormone supplementation and ovulation induction with HMG despite her hypopituitarism following CP resection. It is still worth mentioning that adequate luteal hormone support should be provided until the 12th gestational week when the placental function returns to normal completely.

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## Conflict of interest

The authors declare no potential conflict of interest.

## Author contributions

Wei Zhang provided the treatments and collected the data regarding the patient. Hexia Xia was responsible for the manuscript, which was examined and confirmed by Wei Zhang.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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