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Management of panhypopituitarism during pregnancy: A case report

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ABSTRACT

Clinicians face many challenges regarding conception and pregnancy management for women with panhypopituitarism. Fertility in women with panhypopituitarism is often reduced, and they are at risk of obstetric complications. The authors describe the case of a woman with congenital panhypopituitarism who had a successful pregnancy after ovulation induction and optimization of hormonal replacement therapy. This case report emphasizes the importance of careful adjustment of hormonal replacement therapy in managing pregnant women with panhypopituitarism.

1. Introduction

Panhypopituitarism refers to a complete deficiency of hormones produced by the pituitary. In clinical practice it encompasses growth hormone deficiency, central adrenal insufficiency, central hypothyroidism, central hypogonadism and in some cases central diabetes insipidus and prolactin deficiency [1]. Central hypogonadism is mainly responsible for reduced fertility in women with panhypopituitarism [2]. Assisted reproductive techniques, and in particular ovulation induction, have led to improved pregnancy rates in these women [2] but there is an increased risk of an adverse pregnancy outcome [3,4]. Optimal hormonal replacement therapy is crucial to minimize this risk. To date, data on pregnancy outcome in women with panhypopituitarism is limited.

2. Case Presentation

A 30-year-old woman with panhypopituitarism due to aplasia of the anterior pituitary and an ectopic posterior pituitary (EPP) achieved pregnancy after the first attempt at induction of ovulation. On cycle day 2, stimulation with human menopausal gonadotropin (hMG; 150 IU/day) started and lasted 11 days. After this stimulation period, three follicles were observed and human chorionic gonadotropin (hCG; 250 μg) was administered to induce ovulation.

Preconception counseling and investigations took place in advance of ovulation induction. A vaginal ultrasound scan showed inactive ovaries and a small uterus. Preconception laboratory test results were all within normal ranges (sodium 141 mmol/l, potassium 4.1 mmol/l, hemoglobin 8.8 mmol/l, hemoglobin A1c 38 mmol/mol, free thyroxine (FT4) 15.6 pmol/l, insulin-like growth factor 1 (IGF-1) 29.1 nmol/l and dehydroepiandrosterone sulfate 1.41 μmol/l) except for low levels of thyroid-stimulating hormone (TSH) (< 0.05 mU/l; normal range: 0.56–4.27 mU/l), follicle stimulating hormone (FSH) and luteinizing hormone (LH) (1.1 and 1.0 U/l; normal range: 2–8 U/l). Furthermore, she had normal blood pressure (114/75 mmHg). Investigations of the partner revealed no abnormalities.

Prior to ovulation induction, the treatment regimen consisted of growth hormone (0.54 mg/day), hydrocortisone (20 mg/day), levothyroxine (100 μg/day), dehydroepiandrosterone (DHEA) (50 mg/day), estradiol/dydrogesterone (2 mg/day estradiol plus sequential dydrogesterone 10 mg/day for 14 days of each 28-day cycle), and desmopressin (0.05 mg/day). Immediately upon pregnancy diagnosis, growth hormone, DHEA and estradiol/dydrogesterone administration was stopped and vaginal progesterone (200 mg, three times a day) was administered throughout the first trimester. During pregnancy, the dose of levothyroxine was gradually increased to 200 μg/day based on FT4 levels, which were determined every four to six weeks, thereby maintaining FT4 levels in the upper half of the normal range. The dosage hydrocortisone and desmopressin remained unaltered.

The first and second trimester were uneventful. During the third trimester, she developed gestational diabetes, which was diagnosed using the one-step 75 g oral glucose tolerance test. She had a normal fasting plasma glucose (5.8 (< 7.0) mmol/l) but an abnormal plasma glucose after two hours (8.6 (< 7.8) mmol/l). However, no pharmacological intervention was required.

At 30 weeks of gestation, during a regular checkup, her blood pressure was measured and laboratory tests were performed. Her blood

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pressure was 124/76 mmHg and the laboratory test results did not show any abnormalities: sodium 131 mmol/l, potassium 3.9 mmol/l, hemoglobin A1c 38 mmol/mol, FT4 20.7 pmol/l and IGF-1 31.2 nmol/l. An adrenal crisis at 31 weeks of gestation was successfully treated with 30 mg hydrocortisone.

At 38 weeks of gestation, she was physically exhausted, and therefore admitted for induction of labor. Intracervical insertion of a Foley catheter and misoprostol for cervical ripening resulted in no more than 3 cm of cervical dilatation. A cesarean section was performed on maternal request. During the cesarean section, a steroid replacement protocol was followed (two intravenous boluses of 50 mg and 100 mg hydrocortisone respectively, followed by a continuous infusion of 200 mg hydrocortisone over 24 hours). The procedure was complicated by a hemorrhage of 1000 ml caused by a surgical uterine bleed. In order to prevent further hemorrhage, an intravenous bolus of 5 IU oxytocin and a continuous infusion of 10 IU oxytocin over four hours were administered.

A boy weighing 3515 g was delivered in good condition. One day after the cesarean section, the continuous infusion of hydrocortisone was lowered to 100 mg over 24 hours. Thereafter, the continuous infusion of hydrocortisone was switched to oral administration (30 mg, three times a day) and the dosage was gradually lowered to 20 mg/day. Directly after the cesarean section, the dose of levothyroxine was lowered to 175 mg/day and the pre-pregnancy dosages of DHEA and growth hormone were restarted. Three days postpartum she experienced engorgement, but lactation was not initiated. She and her son were discharged from the hospital five days postpartum. The puerperium showed no abnormalities for either mother or child.

3. Discussion

Hormonal replacement therapy in women with panhypopituitarism mimics the normal physiological production and release of pituitary hormones. Especially during the preconception period and pregnancy, the status of the hormonal replacement therapy is extremely important.

Prior to ovulation induction, we recommend that blood pressure is checked and the following laboratory tests are performed (normal range in parentheses): sodium (136–145 mmol/l), potassium (3.5–5.1 mmol/l), hemoglobin (7.5–9.5 mmol/l), hemoglobin A1c (26–42 mmol/mol), FT4 (13.5–24.3) pmol/l, TSH (0.56–4.27 mU/l), IGF-1 (9.6–33.9 nmol/l), FSH and LH (both 2–8 U/l). Ovulation induction in patients with central hypogonadism involves FSH/hCG or hMG/hCG [5]. We treated our patient with the latter. Messinis [6] elaborates in more detail the different protocols of ovulation induction for patients with hypogonadotropic hypogonadism. Data on pregnancy rates in patients with congenital panhypopituitarism are scarce. However, Hall et al. [7] determined a pregnancy rate of 42% after ovulation induction in a group of women with pan- or partial hypopituitarism, and Overton et al. [3] showed that those who achieved pregnancy after ovulation induction had only a 61% chance of a live birth.

As pregnancy alters both the physiology and anatomy of the pituitary gland, hormonal replacement therapy during pregnancy is challenging [8]. We strongly recommend using the guidelines produced by Fleseriu et al. [5] as a roadmap for management of panhypopituitarism during pregnancy. Their advice is to stop growth hormone replacement, as the evidence for safety during pregnancy is controversial and the placenta also produces growth hormone [5].

Increasing the dosage of glucocorticoid replacement, preferably hydrocortisone, during pregnancy, depending on the individual course, is recommended (suggested dose: 12–15 mg/m^2/day) [5]. The best means to monitor glucocorticoid replacement is clinical judgement; assessing for signs of under- or over-replacement [9]. On the one hand, glucocorticoid underexposure can cause an electrolyte imbalance, hypoglycemia and, in the worst case, an adrenal crisis [10]. On the other hand, glucocorticoid overexposure is associated with gestational diabetes, excessive weight gain, hyperglycemia, and hypertension [10]. Both are associated with low birth weight, preterm birth, and increased risks of developing cardio-metabolic disease in later life [10,11]. In order to avoid these adverse pregnancy outcomes, we recommend monitoring the weight, blood pressure and blood glucose levels (normal range glucose: 4.0–6.1 mmol/l, and hemoglobin A1c: 26–42 mmol/mol) of women with central adrenal insufficiency at least every trimester [10]. During labor and delivery, a stress dose of hydrocortisone is recommended (50 mg intravenous in the second stage of labor; 50–100 mg intravenous preoperatively and every 8 hours postoperatively for a cesarean section) [2,5].

As the response of thyrotropin receptors to hCG varies in pregnant women with panhypopituitarism [5], we advise the determination of FT4 levels every four to six weeks and adjustment of the levothyroxine dosage accordingly. In order to minimize the risks of under-replacement of thyroid hormone for the fetus, we recommend FT4 levels in the upper half of the normal range (normal range: 13.5–24.3 pmol/l) [12].

Vaginal progesterone improves pregnancy rates after ovulation induction with gonadotrophins as it supports the luteal phase [13]. Data on the safety and effectiveness of DHEA replacement is limited and is therefore not advised [5]. Remarkably, our patient used DHEA prior to conception.

Pregnant women with pre-existing diabetes insipidus are recommended to continue their treatment with desmopressin [5]. We recommend to evaluate the need for desmopressin during pregnancy clinically (polyuria-polydipsia) and biochemically (sodium levels, normal range: 136–145 mmol/l) every trimester [5].

Currently, there are no fetal gender-specific recommendations regarding hormonal replacement therapy during pregnancy. However, this might be an interesting topic for future research.

Panhypopituitarism diagnosed in childhood, as in our patient, is associated with smaller ovarian and uterine size. These morphological disturbances may contribute to the reduced fertility and adverse pregnancy outcomes in this group [2]. In several prior cases, women with panhypopituitarism delivered vaginally [14]. In contrast, our patient showed no signs of active labor after induction of labor. Usually, the function of the posterior pituitary remains preserved with EPP. However, the posterior pituitary of our patient was affected as she had diabetes insipidus. Therefore, her oxytocin-releasing cells could be impaired as well.

To our surprise, the patient experienced engorgement three days after cesarean section. Even though no lactation was initiated, the fact that she experienced engorgement suggests her hypothalamic-pituitary axis regulating prolactin is partly intact.

In conclusion, this case report contributes to the evidence that successful conception and pregnancy are possible in women with panhypopituitarism, and highlights that this complex condition requires a multidisciplinary approach to reduce the risk of adverse pregnancy outcomes.

Contributors

Sofie Karolina Maria van Zundert drafted the manuscript.

Dr. Charlotte Georgette Krol critically revised the manuscript.

Dr. Julia Jeltje Spaan was involved in patient care and critically revised the manuscript.

All authors contributed to the interpretation of data and approved the final version to be submitted.

Conflict of interest

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