



CASE REPORT

In Vitro Fertilization Treatment of a Patient with Primary Partial Empty Sella and Other Co-Factors

Tünde Herman¹, Péter Török^{2*}, Antonio Simone Laganà³ and Attila Jakab²

¹Assisted Reproduction Center, University of Debrecen, Debrecen, Hungary

²Department of Obstetrics and Gynecology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

³Department of Obstetrics and Gynecology, "Filippo Del Ponte" Hospital, University of In-subria, Italy

*Corresponding author: Péter Török, PhD, MD, Department of Obstetrics and Gynecology, Faculty of Medicine, University of Debrecen, Nagyerdei krt 98, 4032 Debrecen, Hungary, Tel: 003-670-315-8024



Abstract

We report the case of a patient with primary empty sella, who had successful assisted reproductive treatment. The patient is a 28-years-old infertile female with primary amenorrhoea and hypogonadotropic hypogonadism. Serum FSH, LH, E2 indicated central anovulation, but the production of GH, ACTH, TSH and PRL were normal. Obesity and insulin resistance were present. Male partner had asthenozoospermia and hyperprolactinaemia. After three failed intrauterine inseminations, she was addressed to gynecologic endocrinology where cerebral MRI was done, which revealed partial empty sella. Due to the combination of several infertility factors, the couple was referred for IVF. Since the initial fertilization rate was low at IVF-ICSI and implantation failed, intensive lifestyle modification and endocrinological care was introduced for 5 months, then the second IVF treatment was effective and, after a relatively uneventful pregnancy, healthy twin boys were born near-term.

Keywords

Hypogonadotropic hypogonadism (HH), Primary empty sella (PES), Astheno-teratozoospermia (AT), *In vitro* fertilization (IVF)

Introduction

Partial empty sella (PES) syndrome is a rare condition which causes central hypogonadism and could account for female infertility. Central anovulatory infertility is a relatively rare indication for assisted reproduction.

Total or partial empty sella is an anatomical condi-

tion in which the subarachnoid space expands into the pituitary fossa due to a congenital or acquired defect of the sellar diaphragm covering the sellar cavity [1]. In the primary cases, etiology of this defect of the sellar diaphragm (formed by a layer of the dura mater) is unknown, although weakness of the diaphragm or increased intracranial pressure can be suspected [2]. The sella is distended by cerebrospinal fluid and the pituitary gland may either be compressed or displaced [3]. The incidence of empty sella is approximately 5% and the vast majorities (85%) of the patients are women [4]. In patients with amenorrhoea/galactorrhoea, the prevalence is 4-16% [5,6]. Leading complaint is headache and symptomatic patients are usually (80%) middle aged, overweight and have hypertension [7].

Empty sella is most often an incidental diagnosis at brain CT or MRI, if endocrinological signs of neurologic symptoms are missing. Even if pituitary hormone deficiencies are present, they are usually partial. In reproductive age women, amenorrhea and oligomenorrhea are the frequent symptoms associated with decreased Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) production [8]. Primary central hypogonadotropic hypogonadism is associated with chronic anovulation and low estrogen levels, thus the uterus remains infantile, fallopian tubes appear extremely thin and the ovaries are of a small size. In addition, body hair may be thin or completely missing, the secondary sex

characteristics are less expressed. Reduced libido and infertility are also characteristic for this syndrome [9]. The less frequent absence of other pituitary hormones can cause other abnormalities: Delayed growth is associated with the decreased level of Growth hormone (GH), while the lack of Adrenocorticotrophic hormone (ACTH) production may lead to clinical symptoms typical of adrenal insufficiency. Other symptoms of central hypothyroidism include weight gain, hair loss, dryness of the skin. Secondary empty sella most often occurs after treatment of pituitary tumors (surgical, medical or radiologic) or hypophysis apoplexia [10].

Congenital malformations and acquired defects of hypothalamus and hypophysis (tumors, cysts, vessel anomalies, bleeding, infection, trauma, irradiation) should be considered at differential diagnosis. In this article, we report the case of a patient with primary empty sella and other endocrinological, metabolic and male infertility factors, who underwent successful assisted reproductive treatment.

Case Report

In 2016, a 28-year-old infertile female with primary amenorrhea attended at her local gynecologists. Previously, no diagnostic attempts were made, once a withdrawal bleeding was provoked with sequential estrogen-progesterone replacement.

She did not report cranial trauma or neurological disease, headaches, double vision or other visual disturbances. There were no previous surgical, chemotherapeutic or radiological treatments. With the height of 165 and weight of 110 kg, she had BMI 40.4, without androgenic signs. Her breasts had not developed yet, and the pubic hair was scarce.

Initial laboratory results are shown in Table 1. Oral glucose tolerance test (OGTT) confirmed insulin resistance, thus metformin treatment was introduced (1000 mg twice daily). Due to her phenotype, PCOS was suspected and lifestyle modification was indicated. She lost 10 kg in 12 months, but amenorrhoea was still present. In 2017, the patient had Laparoscopy and chromohydrotubation LSC-CHT), which revealed an infantile uterus, bilaterally very thin tubes and small ovaries. Subsequently, intrauterine insemination was performed in three cycles, but she failed to conceive.

After these failed attempts, she was referred to the Gynecologic Endocrinology Unit (Department of Obstetrics and Gynaecology, Clinical Centre, University of Debrecen, Hungary). Her tests were negative for Anti-thyroid peroxidase (anti-TPO) antibody, Anti-thyroglobulin (anti-Tg) antibody, TSH stimulating receptor antibody.

After three failed inseminations the AMH level decreased (0.59 mg/ml), so we were able to set up the diagnose of diminished ovarian reserve.

Transvaginal sonography (TVS) found 41 × 16 × 27

Table 1: Initial blood test results.

	FSH mIU/ml	LH mIU/ml	E2 ng/ml	progesterone nmol/l	sTSH µIU/ml	ACTH ng/l	cortisol nmol/l	prolactin ng/ml	AMH ng/ml	TRAK U/l	anti-TPO IU/ml	anti-TG IU/ml	HOMA index
Initial hormone level	1	7	29		2.19			7.48	1.43				
Hormone level	1.3	1.3	26	0.3	1.14	25.0	142.2	4.8	0.59	< 0.3	16	11.0	1.7

anti-TPO: Anti-thyroid peroxidase antibody; anti-Tg: Anti-thyroglobulin antibody; HOMA: Homeostasis model assessment index

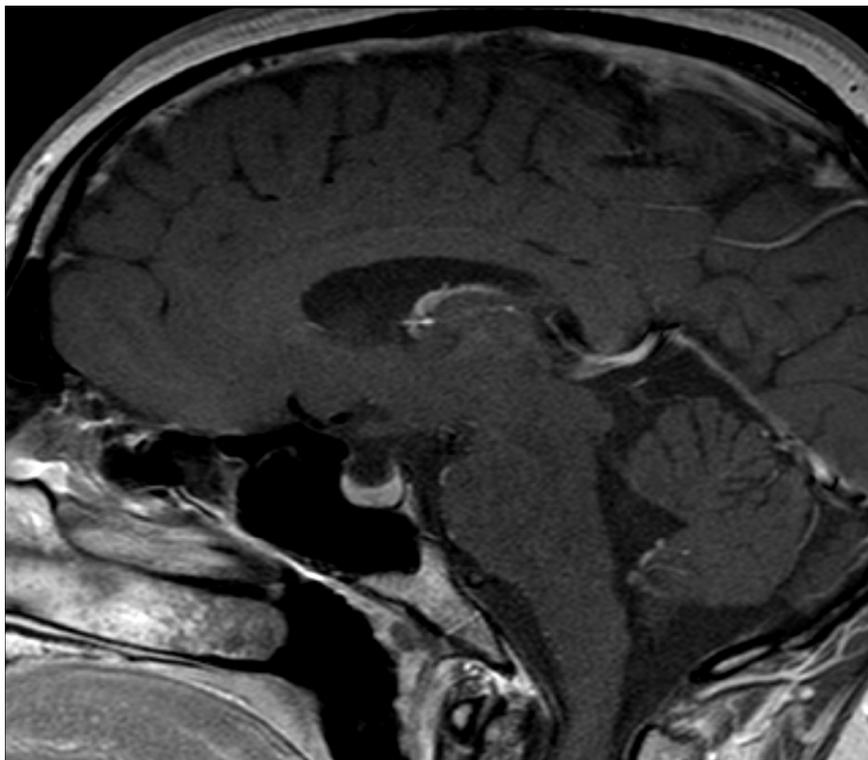


Figure 1: MR Image of the sella.

mm uterus, thin (2 mm) endometrium, highly hypoechoic sub-endometrial zone and the ovaries were not seen. Due to the low gonadotropin and estrogen levels and ultrasound signs of hypoestrogenism, central origin of amenorrhea (hypogonadotropic hypogonadism) was diagnosed and a brain MRI was done, on which a partial empty sella was described ([Figure 1](#): Light deepening of the sella was detected, with the size of 11 × 11 × 7 mm). The suprasellar cyst with largest craniocaudal diameter was 5 mm, and protruded into the sella. Exerting pressure on the pituitary gland, the cyst slightly compressed its anterior lobe (adenohypophysis) to the bottom of the sella. The posterior lobe (neurohypophysis) appears normal. After intravenous administration, normal accumulation of the contrast medium in the substance of the gland was observed. The infundibulum was slightly wider (2 mm at its widest part) and was shifted to the left. The optic chiasm was unobstructed. The parasellar regions appeared regular on both sides.

The diagnosis of primary partial empty sella with hypogonadotropic hypogonadism was made, associated with pituitary hormone production defect of FSH, LH with maintained TSH, GH, ACTH and PRL levels. Obesity, insulin resistance and vitamin-D deficiency were also considered as cofactors of infertility, and further corrections were indicated (metformin 1000 mg twice a day, Vitamin-D 30000 IU once a week for 12 weeks, weight loss). The patient was referred to the Centre of Assisted Reproduction.

Partner's andrological examination revealed astheno-teratozoospermia. Semen concentration was 21 M/

mL with 30% motility and 95% of abnormal morphology. He was obese and in addition, due to hypertension and reflux oesophagitis, and he was put on metoprolol and acid-suppressant therapy (proton pump inhibitor).

After successful weight loss of 15 kg (BMI 35.1) the indication for IVF-ICSI was established, Controlled ovulation hyperstimulation (COH) was performed according to the dosing steps ([Table 2](#)).

Four mature eggs were retrieved and ICSI was performed. On the day following oocyte aspiration, 3 × 200 mg oral and 90 mg vaginal progesterone supplementation, 0.4 ml Low-molecular-weight heparin (LMWH) subcutaneously and 100 mg acetylsalicylic acid per os were administered. We started the administration of 16 mg methylprednisolon daily and 1000 mg of potassium every other day. On day 2, regular fertilization signs were observed in one embryo only, and on day 3 this 8-cell non-fragmented embryo was transferred, but negative serum Human chorionic gonadotropin (hCG) indicated failure of implantation.

Few months later, the second attempt of COH was performed ([Table 2](#)).

Seven eggs were retrieved, all of them were matured (MTII) and six eggs fertilized normally. She refused the recommended Single embryo transfer (SET) and insisted on transfer of two embryos. On day 5, the patient received two blastocysts with an endometrial thickness of 10 mm and progesterone level of 32 nmol/l. Progesterone supplementation, LMWH, acetylsalicylic acid and transdermal estrogen treatment were administered,

Table 2: Treatment and data of folliculometry in first and second attempt of IVF therapy.

Cycle day	1	2	3	4	5	6	7	8	9	10	11	12	13
rFSH IU	300	300	300	300	300	300	300	300	300	300	300	300	-
hMG IU	-	-	-	150	150	150	150	150	150	150	-	-	-
rec hCG 375 µg													x
E2 level (pg/ml)	13.4	-	-	18.1	-	-	-	155.3	-	-	486.6	-	-
Follicular size (mm)	-	-	-	-	-	-	-	5 x 10	-	-	5 x 14-15	-	-
Endometrial thickness (mm)	-	-	-	-	-	-	-	7	-	-	9	-	-
rFSH IU	225	225	225	225	225	225	225	225	225	225	225	225	-
hMG IU	75	75	150	150	150	225	225	150	150	150	150	150	-
Transdermal oestradiol (mg)	4.59	4.59	4.59	4.59	4.59	4.59	4.59	4.59	4.59	4.59	4.59	4.59	-
rec hCG 375 µg													x
E2 level (pg/ml)	8.5	-	6.3	-	-	15.9	-	-	112.3	-	-	1152.1	-
Follicular size	-	-	-	-	-	-	-	-	5 x 10	-	-	7 x 16-17	-
Endometrial thickness (mm)	-	-	-	-	-	-	-	-	8	-	-	10	-

rFSH: Recombinant- follicle stimulating hormone, hMG: Human menopausal gonadotropine; rec hCG: Recombinant human choriogonadotropin; E2: Estrogen

similar to the first attempt. On day 12, serum hCG level of 460.0 mIU/mL indicated pregnancy; then ten days later two regular intrauterine gestational sacs were seen on ultrasound. Hormone replacement therapy was continued with 2 × 1.53 mg transdermal estrogen per day, 600 mg oral progesterone per day, 90 mg vaginal progesterone per day, 25 mg sc. progesterone per day, until the 14th week of pregnancy, then the patient received daily 400 mg progesterone until the 20th week.

The dichorionic twin pregnancy was relatively uneventful. ACTH, cortisol, TSH levels were monitored monthly, to assess if there was a need of hydrocortisone or thyroxine therapy. After the 24th gestational week, minimal decrease in free thyroid hormone levels appeared and daily low-dose (25 µg) L-thyroxin was administered; gestational diabetes mellitus was not detected by the OGTT at week 24. Fetal morphometry mild growing discordance of fetuses was detected in the third trimester and serial fetal Doppler examinations were done to monitor the intrauterine well-being. Despite the recommended low carbohydrate diet, the weight gain reached 16 kg till delivery. No sign of pre-eclampsia was detected. Due to the increased subjective complaints (severe dyspnea), after dexamethasone prophylaxis for Infantile respiratory distress syndrome (IRDS) caesarean section was performed on the 36th week of pregnancy, at which we introduced i.v. hydrocortisone perioperative prophylaxis (50 mg i.v. hydrocortisone twice in 6 hrs) to prevent Addisonian crisis. Two male infants were born in good condition with the weight of 2940 and 2750 grams. Postoperative and early puerperal periods were uneventful, and effective lactation commenced.

Discussion

Here we reported a successful Assisted reproduction technique (ART) treatment of a patient with hypogonadotropic hypogonadism caused by primary empty sella, complicated by several female and male cofactors for infertility. Empty sella syndrome is a rarity among disorders of hypophysis, so very few data could be found in literature about complete and incomplete hypopituitarism fertility issues.

To best of our knowledge, this is the first report of a young infertile patient with primary amenorrhoea and central hypogonadism without other typical complaints or endocrine disorders, diagnosed with partial empty sella syndrome. In a review of 175 empty sella cases (150 women) [10] pituitary scans were indicated for headache (33.1%), endocrine disorders (30.6%), neurological symptoms (12.5%), visual disturbances (8.75%), abnormalities on sella radiograph (8.75%) and others (6.25%) and the average age at the diagnosis was 48.2 ± 14 years. Multiple pregnancies were observed in 58.3% of women; headaches, obesity, and hypertension were found in 59.4, 49.5, and 27.3% of the studied population, respectively.

The prevalence of hypopituitarism in patients with partial empty sella syndrome is variable: in the review mentioned above was found in 28% of patients. Pan-hypopituitarism was present in 40% of these patients, while partial or isolated hormone deficiencies were diagnosed in 60% of hypopituitary patients. The most prevalent pituitary deficiency was growth hormone deficiency. In a pooled meta-analysis [2], which included 4 studies, the incidence of hypopituitarism was 52%. Multiple pituitary hormone deficiencies were present in 30%, and isolated in 21% of patients with partial empty sella syndrome. Growth hormone and the gonadotropins were most common isolated insufficiencies. In our case, we found an isolated form of the gonadotropin deficiency, which is very rare.

Although in this case there were no other signs of elevated Intracranial pressure (ICP), neurological assessment was not indicated. Incompetent sellar diaphragm and concomitant chronic or Intermittently elevated (ICP) are considered to be significant factors in PES formation, so every case of elevated ICP has an underlying cause which is necessary to be identified in order to determine the correct treatment modality [11].

Ovulation induction is usually successful in central hypogonadism; nevertheless, theoretically in primary cases uterine hypoplasia may decrease the chance for a successful pregnancy. In our case, although uterine hypoplasia was detected by ultrasound and confirmed by laparoscopy, the first pregnancy with twins was uneventfully carried almost to term.

Several co-factors of infertility complicated the management of this case. Female metabolic disorders such as obesity, insulin resistance and vitamin-D deficiency were present on the female side, while obesity, asthenoteratozoospermia with mild hyperprolactinaemia on the male side. After the failure of intrauterine inseminations and the first IVF, partially successful corrections with life-style modification and medication, the conditions became more optimal for the successful IVF treatment.

Although in our case a hypophyseal hormone production defect was restricted for the gonadotropins only, the question of the perioperative management to prevent Addisonian crisis was also raised. Since there are no tests to detect the pituitary reserve in pregnancy, as well as no clear recommendation exists for this situation, we introduced a low dose of hydrocortisone prevention protocol.

Conclusion

Partial empty sella syndrome with partial hypopituitarism is a rare cause of hypogonadotropic hypogonadism and infertility, but it can be the background in patients presenting with primary amenorrhea and infantile female development. If central hypogonadism is suspected, sella MRI is the key for the diagnosis. Elevat-

ed doses of gonadotropins are necessary for ovulation induction, but uterine hypoplasia is not an element that prevents a successful pregnancy. In addition, multifactorial endocrinologic and andrological evaluation and personally tailored approach is necessary for the successful treatment. In pregnancy, follow-up of hypophyseal endocrine profile is recommended and peripartum Addisonian prophylaxis could be considered.

Acknowledgements

We wish to thank Zoltán Tándor MD, Béla Bodnár MD, Tamás Török, Emese Varga, Éva Csiszár in Assisted Reproduction Center, University of Debrecen, for taking part in the treatment and management of the patient.

References

1. Zuhur SS, Kuzu I, Ozturk FY, Uysal E, Altuntas Y (2014) Anterior pituitary hormone deficiency in subjects with total and partial primary empty sella: Do all cases need endocrinological evaluation?. *Turk Neurosurg* 24: 374-379.
2. Auer MK, Stieg MR, Crispin A, Sievers C, Stalla GK, et al. (2018) Primary empty sella syndrome and the prevalence of hormonal dysregulation. *Dtsch Arztebl Int* 115: 99-105.
3. Chiloiro S, Giampietro A, Bianchi A, Tartaglione A, Capobianco, et al. (2017) Diagnosis of endocrine disease: Primary empty sella: A comprehensive review. *Eur J Endocrinol* 177.
4. Hodgson SF, Randall RV, Holman CB, MacCarty CS (1972) Empty sella syndrome. Report of 10 cases. *Med Clin North Am* 56: 897-907.
5. Schlechte J, Sherman B, Halmi N, John vanGilder, Frederick Chapler, et al. (1980) Prolactin-secreting pituitary tumors in amenorrheic women: A comprehensive study. *Endocr Rev* 1: 295-308.
6. Speroff L, Levin RM, Haning RV Jr, Kase NG (1979) A practical approach for the evaluation of women with abnormal polytomography or elevated prolactin levels. *Am J Obstet Gynecol* 135: 896-906.
7. Neelon FA, Goree JA, Lebovitz HE (1973) The primary empty sella: Clinical and radiographic characteristics and endocrine function. *Medicine (Baltimore)* 52: 73-92.
8. Rani PR, Maheshwari R, Reddy TS, Prasad NR, Reddy PA (2013) Study of prevalence of endocrine abnormalities in primary empty sella. *Indian J Endocrinol Metab* 17: S125-S126.
9. Ascoli P, Cavagnini F (2006) Hypopituitarism. *Pituitary* 9: 335-342.
10. Guitelman M, Garcia Basavilbaso N, Vitale M, A Chervin, D Katz, et al. (2013) Primary empty sella (PES): A review of 175 cases. *Pituitary* 16: 270-274.
11. Krejci T, Krejci O, Mruzek M, Roschlova I, Lipina R (2020) Non-communicating hydrocephalus with a primary empty sella presenting with growth hormone deficiency and delayed puberty successfully treated by endoscopic third ventriculocisternostomy. *Acta Neurochirurgica*.