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Successful Pregnancies After Adequate Hormonal Replacement in Patients With Combined Pituitary Hormone Deficiencies

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Context: Women with hypopituitarism have lower pregnancy rates after ovulation induction. Associated pituitary hormone deficiencies might play a role in this poorer outcome.

Objective: We evaluated fertility treatment and pregnancy outcomes in five women with childhood-onset combined pituitary hormone deficiencies (CPHD).

Patients and Methods: Five women with CPHD were referred for fertility treatment after adequacy of hormone replacement was determined. Patients were subjected to controlled ovarian stimulation (COS) for timed intercourse, intrauterine insemination, or *in vitro* fertilization, according to the presence or absence of other infertility factors (male or tubal).

Results: All women became pregnant. The number of COS attempts until pregnancy was achieved varied between 1 and 5. The duration of COS resulting in at least one dominant follicle varied between 9 and 28 days, and total gonadotropin consumed varied between 1200 and 3450 IU. Two patients with severely suppressed basal gonadotropin levels since an early age had a cancelled COS cycle. All pregnancies were singleton except one (monochorionic twin gestation). The gestational ages at birth ranged from 35 weeks to 39 weeks and 4 days; three patients underwent cesarean section, and two had vaginal deliveries. Only one newborn was small for gestational age (delivered at 35 weeks).

Conclusion: Adequate hormonal replacement prior to ovarian stimulation resulted in successful pregnancies in patients with childhood-onset CPHD, indicating that hormone replacement, including growth hormone, is an important step prior to fertility treatments in these patients.

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Freeform/Key Words: fertility, gonadotropin deficiency, growth hormone deficiency, hypopituitarism, IGF1, ovarian stimulation

Abbreviations: ACTH, adrenocorticotropic hormone; AFC, antral follicle count; AMH, antimullerian hormone; COS, controlled ovarian stimulation; CPHD, combined pituitary hormone deficiency; DI, diabetes insipidus; eSET, elective single-embryo transfer; FSH, follicle-stimulating hormone; GH, growth hormone; GHRT, growth hormone replacement therapy; HH, hypogonadotropic hypogonadism; IGF, insulin-like growth factor; IUI, intrauterine insemination; IVF, *in vitro* fertilization; LH, luteinizing hormone; OCP, oral contraceptive pills; SD, standard deviation; TI, timed intercourse.

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Combined pituitary hormone deficiencies (CPHDs), defined as a deficiency of two or more pituitary hormones, can be congenital or acquired. The estimated prevalence of CPHD varies between 300 and 455 per million inhabitants, according to European data [1]. Mutations in transcription factors such as *PROP1*, *POU1F1*, *GLI2*, *HESX1*, *LHX3*, *LHX4*, *SOX2*, *SOX3*, and *OTX2* are known genetic causes of congenital cases, but they are identified in only a small fraction of patients [2].

Women with isolated hypogonadotropic hypogonadism (HH) have good pregnancy prospects after reproductive treatments [3]. In contrast, case reports and series reporting on the outcomes of ovulation induction in women with CPHD (involving HH) have shown a high number of cancelled cycles due to low or absent ovarian response to stimulation [4, 5]. Also, lower pregnancy and live birth rates [4] and increased risk of obstetrical complications [6] have been reported in these women; multiple pregnancies had even poorer outcomes in this group [7]. Hence, it could be hypothesized that associated pituitary hormone deficiencies beyond gonadotropins have an adverse effect on fertility and pregnancy outcomes [8].

Growth hormone (GH), which has multiple effects on the reproductive system, has been described as a possible treatment [4, 9, 10]. However, GH replacement during pregnancy carries some controversy in the literature, with some researchers advocating its usefulness and safety and others advocating its discontinuation due to increasing placental GH and consequently maternal insulin-like growth factor (IGF)-1 [11, 12]. Vila *et al.* [13] recently reported gestational data from a large cohort of women with GH deficiency (isolated or combined with other pituitary deficiencies) showing that the outcome of pregnancy was not influenced by the GH replacement therapy (GHRT) regimen. However, only 7.5% of pregnant patients in that cohort had stopped GHRT at some point before conception. Also, because it was not that study's objective, the effect of GHRT on women's fertility was not evaluated (*i.e.*, the study does not report on the proportion of women who conceived in relation to the total number of patients attempting pregnancy); nor was it determined if this proportion changed due to the GHRT.

Women with CPHD, particularly those with severely suppressed luteinizing hormone (LH)/ follicle-stimulating hormone (FSH) levels since childhood, have been reported to have lower serum antimullerian hormone (AMH) levels compared with women of the same age group without complete gonadotropin deficiency [14, 15]. The serum AMH levels and the ovarian antral follicle count (AFC) through transvaginal sonography are used to estimate the ovarian follicular reserve (ovarian reserve tests) and, therefore, to predict the ovarian response to stimulation with exogenous gonadotropins [16, 17]. However, it has been hypothesized that AMH levels probably do not accurately reflect the ovarian follicular reserve or predict the efficacy of fertility treatments in this group of patients. Still, to our knowledge, there has been no report of ovarian stimulation outcomes in women with CPHD in relation to their ovarian reserve tests results and basal gonadotropin levels.

We present here the clinical and hormonal data, the previous ovarian reserve status, pregnancy outcomes, and puerperium details of five patients with childhood-onset CPHD who had successful pregnancies.

1. Patients, Materials, and Methods

A. Patients

In this prospective study, we evaluated five patients with childhood-onset CPHD who requested fertility treatment. They were all diagnosed in childhood with severe short stature; the diagnosis was based on failure to have a normal response to combined pituitary stimulation test (0.05–0.1 U/kg insulin, 200 μg thyrotropin-releasing hormone, and 100 μg gonadotropin-releasing hormone, intravenously) and/or low basal IGF-1, IGF binding protein 3, free thyroxine, LH, FSH, estradiol or testosterone, and cortisol levels. IGF-1 levels were measured using an immunometric assay (IMMULITE 2000; Siemens Health Care Diagnostics, Llanberis, Gwynedd, United Kingdom). Magnetic resonance imaging scans were

performed in a 1.5 Tesla unit (Sigma; GE, Milwaukee, WI) using T1- and T2-weighted sagittal and coronal scans.

These five women made up the first set of patients with CPHD referred to this infertility care unit. For comparison purposes, we report the overall pregnancy rates achieved by women being treated for other infertility factors besides CPHD during the same period of this study and at the same facility.

B. Basic Infertility Workup

All women underwent a basic infertility workup consisting of hysterossalpingography, serum determinations of LH, FSH, and estradiol, transvaginal ultrasound for AFC, and uterine morphology assessment. Three patients had also serum AMH determination. All male partners underwent semen analysis.

C. Fertility Treatment

Patients with no other identifiable infertility factor than anovulation (HH) were submitted to controlled ovarian stimulation (COS) for timed intercourse (TI). Couples in which a mild male factor (altered semen analysis but ≥5 million motile sperm and >4% normal sperm according to strict morphology criteria) was identified were submitted to COS and intrauterine insemination (IUI). When a tubal abnormality or severe male factor (<5 million motile sperm or ≤4% strict morphology in at least two semen analyses) was identified or when couples had three consecutive failures of TI/IUI, they were offered *in vitro* fertilization (IVF).

COS was performed with human menopausal gonadotropin (Menopur; Ferring Pharmaceuticals, Kiel, Germany), containing both FSH and LH activity (1:1). Daily subcutaneous gonadotropin administration started between menstrual cycle days 3 through 7. The initial dose varied from 75 IU/d (TI and IUI) to 150 IU/d (IVF). Patients were subjected to transvaginal ultrasound scans on stimulation days 5 and 6 and every 2 to 3 days after that; at each examination, the endometrial thickness and the mean diameter of each ovarian follicle were recorded. If after 7 days of stimulation there were no follicles ≥10 mm in mean diameter, the daily human menopausal gonadotropin dose was increased in 75 IU. Cycles were canceled when there was no follicle ≥10 mm after 14 days of stimulation or no follicle ≥15 mm after 28 days of stimulation. When the leading follicle reached >18 mm in mean diameter, 250 μg of recombinant hCG (Ovidrel; Merck, Bari, Italy) were administered, and TI, IUI, or transvaginal ultrasound–guided follicle aspiration was performed 36 hours later according to each patient's treatment protocol.

Gamete processing, fertilization, and embryo culture and transfer to the uterus proceeded as previously described [18]. Elective single-embryo transfers (eSETs) were performed in all IVF cycles. Also, because multiple pregnancies were associated with poor prognosis in women with CPHD [7], when COS for TI or IUI resulted in more than one growing follicle, the treatment was converted to IVF and eSET to reduce the risk of multiple gestation. All embryos were transferred at the blastocyst stage. When more than one viable embryo was obtained, the extra embryos were cryopreserved (vitrification).

Patients undergoing IVF or IUI received luteal-phase support with vaginal micronized progesterone (400 mg/d in IUI and 600 mg/d in IVF). When frozen-thawed embryo transfer was required, patients had endometrium preparation with oral estradiol valerate (6 mg/d) from menstrual cycle day 3 on. Transvaginal ultrasound was performed weekly, and, when the endometrial thickness reached ≥7 mm (after at least 10 days of estradiol valerate), micronized progesterone was added to the regimen (600 mg/d, vaginally). Five days later, embryos were thawed (one at each transfer attempt) and transferred to the uterus. The remaining embryos were kept frozen.

Pregnancy was confirmed with serum β-hCG test 14 days after TI, IUI, or embryo transfer. The first obstetric transvaginal ultrasound, to confirm an intrauterine pregnancy, was performed 14 days after the initial positive β-hCG test.

2. RESULTS

A. Hormonal Replacement Before Fertility Treatment

All five patients were deficient for GH, LH/FSH, and TSH. Patient 2 also had adrenocorticotropic hormone (ACTH) deficiency and diabetes insipidus (DI), patient 3 had ACTH deficiency, and patient 4 had DI. Neuroimaging was abnormal in all of them (Table 1). The patients were treated for all deficiencies since first presentation (ages ranging from 9 to 12 years) with standard doses of levothyroxine, cortisone acetate, and desmopressin; patients were moved to prednisone after reaching adult height. GH replacement doses ranged from 0.33 to 0.50 μg/kg/d. The age of pubertal induction varied from 12 to 16 years using conjugated estrogen tablets and medroxyprogesterone acetate. Adult height varied from 140 to 165 cm. The genetic diagnosis could be established in only patient 1, who harbors a *GLI2* (p. L788fsX794) loss-of-function mutation [19]. The clinical and radiological features of this cohort are shown in Table 1.

Once the desire to conceive was expressed, patients were referred to the infertility care unit, and their hormonal replacement regimen was optimized. GH was reinstituted or optimized (0.3 to 1.0 mg daily) in all patients prior to ovarian stimulation treatment. IGF-1 after GH optimization ranged from 129 to 224 ng/mL (normal range for age and sex, 109 to 358 ng/mL) (Table 2). Conjugated estrogen tablets and medroxyprogesterone acetate or oral contraceptive pills (OCPs) were replaced by a regimen of oral estradiol valerate (2 mg for 21 days) + levonogestrel (0.25 mg) in the last 10 days of menstrual cycle with a 7-day interval between cycles; patient 3 kept using OCPs (20 μg ethinyl estradiol and 75 μg gestodene). Patients were 25 to 37 years old at the beginning of infertility treatment (Table 2).

B. Basic Infertility Workup

Results of the basic infertility workup are presented in Table 2. Of note, three women (patients 2, 3, and 5) had very low AFCs for their ages. They also had severely suppressed basal serum LH and FSH levels.

Patients 1 and 5 had partners with mild alterations on semen analysis; therefore, they were initially submitted to IUI. The treatment protocol for patient 5 was converted to IVF due to multifollicular growth in the second and third COS attempts. Patient 4 had an associated tubal abnormality and proceeded to IVF. Patients 2 and 3 had no tubal abnormalities or

Table 1. Phenotype of Patients With CPHD Referred to the Fertility Treatment

Patient	Hormonal Deficiencies	Diabetes Insipidus	MRI			Age of Pubertal Induction (y)	Adult Height (cm)	Other Features
			Anterior Pituitary	Stalk	Posterior Pituitary			
1	GH, LH, FSH, TSH	No	Normal	Absent	Ectopic	16	140	GLI2 mutation
2	GH, LH, FSH, TSH, partial ACTH	Yes	Small	Thin	Nonvisualized	14	165	Septo optic dysplasia
3	GH, LH, FSH, TSH, ACTH	No	Small	Absent	Ectopic	12	161	Right cerebellar hypoplasia, dilated ventricle
4	GH, LH, FSH, TSH	Yes	Small	Thick	Nonvisualized	16	154.5	Cerebellar and brain stem hypoplasia
5	GH, LH, FSH, TSH, ACTH	No	Small	Absent	Ectopic	16	158	

Table 2. Basic Infertility Workup of Patients With CPHD Wishing Fertility Treatment

Patient	Age (y)	FSH (U/L)	LH (U/L)	Estradiol (pg/mL)	IGF-1 (ng/mL)	AMH (ng/mL)	Uterine Volume (mL)	Antral Follicle Count	Infertility Factors
1	25	4.6	4.5	19	224	NA	57	10	HH + mild male
2	27	<1.0	<0.1	19	192	0.38	63	1	HH
3	26	1.6[a]	0.9[a]	<13[a]	147	2.5	21	0[a]	HH
4	35	6.4	3.9	<13	129	1.5	50	4	HH + Tubal
5	37	<0.6	<0.1	<15	159	NA	40	2	HH + mild male

Abbreviation: NA, not available.
[a]Using oral contraceptives (at the pill-free interval).

associated male infertility; hence, they were offered TI. After three unsuccessful TI attempts, patient 3 was submitted to two IVF cycles.

C. Fertility Treatment and Outcome

Treatments were performed between July 2012 and April 2014; outcomes are summarized in Table 3. All women became pregnant. Patients 2 and 5 had their first COS attempts cancelled due to low ovarian response to stimulation. In IVF cycles, the number of retrieved oocytes varied between 3 and 10, resulting in one to three viable embryos for transfer in each cycle. Patient 4 had a singleton pregnancy after a fresh eSET. In patient 3, a frozen-thawed eSET resulted in a singleton pregnancy. Patient 5 had a spontaneous first trimester miscarriage after her first IVF and a monochorionic twin gestation after a frozen-thawed eSET. All other pregnancies were singleton.

While these women were treated (2012 to 2014), the overall pregnancy rates (per initiated cycle) at this infertility care unit were 12% (TI), 12.4% (IUI), and 24.4% (IVF).

D. Hormonal Replacement During Pregnancy: Outcomes and Puerperium Details

Hormonal replacement therapy was monitored during pregnancy. GH was not discontinued, with the goal to maintain IGF-1 levels in the normal range. IGF-1 monitoring was possible in

Table 3. Assisted Reproduction Treatments and Outcome in Five Patients With CPHD

Patient	Treatment	Stimulation Duration (d)	Total Gonadotropin Consumed (IU)	Number of Oocytes Harvested	Number of Viable Embryos for Transfer	Treatment Result
1	IUI	20	2175	NA	NA	SP
2	TI	28	3375	NA	NA	CC
	TI	25	3450	NA	NA	SP
3	TI	15	1125	NA	NA	N
	TI	15	1125	NA	NA	N
	TI	28	2250	NA	NA	N
	IVF	20	2175	4	3	*N*-N-N[a]
	IVF	9	1200	6	1	SP
4	IVF	9	1800	5	3	SP
5	IUI	14	1575	NA	NA	CC
	IVF	10	1500	3	1	N
	IVF	12	1880	10	2	Mis-TP[b]

Each row represents one attempt.
Abbreviations: CC, cancelled cycle; Mis, miscarriage; N, negative; NA, not applicable; SP, singleton pregnancy; TP, twin pregnancy.
[a]Patient 3 underwent three elective single embryo transfers.
[b]Patient 5 underwent two elective single embryo transfers in her second IVF cycle.

four patients. Patients 1 and 3 achieved normal IGF-1 levels with doses of GH ranging from 0.33 to 0.5 mg/d. Patient 2 refused to use GH during pregnancy, and her IGF-1 levels remained below −2 standard deviation (SD) during all pregnancies. Patient 5 had a twin pregnancy. Her IGF-1 levels started to rise above +2SD during the second trimester, and GH was discontinued in the third trimester (Fig. 1). Regarding the treatment of other pituitary deficiencies, patients 2, 3, and 5 had ACTH deficiency, and there was no need to adjust the doses during pregnancy (doses of prednisone ranged from 2.5 to 5.0 mg/d). Patients 2 and 4 had DI, and the previous replacement dosage was maintained throughout pregnancy. Patients 2 and 4 were on desmopressin nasal spray (10 μg twice daily). Free thyroxine levels were within the normal range before and throughout pregnancy. As expected, there were changes in levothyroxine replacement therapy: all patients but patient 2 had increases in their daily doses (Table 4). The doses were increased in the first trimester, and the average increase was 32%.

The gestational age at birth ranged from 35 to 39 weeks and 4 days. One fetus had breech presentation. There were three cesarean and two vaginal deliveries. The cesarean sections were indicated due to breech presentation (patient 1), labor dystocia (patient 2), and fetal distress (patient 4). Only patient 4 had a newborn small for gestational age (1650 g). This newborn needed orotracheal intubation for 24 hours and was discharged from the hospital 19 days after birth. This was the only case of perinatal complications. The other five newborns, including the twins, were born with adequate birth weight. Three patients were able to breastfeed (Table 4). All six infants/toddlers were healthy and had no signs of hypopituitarism.

3. DISCUSSION

Assisted reproduction treatment in women with hypopituitarism has been associated with fewer ovulatory cycles, prolonged stimulation duration until ovulation, lower pregnancy rates, and higher miscarriage rates compared with women with isolated HH, suggesting that deficiencies of pituitary hormones other than gonadotropins have a major adverse effect on infertility treatment success [8]. Moreover, a tendency to poorer outcomes has been reported when hypopituitarism is diagnosed at a young age [4].

We present here the fertility outcomes of the largest case series from a single center of women with childhood-onset CPHD. In our cohort, all women ovulated and achieved pregnancy in one to five COS cycles; only two COS cycles had to be cancelled due to low response to stimulation, and there was only one miscarriage (subsequently, the same patient had a monochorionic twin pregnancy and live birth). The patients' young age at treatment may have

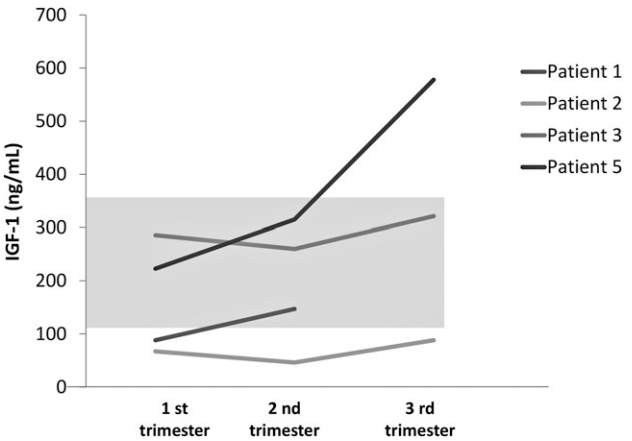

Figure 1. Longitudinal evaluation of IGF-1 levels in four patients with CPHD during pregnancy. Patients 1, 3, and 5 were receiving GH replacement (dose ranging from 0.33 to 0.66 mg/d). Patient 2 did not receive GH treatment. IGF-1 normative reference values according to age and sex are shown by the gray area (109 to 358 ng/mL).

Table 4. Adjustment of Levothyroxine (LT4) Doses During Pregnancy and Pregnancies Outcomes of Patients with CPHD After Fertility Treatment

Patients	LT4 Dosage Before Pregnancy (μg)	LT4 Dosage During Pregnancy (μg)	Gestational Age at Birth (weeks/ days)	Type of Delivery	Fetal Presentation	Birth Weight (g)	Newborn Length (cm)	Breastfeeding
1	50	75	39/4	Cesarean	Breech	3365	48	Yes
2	75	75	38/5	Cesarean	Cephalic	3270	47	No
3	100	125	38	Vaginal	Cephalic	2870	45	Yes
4	125	150	35	Cesarean	Cephalic	1650	44	Yes
5[a]	75	125	36	Vaginal	Cephalic	2740, 2400	48 45.5	No

[a]Twin pregnancy.

contributed to the good outcomes observed, but adequate hormonal supplementation, particularly GH, might have also influenced the results of treatments. Indeed, in case reports, GH supplementation to women with acquired hypopituitarism (including GH deficiency) during COS has been shown to improve both ovarian response to stimulation [5, 10, 20] and endometrial growth [21]. One previous study reported six patients who resemble ours (i.e., idiopathic CPHD); three of them became pregnant, and only one used GH replacement prior to fertility treatment [22].

Serum AMH concentration and the number of antral follicles identified in the ovaries during a transvaginal ultrasound at the beginning of a menstrual cycle (AFC) have been used to predict the ovarian response to COS in terms of oocyte yield [17]. Sonntag *et al.* [14] and Deubzer *et al.* [15] observed reduced AMH levels in patients diagnosed at a young age with CPHD with very low or undetectable gonadotropin serum levels. The authors hypothesized that severe gonadotropin deficiency affects AMH production in granulosa cells. Therefore, AMH does not precisely reflect the ovarian follicular reserve, although a lower level indicates a poorer prognosis of infertility treatments in patients with hypopituitarism, particularly those with severely suppressed gonadotropins since an early age. Our findings are in agreement with this hypothesis. Three women in our series (patients 2, 3, and 5) had very low AFC levels considering their ages [23, 24]. They also had markedly suppressed serum gonadotropin levels. However, whereas the AMH level was reduced in the serum of patient 2, in agreement with her AFC, in patient 3 the AMH level was normal, contrasting with her AFC. Of note, patient 3 was taking OCPs when she was evaluated before the infertility treatment; OCPs are known to interfere not only with basal gonadotropin levels but also with AFC and uterine volume [25]. Patient 3 was the only one in this series with reduced uterine volume. Indeed, gonadotropin serum levels in patient 3 were higher upon CPHD diagnosis. Therefore, only two women in our series (patients 2 and 5) had severely suppressed gonadotropin levels from childhood and reduced ovarian reserve tests results concomitantly. Both of these patients had their first attempt of COS cancelled due to low ovarian response. However, subsequent attempts promoted follicular development, pregnancies, and live births. These observations suggest that, in women with CPHD, reduced ovarian reserve tests results might be associated with longer stimulation duration and probably with cancelled cycles before ovulation is reached, but they do not preclude pregnancy.

Placental growth hormone, also known as growth hormone variant, is encoded by GH2. Its concentration gradually increases during pregnancy and replaces the pituitary GH. In normal pregnancies, placental growth hormone concentrations correlate with IGF-1, and, even in one patient with hypopituitarism due to *POU1F1* mutation, this pattern was maintained [26, 27]. Nevertheless, some researchers advocate the use of GH in the first two trimesters in patients with GH deficiency because IGF-1 levels can be very low in these patients, and this approach has proven to be safe [12, 27, 28]. In the present study, we maintained the use of GH throughout the pregnancy, monitoring IGF-1 levels in four patients. Three patients were

adherent to GH use and one patient refused the treatment. The latter patient remained with IGF-1 levels below −2SD throughout pregnancy, which is not in accordance with many reports in the literature, where IGF-1 levels steadily rise along the second and third trimesters [12, 27]. In the patient with twin pregnancy, GH was discontinued in the third trimester due to IGF-1 levels above +2SD. The other two patients on GH replacement had IGF-1 levels in the normal range along all pregnancy.

High rates of obstetric complications are reported in pregnancies of women with hypopituitarism, including fetal malpresentation, small for gestational age neonates, postpartum hemorrhage, and a high rate of cesarean deliveries [6]. Also, in one large study there were no survivors from four sets of twins, leading to a strict recommendation to avoid multiple pregnancies in these women [7]. Against all odds, an elective single embryo transfer in our series resulted in a monochorionic twin gestation with a successful vaginal delivery. The only case of perinatal complications was one fetus with intrauterine growth restriction that presented with fetal distress and needed neonatal intensive care. There was one fetal malpresentation (breech lie), three cesarean deliveries, and no cases of postpartum hemorrhage. All six infants/toddlers are now healthy with no signs of hypopituitarism.

In summary, optimized hormonal replacement, including GH, in women with childhood-onset hypopituitarism resulted in successful pregnancies and healthy babies after individualized fertility treatment. Diminished ovarian reserve tests results should not preclude fertility treatment in these women.

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