RESEARCH

Normal-high IGF-1 level improves pregnancy rate after ovarian stimulation in women treated with growth hormone replacement therapy

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Abstract

Objective: Growth hormone (GH) and insulin-like growth factors (IGFs) are not mandatory for reproductive life, but data suggest their synergistic action with follicle-stimulating hormone throughout ovarian folliculogenesis. We aimed to evaluate the association of IGF-1 level on clinical pregnancy rate after ovarian stimulation, with or without intrauterine insemination, in women with GH deficiency (GHD) treated with GH replacement therapy (GHRT) at conception.
Design and methods: Data from 19 women with both GHD and hypogonadotropic hypogonadism referred to our reproductive medicine department were retrospectively collected. IGF-1 levels were assessed in a single laboratory, and values were expressed in s.d. from the mean.
Results: Amongst the seven patients receiving GHRT during ovarian stimulation, higher IGF-1 levels were significantly associated with clinical pregnancy (+0.4 s.d. vs –1.6 s.d., *P* = 0.03). Amongst the 24 pregnancies obtained by the 19 infertile patients, pregnancy loss was less frequent with the addition of GHRT than without (1 miscarriage out of 8 total pregnancies vs 4 miscarriages out of 16 total pregnancies).
Conclusions: This is the first study evaluating the association of IGF-1 level on clinical pregnancy rate in GH-treated women at conception. When taking care of female infertility due to hypogonadotropic hypogonadism, practitioners should enquire about the associated GHD and IGF-1 levels. To ensure higher clinical pregnancy chances, practitioners should aim for IGF-1 values at conception, ranging from 0 s.d. to +2 s.d., and, if necessary, could discuss initiation or increase GH treatment. Prospective studies should help strengthen our results.

Introduction

Growth hormone (GH) is a pituitary hormone with pleiotropic effects. After being secreted into the general circulation, GH binds to its receptor with subsequent direct effects and insulin-like growth factor (IGF)-mediated effects (1). IGF-1 concentration is routinely used to assess both treatment's efficacy and patient's adherence when treated with GH replacement therapy (GHRT). The paramount importance of the GH–IGF axis on bone growth during childhood is well documented, as well as its roles on tissue growth and metabolism in adults (2, 3). However, its effects on reproductive life and ovarian function are not fully understood yet.

Data over the last 30 years enlighten GH role in women's reproductive life (follicular growth, ovarian steroidogenesis, ovulation and oocyte quality). GH and its receptor have been detected at each step of ovarian folliculogenesis (4). *In vitro*, GH stimulates estradiol production by follicles (2, 3, 5, 6) and progesterone production by corpus luteum (2, 3, 5, 7), both directly and synergistically with follicle-stimulating hormone (FSH) and human chorionic gonadotrophin (hCG) action. GH also has a role on oocyte quality. *In vivo*, Mendoza *et al.* show a positive correlation between GH levels in the follicular fluid and oocyte capacity to evolve into a good-quality embryo (8).

The GH–IGF axis integrity is not mandatory for spontaneous fertility: spontaneous pregnancies have been described in women with GH deficiency (GHD) without GHRT (9, 10, 11, 12). However, spontaneous pregnancies are scarce, as hypogonadotropic hypogonadism is frequently concomitant with GHD. Vila *et al.* report the largest international cohort of 8152 women with GHD, who received GHRT at least once between 1994 and 2012 (9): 62% of women had hypogonadotropic hypogonadism, and out of the 173 pregnancies achieved, only 32 pregnancies were known to be spontaneous (without ovarian stimulation nor assisted reproductive technology (ART)).

Few studies have evaluated the impact of GHRT on spontaneous and nonspontaneous fertility outcomes in GHD women, most of them displaying a low level of evidence. Giampietro was the only one to report cases of four GHD women, with infertility but no hypogonadism; adjunction of GHRT allowed spontaneous pregnancies (13). In GHD infertile women, some authors have reported nonspontaneous pregnancies without GHRT (9, 11, 14, 15), while others reported nonspontaneous pregnancies with the adjunction of GHRT after ovarian stimulation (16, 17, 18) or ART (17, 19, 20). When comparing ovarian stimulation cycles with or without GHRT adjunction, opposite results were found. Some authors found beneficial effects of GHRT such as reduction of total human menopausal gonadotropins (hMG) dose used (21), more mono-follicular recruitment (10), shorter duration of stimulation before pregnancy (22), better embryo quality and higher fertilization rate in intracytoplasmic sperm injection or in vitro fecondation (IVF), without modification of the number of harvested oocytes (23, 24), while others did not find any difference (25, 26). The only randomized crossover study, by Blumenfeld, evaluated seven GHD infertile women requiring ovarian stimulation or ART and found a beneficial effect of GHRT (21).

To date, the utility of GHRT to improve GHD women's fertility remains debated, and, to our knowledge, no published study has ever evaluated the association of GHRT on clinical pregnancy rate in this population. Because of these inconsistent data, the 2019 AACE guidelines do not routinely recommend the use of GHRT during conception and GHRT continuation during pregnancy (27).

Our goal is to evaluate the association of IGF-1 level on clinical pregnancy rate after ovarian stimulation, and obstetrical outcomes, in women with GHD, with or without GHRT at conception.

Subjects and methods

Study design and participants

We retrospectively analyzed the endocrine and reproductive data of a group of 156 female patients referred to a single tertiary department of Endocrinology and Reproductive Medicine (Pitie-Salpetriere Hospital, Paris, France), presenting with GHD. All patients gave their written informed consent. This study did not require any approval from the local ethics committee, as it is not relevant to the French law (Loi sur les recherches Biomédicales).

Endocrine parameters and assay methods

All pituitary functions were screened. GHD was defined as an insufficient GH peak during insulin tolerance test (ITT) (severe GHD if GH peak < 10 mU/L; partial GHD if GH peak between 10 and 20 mU/L). According to 2007 consensus guidelines, patients with three or more pituitary hormone deficiencies and an IGF-1 level below the reference range were also considered to have GHD, without needing an ITT (28). All GH and IGF-1 samples were measured in Pitie-Salpetriere's biochemistry laboratory, Paris, France. GH was measured using chemiluminescent immunoassay DiaSorin Liaison® (Saluggia, Italy). IGF-1 samples were measured using different assays: radioimmunological assay Cisbio IGF1-RIACT® (Codolet, France) before June 2009 and chemiluminescent immunoassay since June 2009 – DiaSorin Liaison® between June 2009 and February 2013 and DiaSorin Liaison XL® since March 2013 (Saluggia, Italy). IGF-1 values were expressed in S.D. scores. We obtained S.D. values according to the methods provided by Chanson *et al.* (29), allowing value homogenization and inter-assay comparison.

Reproductive history

Gravidity, parity, mode of conception (spontaneous, after ovarian situation or ART), use of GHRT during conception, time of GHRT discontinuation, last available IGF-1 s.d. score before pregnancy, pregnancy outcomes and obstetrical and fetal complications were thoroughly collected.

Statistical analysis

Descriptive statistics are expressed in percentage, mean and minimal and maximal values according to the variables. Because of the small number of patients, non-parametric tests were used to compare groups: Mann–Whitney for quantitative variables and Fisher's exact test for qualitative variables. All reported *P* values are two-sided. *P*-values <0.05 were considered statistically significant. GraphPad Prism 7.0 software and R Core Team software (Vienna, Austria) were used to perform those analysis.

Results

Population description and GHD status

Between March 2006 and January 2022, 156 GHD female patients presented with GHD. Patients were followed-up from 1 to 16 years, (mean 7 years). GHD was the only pituitary deficiency in 17.9% of patients, and one or multiple pituitary deficiencies were present in other cases, such as hypogonadotropic hypogonadism in 114 patients (73.1%).

GHD was diagnosed before the age of 50 in 143 patients (91.7%). Amongst them, only 27 (18.9%) expressed the wish to get pregnant during follow-up. Twenty-four patients required ovarian stimulation or ART because of associated hypogonadotropic hypogonadism, but five were lost to follow-up (Fig. 1). Nineteen infertile patients were analyzed: 14 achieved at least one clinical pregnancy, while the other 5 never had a clinical pregnancy. Both groups were similar regarding maternal age (30.2 vs 30 years old), BMI (28.4 vs 27 kg/m^2) and FSH level (1.79 vs 1.83 UI/L) at first infertility checkup. Three patients with no hypogonadism had spontaneous pregnancies.

Effect of GHRT adjunction and of IGF-1 level control in our GHD infertile cohort

Out of the 19 infertile patients, 7 received GHRT during ovarian stimulation or ART, and 12 did not. Clinical data concerning these two populations are presented in Table 1. BMI was higher in the population with GHRT

when compared to the rate of corticotropin deficiency, which was lower in such population. Finally, two patients with congenital deficiency were not under GH at the time of conception. The first one has been diagnosed when she was 24 years old because of GHD cases in her family (a *TBX3* mutation has been discovered). The second one had a pituitary stalk interruption syndrome; she received GH up to the age of 15 and thereafter stopped it.

A total of eight nonspontaneous pregnancies were achieved with GHRT during conception (five with ovarian stimulation and three with IVF) and 16 nonspontaneous pregnancies without GHRT (15 with ovarian stimulation and 1 with IVF). Clinical pregnancy rate was 57.1% with GHRT and 83.3% without GHRT (*P*=0.3) (Fig. 2). However, amongst patients declaring to receive GHRT injections during conception, a higher IGF-1 s.d. score was significantly associated with clinical pregnancy: +0.4 s.d. vs –1.6 s.d. (*P*=0.03) (Fig. 3). Pregnancy losses were less frequent in the GHRT group (1 miscarriage out of 8 total pregnancies in the GHRT group and 4 miscarriages out of 16 total pregnancies in the group without GHRT).

Effect of GHRT adjunction on pregnancy follow-up and births in our GHD cohort

Six spontaneous and 16 nonspontaneous clinical pregnancies were obtained from, respectively, 3 and 14 patients (Fig. 1). Out of these 22 total clinical pregnancies, six (27.3%) were exposed to GHRT during conception.

Amongst these six pregnancies (two spontaneous and four nonspontaneous), no fetal malformation was reported. GHRT was started 33 months (4–94 months) before conception, at 0.7 mg/day (0.4–1.4 mg/day), with an IGF-1 s.d. score during conception of +0.35 s.d. (–0.5 s.d. to +1.2 s.d., two missing data). GHRT was discontinued at an early stage of pregnancy (around the seventh week of gestation) in four patients and at the end of the first trimester in the other two patients. Only one patient had obstetrical complications. The mother had a congenital GHD and hypogonadotropic hypogonadism. This pregnancy was achieved at the third ovarian stimulation cycle using hMG. She presented incoercible vomiting during the first trimester and intrauterine growth restriction (IUGR) below the fifth percentile with normal umbilical artery Doppler and no preeclampsia. She had a cesarean section at 39 weeks and gave birth to a baby girl with a weight-for-age below the first percentile. The girl is now aged 4 years old and is healthy. All the other five patients had vaginal delivery. There was no premature birth.
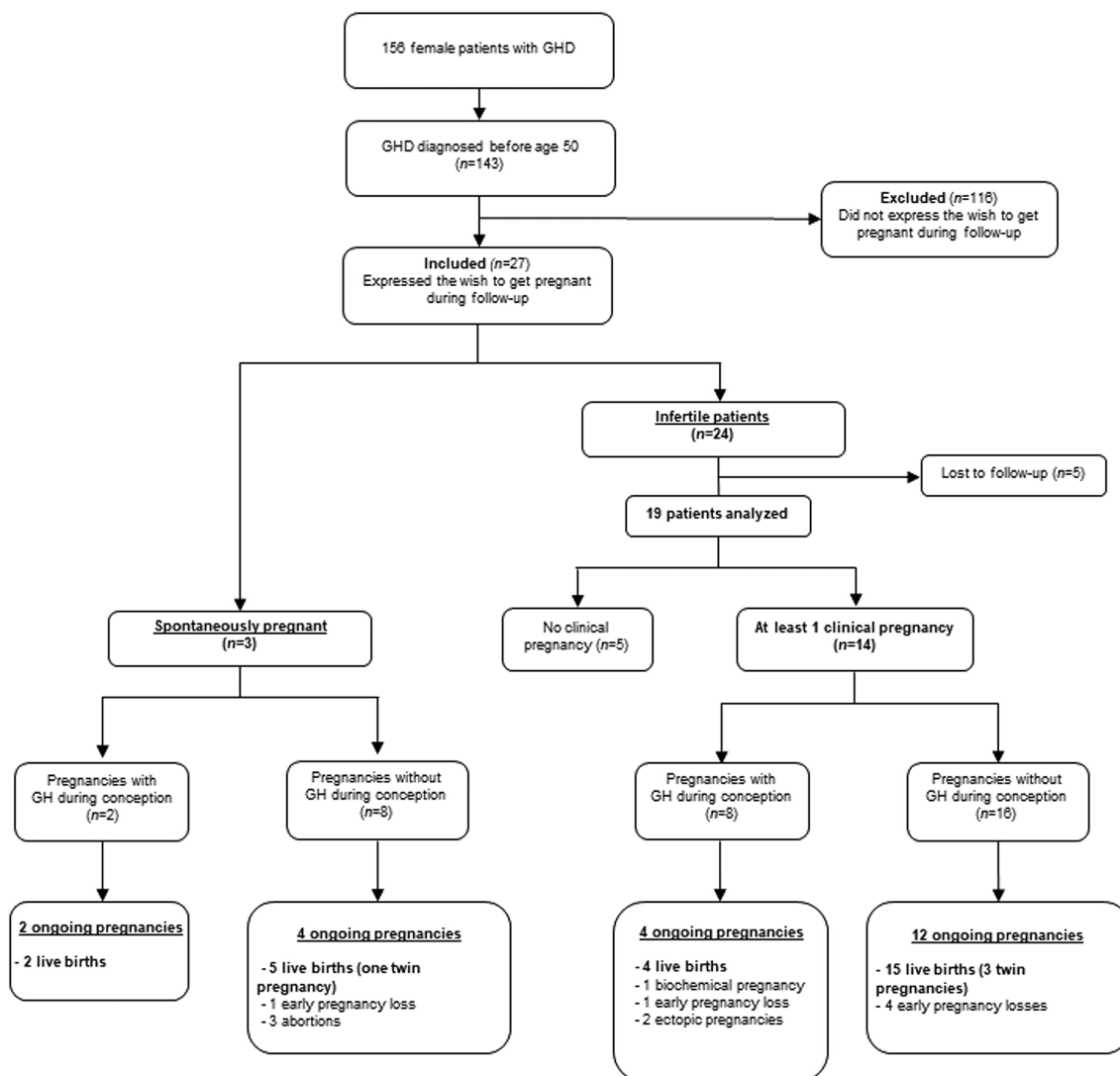
Figure 1
Flowchart of our GHD cohort.

Amongst the 16 pregnancies obtained without GHRT (4 spontaneous, 11 with ovarian stimulation and 1 with IVF), 4 presented obstetrical complications, 4 had a cesarean section and 12 had vaginal delivery. One patient had preeclampsia without IUGR; she had an emergency cesarean section at the 35th week of gestation for retroplacental clot suspicion (subsequently refuted) and gave birth to a eutrophic baby. Another patient had preeclampsia with severe IUGR below the third percentile caused by imperfecta osteogenesis and fetal bone mineralization defects diagnosed on a fetal CT scan. Because of an absent end-diastolic flow of umbilical artery Doppler, a cesarean section was performed at the 34th week of gestation after antenatal corticosteroids, giving birth to a 830 g (below 0.1 percentile) baby boy. There was

no premature birth in the other 14 pregnancies (without preeclampsia), including the twin pregnancies. Lastly, one patient had two consecutive pregnancies with gestational hypertension, she gave birth vaginally to eutrophic babies. In total, three babies were born hypotrophic: the one born at the 34th week of gestation and the twins that were not born premature.

Discussion

To our knowledge, our study is the first to evaluate the association of IGF-1 level on clinical pregnancies in GHD women receiving GHRT during conception. We chose to evaluate IGF-1 level over self-declared use of GHRT,

Table 1 Description of cohorts of patients receiving GHRT or not receiving GHRT.

	With GHRT (a) (*n* = 7), *n* (%)	**Without GHRT** (b) (*n* = 12), *n* (%)	*P* (b vs a)
Etiology of pituitary disease			
Congenital or genetic	0	2 (16.7)	<0.01
Idiopathic	2 (28.6)	0	
Tumor	1 (14.3)	8 (66.7)	
Post-radiation	0	1 (8.3)	
Infiltrative	2 (28.6)	0	
Other	2 (28.6)	1 (8.3)	
Mean age at GHD onset (min; max)	25.1 years (10; 39)	18.4 years (0.9; 35)	<0.01
Associated pituitary disease			
Gonadotropin deficiency	7 (100)	12 (100)	<0.01
Corticotropin deficiency	3 (42.9)	10 (83.3)	
Thyrotropin deficiency	5 (71.4)	10 (83.3)	
Hyperprolactinemia	2 (28.6)	4 (33.3)	
Diabetes insipidus	4 (57.1)	8 (66.7)	
Mean age when first referred for infertility (min; max)	31.6 years (22; 40)	27.9 years (23; 36)	
Mean BMI when first referred for infertility (min; max)	34.5 kg/m^2 (19.5; 41)	27 kg/m^2 (20; 33), two missing data	<0.01 (a vs b)

because the former better reflects adherence to the latter (daily s.c. injections). Although all IGF-1 samples were measured in a single laboratory, assays varied over time; therefore IGF-1 levels were expressed in s.d. scores from the mean to allow inter-assay comparisons. Amongst our patients' self-declaring use of GHRT during conception, IGF-1 s.d. score values ranged from –2.7 s.d. to +1.2 s.d., but higher IGF-1 values were significantly associated with clinical pregnancy (+0.4 s.d. vs –1.6 s.d., *P*=0.03). Our results are consistent with Giampietro who was the first to report GHRT as an effective treatment of infertility in four eugonadal women with GHD, thus avoiding the need of ovarian stimulation (13). Another publication by Scheffler reported an increase of GH concentration in the follicular fluid and improvement in oocyte quality (no abnormal morphologies) and in embryo quality (grade A) in a woman after the addition of GHRT

during IVF procedure, allowing an embryo transfer with subsequent successful pregnancy (30). Pregnancy losses were also less frequent in our GHRT group (1 miscarriage out of 8 total pregnancies vs 4 miscarriages out of 16 total pregnancies in the group without GHRT), and we found no other data in the published literature. Altmäe suggests a role of GH in endometrial receptivity and implantation (31).

Nineteen patients have been studied among the whole cohort. Endocrine deficiencies are not significantly different except for the presence of corticotropin deficiency at a lower rate in the cohort of patients with GHRT. The point to be underlined is the fact that most of the patients without GHRT has a diagnosis of tumor, suggesting the
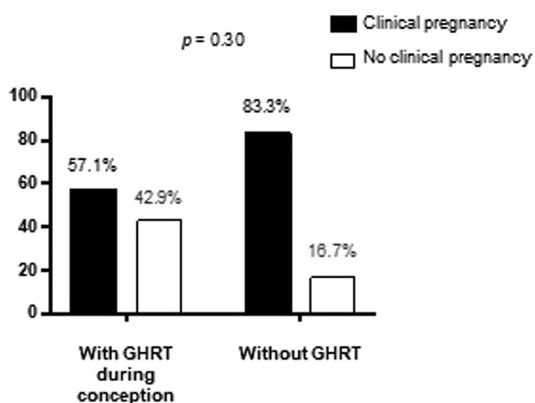
Figure 2
Clinical pregnancy rate according to GHRT adjunction during conception in our GHD cohort (ovarian stimulation and ART).
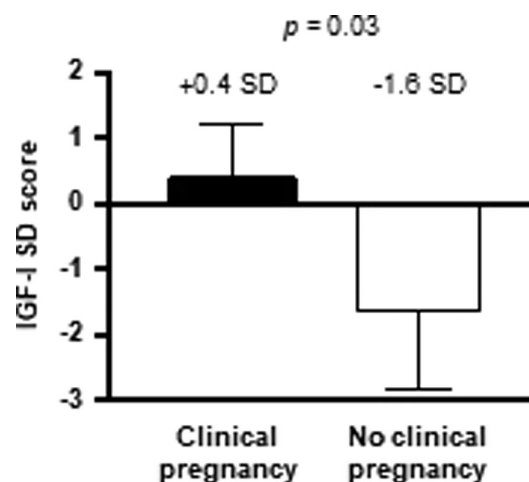
Figure 3
IGF-1 s.d. score value according to pregnancy outcome in GHD infertile women treated with GHRT during ovarian stimulation or ART.

absence of treatment and also maybe the fear from adult endocrinologists to treat such patients with GH.

In our cohort, amongst six clinical pregnancies exposed to GHRT during conception, treatment was discontinued either around the seventh week of gestation, or by the end of the first trimester, as previously described (32). No fetal malformation was reported, there was no premature birth and only one patient had non-vascular IUGR (with normal umbilical artery Doppler). There was no gestational hypertension or preeclampsia. On the other hand, amongst the 16 pregnancies obtained without GHRT exposure, 1 had gestational hypertension, 1 had preeclampsia without IUGR and another 1 had both preeclampsia with severe IUGR below the third percentile and imperfecta osteogenesis and fetal bone mineralization defects. Although our samples are small, it is surprising to notice the absence of any vascular event in the GHRT group. Wider data can be found in the Vila's international cohort (9). In this publication, 160 out of 173 pregnancies were exposed to GHRT during conception; treatment was discontinued at an early stage of pregnancy in 40.1%, by the end of the secondtrimester in 24.7% and was continued through the whole pregnancy in 26.7%, according to practitioner's habits. No correlation was found between the time of GHRT discontinuation, obstetrical complications (data were available for 67 pregnancies) or fetal complication and malformation (data available for 47–139 patients). Placental GH is exclusively produced during pregnancy and slowly replaces pituitary GH. In our opinion, GHRT can be continued safely at the beginning of the pregnancy because it does not prevent placental GH production (33), and GHRT is no longer needed after the end of the first trimester, as placental GH becomes the only detectable GH in maternal serum sample from the secondtrimester on (34) and is produced even in women with documented GHD (35). The 2019 AACE guidelines also do not routinely recommend GHRT continuation during pregnancy (27).

Another surprising finding of our study is the very high proportion of patients who did not express the wish to get pregnant (33) during follow-up (116 out of 156 for whom GHD was diagnosed during reproductive years), just as in the Vila's international cohort (97.2% did not have children or report infertility). We thus have small samples and lack statistical power. This could be mostly explained by the median age of our patients at the last endocrine checkup (25 years old), maybe by the fear of transmitting one's pathology, or by the medicalization required to obtain a pregnancy in these patients who often present with associated hypogonadotropic hypogonadism. Some of our patients also had premature ovarian failure associated with GHD, both being the consequence of chemotherapy and cerebral radiotherapy. Moreover, because many infertile patients were taken charge of before AMH dosage standardization in France, AMH values were not comparable so we did not evaluate this parameter.

Lastly, our study confirms that GH–IGF axis integrity is not mandatory for both spontaneous and nonspontaneous fertility. This result is consistent with the available literature, as spontaneous fertility has been described in women with two types of genetic conditions: Laron syndrome (12) and deletion of *GH-V* (placental GH gene) (36).

Strengths of the present study are the use of IGF-1 S.D. score values allowing inter-individual comparisons and reflecting patient's real use of GHRT and the evaluation of clinical pregnancies and obstetrical outcomes, instead of less relevant non-clinical parameters. Study limitations include the monocentric data, retrospective data collection and small samples, although we are confident we did not miss too many infertility data because of the tight collaboration between endocrinologists and gynecologists in our department and expect to have more data to study in the future as our patients grow older.

In conclusion, our study emphasizes the association of normal-high IGF-1 levels and clinical pregnancy rate under stimulation in a small group of GH-treated patients at conception. When taking care of female infertility due to hypogonadotropic hypogonadism, practitioners could enquire about associated GHD and IGF-1 levels. If GH treatment is established, practitioners should probably aim for IGF-1 values at conception, ranging from 0 S.D. to +2 S.D.. However, further prospective studies should help strengthen our results.

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