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

Nathalie Ly¹,³*, Sophie Dubreuil¹,³*, Philippe Touraine¹,²,³

¹Department of Endocrinology and Reproductive Medicine, Reference Center for Rare Endocrine Diseases of Growth and Development, Reference Center for Gynecological Rare Diseases, Hôpitaux Universitaires Pitié Salpêtrière-Charles Foix, Paris, France. ²Sorbonne University, Paris, France. ³EndoERN, APHP Consortium Pitie Salpetriere Hospital, Necker Hospital

Correspondence should be addressed to P Touraine: philippe.touraine@aphp.fr - 47-83 boulevard de l’Hôpital, IE3M, 75013 Paris, France

Short title: IGF-I levels and pregnancy rate in GHD patients

Key words: Growth hormone, growth hormone deficiency, hypopituitarism, pregnancy, IGF-I, ovarian stimulation, intra-uterine insemination, assisted reproductive technology

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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 (FSH) throughout ovarian folliculogenesis. We aimed to evaluate the association of IGF-I level on clinical pregnancy rate after ovarian stimulation, with or without intra-uterine insemination, in women with GH deficiency treated with GH replacement therapy at conception.

**Design and Methods:** Data from 19 women with both GH deficiency and hypogonadotrophic hypogonadism referred to our reproductive medicine department, were retrospectively collected. IGF-I levels were assessed in a single laboratory, values were expressed in standard deviations (SD) from the mean.

**Results:** Amongst the 7 patients receiving GH replacement therapy during ovarian stimulation, higher IGF-I level was significantly associated with clinical pregnancy (+0.4 SD vs -1.6 SD, \(p=0.03\)). Amongst the 24 pregnancies obtained by the 19 infertile patients, pregnancy loss was less frequent with the addition of GH replacement therapy, 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-I level on clinical pregnancy rate, in GH-treated women at conception. When taking care of female infertility due to hypogonadotrophic hypogonadism, practitioners should enquire about associated GH deficiency and IGF-I level. To ensure higher clinical pregnancy chances, practitioners should aim for IGF-I values at conception ranging from 0 SD to +2 SD, 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-I 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 energetic metabolism in adults (3, 5). 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, oocyte quality). GH and its receptor have been detected at each step of ovarian folliculogenesis (2). In vitro, GH stimulates estradiol production by follicles (3–6), and progesterone production by corpus luteum (3–5,7), both directly and synergistically with 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 follicular fluid and oocytes 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 (9–12). 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 4 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 (16–18) or ART (17,19,20). When comparing ovarian stimulation cycles with or without GHRT adjunction, opposite results were found. Some authors found a beneficial effect of GHRT: reduction of total hMG dose used (21), more mono-follicular recruitment (10), shorter duration of stimulation before pregnancy (22), better embryo quality and higher fertilization rate in Intra-Cytoplasmic-Sperm-Injection (ICSI) or In-Vitro-Fecundation (IVF), without modification of the number of harvested oocytes (23,24), while others did not find any difference (25,26). The only randomized cross-over study, by Blumenfeld, evaluated 7 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 use of GHRT during conception, and GHRT continuation during pregnancy (27).

Our goal is to evaluate the association of IGF-I 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-I level below reference range were also considered to have GHD, without needing an ITT (28). All GH and IGF-I samples were measured in Pitie-Salpetriere’s biochemistry laboratory, Paris, France. GH was measured using chemiluminescent immunoassay DiaSorin Liaison® (Saluggia, Italy). IGF-I 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-I values were expressed in standard deviation (SD) scores. We obtained SD values accordingly to the methods provided by Chanson et al (29), allowing values 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-I SD score before pregnancy, pregnancies outcomes, and obstetrical and fetal complications were thoroughly collected.
Statistical analysis:

Descriptive statistics are expressed in percentage, mean, 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 for qualitative variables. All reported $p$ values are two-sided. $P$-values < 0.05 were considered statistically significant. GraphPad Prism 7.0 software (San Diego, CA) 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 7yrs.) GHD was the only pituitary deficiency in 17.9% of patients, and combined with one or multiple pituitary deficiencies in the 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 5 were lost to follow-up (Figure 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/m2) and FSH level (1.79 vs 1.83 UI/L) at first infertility check-up. Three patients with no hypogonadism had spontaneous pregnancies.

Effect of GHRT adjunction and of IGF-I 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 2 populations are presented Table 1. When compared, BMI was higher in the population with GHRT; the rate of corticotropin deficiency was at the contrary lower in such population. Finally, 2 patients with congenital deficiency were not under GH at the time of conception. The first one has been diagnosed when she was 24 yrs-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 8 nonspontaneous pregnancies were achieved with GHRT during conception (5 with ovarian stimulation and 3 with IVF), and 16 nonspontaneous pregnancies without GHRT (15 with ovarian stimulation and 1 with IVF). Clinical pregnancy rate was of 57.1% with GHRT, and 83.3% without GHRT ($p=0.3$) (Figure 2). However, amongst patients declaring to receive GHRT injections during conception, higher IGF-I SD score was significantly associated with clinical pregnancy: $+0.4 \text{ SD vs } -1.6 \text{ SD } (p=0.03)$ (Figure 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 (Figure 1). Out of these 22 total clinical pregnancies, 6 (27.3%) were exposed to GHRT during conception.

Amongst these 6 pregnancies (2 spontaneous and 4 nonspontaneous), no fetal malformation was reported. GHRT was started 33 months (4 to 94 months) before conception, at 0.7 mg/day (0.4 to 1.4 mg/day), with an IGF-I SD score during conception of $+0.35 \text{ SD (-0.5 SD to +1.2 SD, 2 missing data)}$. GHRT was discontinued at an early stage of pregnancy (around the 7th
week of gestation) in 4 patients, and at the end of the first trimester in the other 2 patients. Only 1 patient had obstetrical complication. 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 5\textsuperscript{th} 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 1\textsuperscript{st} percentile. The girl is now aged 4 years old and is healthy. All the other 5 patients had vaginal delivery. There was no premature birth.

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 pre-eclampsia without IUGR; she had an emergency cesarean-section at the 35\textsuperscript{th} week of gestation for retroplacental clot suspicion (subsequently refuted) and gave birth to a eutrophic baby. Another patient had pre-eclampsia with severe IUGR below the 3\textsuperscript{rd} 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 34\textsuperscript{th} week of gestation after antenatal corticosteroids, giving birth to a 830g (below 0.1 percentile) baby boy. There was no premature birth in the other 14 pregnancies (without pre-eclampsia), including the twin pregnancies. Lastly, one patient had 2 consecutive pregnancies with gestational hypertension, she gave birth vaginally to eutrophic babies. In total, 3 babies were born hypotrophic: the one born at the 34\textsuperscript{th} 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-I level on clinical pregnancies, in GHD women receiving GHRT during conception. We chose to evaluate IGF-I
level over self-declared use of GHRT, because the former better reflects adherence to the latter (daily subcutaneous injections). Although all IGF-I samples were measured in a single laboratory, assays varied over time, therefore IGF-I levels were expressed in standard deviation scores from the mean to allow inter-assay comparisons. Amongst our patients self-declaring use of GHRT during conception, IGF-I SD score values ranged from -2.7 DS to +1.2 DS, but higher IGF-I values were significantly associated with clinical pregnancy (+0.4 SD vs -1.6 SD, p=0.03). Our results are consistent with Giampietro who was the first to report GHRT as an effective treatment of infertility in 4 eugonadal women with GHD, thus avoiding the need of ovarian stimulation (13). However, women with GHD and looking to get pregnant are more likely to have associated hypogonadotropic hypogonadism, and thus more likely to require ovarian stimulation or ART (62% of the 8152 GHD women reported in Vila’s study, the largest international cohort of patients who ever received GHRT) (9). Blumenfeld published a randomized cross-over monocentric study amongst seven GHD women with 2 to 11 years of infertility history, with neither pregnancy after ovarian stimulation nor oocyte retrieval in IVF (21). GHRT administration allowed pregnancies in 3 patients after ovarian stimulation using less hMG, it allowed oocytes harvest in 1 patient undergoing IVF and 1 spontaneous pregnancy in another patient with previous multiple IVF failure without use of GHRT. Some physiopathological explanations can be found in Rajesh’s monocentric study that evaluated 20 GHD women who underwent IVF without GHRT, then with GHRT and who got pregnant (23). Use of GHRT was associated with a significant improvement in day 2 embryo quality, and in fertilization rate in ICSI-IVF, with no modification of number of harvested oocytes, nor in endometrial thickness. Another publication by Scheffler reported an increase of GH concentration in follicular fluid, improvement in oocyte quality (no abnormal morphologies) and in embryo quality (grade A) in a woman after 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). Other studies reported either a decrease in hMG dose (21), more monofollicular ovarian response (10), shorter duration of stimulation (22) or no effect at all (25,26) with the adjunction of GHRT during conception.

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 Patients without GHRT has a diagnosis of tumor, suggesting the absence of treatment and also maybe the fear from adult endocrinologists to treat such patients with GH.

In our cohort, amongst 6 clinical pregnancies exposed to GHRT during conception, treatment was discontinued either around the 7th 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 1 patient had non-vascular IUGR (with normal umbilical artery Doppler). There was no gestational hypertension nor 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 3rd 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 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 2nd trimester in 24.7% and was continued through the whole pregnancy in 26.7%, according to practitioner’s habits. No correlation was found between time of GHRT discontinuation, obstetrical complications (data were available for 67 pregnancies).
nor fetal complication and malformation (data available for 47 to 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 2nd trimester 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 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 last endocrine check-up (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 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 is the use of IGF-I SD score values allowing inter-individual comparisons and reflecting patient’s real use of GHRT, 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 GH deficiency and IGF-I level. If GH treatment is established, practitioners should probably aim for IGF-I values at conception ranging from 0 SD to +2 SD. However, further prospective studies should help strengthen our results.
DECLARATION OF INTEREST

The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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AUTHOR CONTRIBUTION STATEMENT

Nathalie LY performed conception and design of the work, acquisition, analysis, interpretation of data, and wrote the manuscript. Sophie DUBREUIL wrote the manuscript and is head of the Reproductive Medicine unit. Philippe TOURAINE performed conception of the work, and interpretation of data and is member of the Department of Endocrinology and Reproductive Medicine.

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LEGENDS

Figure 1: Flow chart of our GHD cohort

Figure 2: Clinical Pregnancy rate according to GHRT adjunction during conception, in our GHD cohort (ovarian stimulation and ART)
Figure 3: IGF-I SD score value according to pregnancy outcome in GHD infertile women treated with GHRT during ovarian stimulation or ART.
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Table 1: Description of cohorts of Patients receiving or not GHRT

<table>
<thead>
<tr>
<th>Etiology of pituitary disease</th>
<th>With GHRT (a)</th>
<th>Without GHRT (b)</th>
<th>P (b versus a)</th>
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<tbody>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n; %</td>
<td>n; %</td>
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<tr>
<td>Congenital or genetic</td>
<td>0</td>
<td>2 (16.7%)</td>
<td>P&lt;0.01</td>
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<tr>
<td>Idiopathic</td>
<td>2 (28.6%)</td>
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<td></td>
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<tr>
<td>Tumor</td>
<td>1 (14.3%)</td>
<td>8 (66.7%)</td>
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<tr>
<td>Post-radiation</td>
<td>0</td>
<td>1 (8.3%)</td>
<td></td>
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<tr>
<td>Infiltrative</td>
<td>2 (28.6%)</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (28.6%)</td>
<td></td>
<td></td>
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<tr>
<td>Mean age at GHD onset (min; max)</td>
<td>25.1 yo (10; 39)</td>
<td>18.4 yo (0.9; 35)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Associated pituitary disease:</td>
<td></td>
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<tr>
<td>Gonadotropin deficiency</td>
<td>7 (100%)</td>
<td>12 (100%)</td>
<td>P&lt;0.01</td>
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<tr>
<td>Corticotropin deficiency</td>
<td>3 (42.9%)</td>
<td>10 (83.3%)</td>
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<tr>
<td>Thyrotrpin deficiency</td>
<td>5 (71.4%)</td>
<td>10 (83.3%)</td>
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<tr>
<td>Hyperprolactinemia</td>
<td>2 (28.6%)</td>
<td>4 (33.3%)</td>
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<tr>
<td>Diabetes insipidus</td>
<td>4 (57.1%)</td>
<td>8 (66.7%)</td>
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<td>Mean age when first referred for infertility (min; max)</td>
<td>31.6 yo (22; 40)</td>
<td>27.9 yo (23; 36)</td>
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<tr>
<td>Mean BMI when first referred for infertility (min; max)</td>
<td>34.5 kg/m² (19.5; 41)</td>
<td>27 kg/m² (20; 33)</td>
<td>P&lt;0.01 (a versus b)</td>
</tr>
</tbody>
</table>
Figure 1: Flow chart of our GHD cohort

Flow chart of our GHD cohort

190x275mm (96 x 96 DPI)
Clinical Pregnancy rate according to GHRT adjunction during conception, in our GHD infertile cohort (ovarian stimulation and ART)
Figure 3: IGF-I SD score value according to pregnancy outcome, in GHD infertile women treated with GHRT during ovarian stimulation or ART

IGF-I SD score value according to pregnancy outcome in GHD infertile women treated with GHRT during ovarian stimulation or ART

190x275mm (96 x 96 DPI)