

Is maternal growth hormone essential for a normal pregnancy?

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Abstract

Objective: It remains uncertain whether there is any disadvantage imposed upon women with pituitary disease who are GH-deficient and become pregnant. The aim of this study was to determine whether maternal GH deficiency adversely affects the outcome of pregnancy.

Design: Retrospective study.

Methods: The case notes of 77 female patients with known GH deficiency were examined. Sixteen patients (a total of 25 pregnancies) were identified who had been pregnant whilst known to be GH-deficient. Peak GH response to provocative testing prior to pregnancy, length of gestation, birth weight, maternal well-being and the incidence of maternal and fetal complications of pregnancy were documented.

Results: Peak GH response to insulin tolerance test ($n = 21$) or glucagon stimulation test ($n = 4$) prior to pregnancy was 8.7 (<1 to 17.3) mU/l (peak ≤ 9 mU/l in 14 cases). There were 25 pregnancies resulting in 26 live births (including one set of twins and one set of quins) and 4 spontaneous first trimester abortions. Eight pregnancies were achieved by ovulation induction. Median gestation of live births was 39 (33 to 42) weeks. Median birth weight excluding multiple births ($n = 19$), uncorrected for gestational age, was 3.09 (1.64 to 4.19) kg, and the numbers with birth weights below the 10th, between the 10th and 90th, and above the 90th centiles were five, nine and five respectively. Pre-eclampsia occurred in two pregnancies and post-partum haemorrhage after one pregnancy. There were three minor congenital abnormalities.

Conclusions: Our data suggest that pregnancy in GH-deficient females is not detrimental to the fetus and the incidence of maternal morbidity is low. We conclude that GH replacement therapy is probably not essential for GH-deficient females during pregnancy.

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Introduction

Recent evidence suggests that growth hormone (GH) has a role in the maintenance of health in adults (1, 2). GH-deficient adults with pituitary disease who are on conventional hormone replacement regimens have an increased mortality rate (2–4). They are at increased risk of osteoporosis (5), have increased fat mass with reduced lean body mass (6–8) and may have a reduced quality of life (9, 10). With the availability of recombinant human GH (rhGH), evidence has accumulated which suggests improvement in these parameters following adult GH therapy (6, 11, 12).

Female patients with pituitary disease may require exogenous gonadotrophin therapy to achieve pregnancy, and those who are adrenocorticotrophic hormone- and thyroid-stimulating hormone-deficient receive conventional corticosteroid and thyroid hormone replacement throughout pregnancy. At present, rhGH therapy is not licensed for use during pregnancy, since very little data related to the efficacy and safety of

rhGH therapy during pregnancy exist. Current practice is to withdraw rhGH therapy in those patients who become pregnant during rhGH treatment, although an isolated case report suggested no adverse effects from continuing therapy (13). Furthermore, it is unknown whether untreated maternal GH deficiency during pregnancy is detrimental to either the mother or the fetus.

During normal pregnancy, there is a progressive increase in maternal serum GH (14) and insulin-like growth factor-I (IGF-I), but not in IGF-II (15). A GH variant which differs from pituitary-derived GH by 13 amino acids has been described (16). This GH variant is encoded by the GH-V gene (17), expressed by the placenta (18, 19), and is known as placental GH. Studies using the monoclonal antibody anti-GH 5B4 (to both pituitary and placental GH) and anti-GH K22 (to pituitary GH alone) have shown that after the 20th week of pregnancy there is a progressive rise in placental GH and a fall in pituitary GH to near zero in the maternal serum (20, 21). Placental GH does not

cross into the fetal circulation (20) and, unlike pituitary GH, secretion is non-pulsatile (21).

Since an alternative source of endogenous (pituitary) GH is unavailable during the first half of pregnancy in female patients with hypopituitarism, we aimed to determine whether pituitary GH deficiency adversely affects the maternal or fetal outcome of pregnancy.

Subjects and methods

We retrospectively reviewed the case notes of 77 adult female patients with GH deficiency. Sixteen patients were identified who had been pregnant whilst known to be GH-deficient (Table 1). A total of 25 pregnancies were achieved in these 16 patients. The case records were reviewed to determine the degree of GH deficiency (as judged by provocative tests) prior to each pregnancy. Each patient was interviewed to determine maternal health during pregnancy, including any perceived problems with weight gain or well-being and the frequency of obstetric complications. Fetal outcome was assessed by birth weight, gestational age and incidence of congenital abnormalities.

Fourteen patients had adult-onset GH deficiency (six prolactinomas, four non-functioning adenomas, three Cushing's disease, one craniopharyngioma) and two patients had childhood-onset GH deficiency (one congenital hypopituitarism, one idiopathic GH deficiency). The median (range) age of the patients whilst pregnant was 31 (23 to 42) years and the median (range) height was 1.64 (1.40 to 1.68) m (including the two patients with childhood-onset GH deficiency, who were 1.40 and 1.56 m in height). Whilst no patient received GH replacement therapy for the duration of pregnancy, two patients conceived whilst receiving rhGH therapy, which was withdrawn later at confirmation of pregnancy.

The severity of GH deficiency was assessed using the peak GH response to a provocative test (insulin tolerance test, $n=21$, or glucagon stimulation test, $n=4$). The result of the most recent provocative test before each pregnancy was used. The median (range) peak GH response was 8.7 (<1 to 17.3) mU/l. In 14 of 25 (56%) pregnancies the peak GH response was ≤ 9 mU/l. Eight pregnancies were achieved with ovulation induction therapy.

Results

There were 25 pregnancies (including one set of twins and one set of quins), resulting in 26 live births and 4 first trimester abortions (Table 1). Three of these abortions occurred in the 8 pregnancies that were achieved with ovulation induction therapy. The median (range) gestation of live births was 39 (33 to 42) weeks. The median birth weight excluding multiple births ($n=19$), uncorrected for gestational age, was 3.09 (1.64 to 4.19) kg. The numbers with birth weights below the 10th, between the 10th and 90th, and above

the 90th centiles were five, nine and five respectively. No correlation (Spearman's) was found between peak GH response to provocative testing before pregnancy and birth weight ($r=0.38$, 95% CI -0.11 to 0.72 , $P=0.11$). Three minor congenital malformations occurred in three infants; one bifid uvula, one inguinal hernia and one positional talipes. Ten infants were admitted to the Special Care Baby Unit (including the quins).

Pre-eclampsia occurred in two pregnancies (patient 12a at 34/40 weeks and patient 14 at 32/40 weeks). Labour was induced in seven pregnancies (three for failure to progress, two for poor maternal weight gain, one for poor fetal growth and one because of 42 weeks gestation). There were seven elective caesarean sections (one for pelvic disproportion, two for multiple births, two for pre-eclampsia and two because of previous caesarean section). Two emergency caesarean sections were performed due to failure of labour to progress, with associated fetal distress. Post-partum haemorrhage occurred in one pregnancy.

Of those pregnancies that resulted in a live birth ($n=21$ pregnancies), 11 pregnancies were reportedly associated with no change in mood or well-being, 6 with improved well-being and 4 with reduced well-being. Twelve pregnancies were reportedly associated with normal weight gain, 6 with poor weight gain and 3 with excessive weight gain.

Discussion

This is the first report to assess the impact of GH deficiency on the outcome of pregnancy in patients with pituitary disease, although isolated case reports have been published previously (13, 22, 23). Overall, we have found no adverse effects of GH deficiency *per se* on the fetal outcome of pregnancy, and the maternal morbidity appears to be low. Although the number of pregnancies examined is relatively small, the data suggest that GH replacement therapy may not be essential for a successful outcome in patients with hypopituitarism.

In terms of fetal outcome, there were 21 successful pregnancies. It is known that 10–20% of confirmed pregnancies and up to 50% of unconfirmed pregnancies are spontaneously aborted (24). Thus the four spontaneous abortions that occurred in the first trimester do not represent an unduly high incidence, particularly when it is understood that three abortions occurred following ovulation induction therapy, and these pregnancies may not have been recognised clinically, except for the specific interest related to their treatment protocol. The fourth abortion occurred in a patient who was 42 years of age. The median gestation was 39 (33 to 42) weeks, and this may be artificially short, since labour was induced in seven pregnancies, and the lengths of gestation of the multiple births are included. If multiple births are excluded ($n=19$), we would have expected approximately 2/19 neonates to have a birth weight less than the 10th centile and similarly 2/19

Table 1 Patient details, therapy at conception, peak GH response to insulin tolerance test or glucagon stimulation test (G) before each pregnancy, and maternal and fetal complications.

| Subject | Diagnosis | Original therapy | Therapy at conception | Peak GH (mU/l) | Height (m) | Birth weight (kg) | Gestational age at delivery (weeks) | Maternal complications | Fetal complications |
|---------|--------------------------------|------------------|-----------------------------------|----------------|------------|------------------------------|-------------------------------------|------------------------|---------------------|
| 1 | Prolactinoma | S, R | Clonidine, Bromocriptine | 3.5 | 1.64 | 3.09 | 40 | | |
| 2a | Cushing's disease | R, A | Pergonal, Cortisone | 16.0 | 1.60 | AB | | | |
| 2b | | | Pergonal, Cortisone | 16.0 | | AB | | | |
| 2c | | | Pergonal, Cortisone | 16.0 | | 3.97 | 38.5 | ES | |
| 2d | | R, A, S | Cortisone | 10.0 (G) | | 3.97 | 37.5 | CS | |
| 3a | Non-functioning adenoma | S, R | Bromocriptine, Cortisone | 6.7 | 1.64 | 3.29 | 40 | | |
| 3b | | | None | 11.0 | | 3.00 | 40 | | |
| 3c | | | None | 9.7 | | 3.97 | 38.5 | Ind | BU |
| 3d | | | None | 6.0 (G) | | AB | | | |
| 4a | Idiopathic | None | Bromocriptine | 16.0 | 1.56 | 3.91 | 40 | Ind | |
| 4b | | | Bromocriptine | 12.0 | | 4.19 | 40 | Ind | |
| 5 | Prolactinoma | Inf | Bromocriptine | 1.3 | 1.67 | 3.91 | 39 | | PT |
| 6 | Prolactinoma | R | None | 17.3 | 1.64 | 3.60 | 40 | | |
| 7 | Non-functioning adenoma | S | GH, Bromocriptine | 1.5 (G) | 1.55 | 2.72 | 40 | ES | |
| 8 | Cushing's disease | S | None | 9.0 | 1.64 | 2.24 | 35 | Ind | |
| 9 | Cushing's disease | R | None | 7.5 | 1.50 | 3.58 | 40 | | |
| 10a | Prolactinoma | S, R | Bromocriptine | 4.6 | 1.65 | 2.95 | 39 | Ind, PPH | |
| 10b | | | GH, Bromocriptine | 1.9 (G) | | 3.00 | 42 | Ind | |
| 11 | Congenital (Pit-1 gene defect) | None | Thyroxine | <1.0 | 1.40 | 3.03 | 38 | Ind, CS | |
| 12a | Prolactinoma | R | Bromocriptine, Thyroxine | 8.7 | 1.67 | 1.64 | 36 | PE (34), CS | |
| 12b | | | Bromocriptine, Thyroxine | 14.0 | | 2.55 | 36 | CS | |
| 13 | Non-functioning adenoma | R | Pergonal, Hydrocortisone | 1.1 | 1.68 | 2.09, 3.00 | 37 | CS | |
| 14 | Non-functioning adenoma | S | Metrodin, Prednisolone, Thyroxine | 2.6 | 1.62 | 1.64 | 34 | PE (32) CS | |
| 15 | Prolactinoma | S | Cabergoline | 14.6 | 1.46 | AB | | | |
| 16 | Craniopharyngioma | S, R | Pergonal, Prednisolone, Thyroxine | 2.5 | 1.53 | 1.16, 1.18, 1.18, 1.22, 1.42 | 33 | CS | IH |

a, b, c... = successive pregnancies, S = pituitary surgery, R = radiotherapy, A = adrenalectomy, Inf = infarction, Ind = induced labour, CS = caesarean section, ES = emergency caesarean section, PE = pre-eclampsia (gestational age at which first developed), PPH = post-partum haemorrhage, AB = abortion, BU = bifid uvula, IH = inguinal hernia, PT = positional talipes.

above the 90th centile. Overall we found a normal distribution of birth weights although there was over-representation at the extremes. The reasons for this are unclear, although two neonates with birth weights below the 10th centile were born to mothers suffering from pre-eclampsia.

Fetal production of GH occurs after the 12th week of gestation (25) and placental GH does not appear to cross the placenta (20), suggesting that maternal GH deficiency would not be expected to influence fetal growth directly. However, intrauterine growth retardation has been associated with low circulating maternal IGF-I and low placental GH concentrations (26), suggesting that maternal IGF-I might influence placental growth and function. It is unclear, however, whether the low IGF-I concentrations found in the intrauterine growth-retarded subjects in that particular study were a cause or a consequence of poor placental function. Hall *et al.* (15) demonstrated a significant correlation between birth weight and maternal IGF-I concentrations during the last trimester, regardless of whether GH deficiency was present. However, the sample size was small and a larger study in normal subjects did not show any correlation (27). We did not measure IGF-I concentrations during pregnancy in our cohort; however, there was no correlation between peak GH response to provocative testing prior to pregnancy and birth weight, suggesting that the severity of GH deficiency prior to pregnancy does not influence birth weight.

The congenital abnormalities that occurred were minor. The prevalence of bifid uvula has been documented at 7.5% in children attending for routine otolaryngeal surgery (28). Minor foot deformities have an incidence of 4.2% at birth, and the vast majority develop normally without intervention (29). Similarly, 17% of male infants with low birth weight develop an inguinal hernia by the age of three (30). In our cohort the talipes corrected spontaneously and the inguinal hernia was successfully repaired.

The North West Region of England has a caesarean section rate of approximately 11.5% (31), and thus there appears to be an excess of caesarean section deliveries in our cohort (9/21 pregnancies). However, the reasons for caesarean section were: failure to progress with fetal distress (2), pre-eclampsia (2), previous caesarean section (2), multiple births (2) and pelvic disproportion (1). As such, it is unlikely that GH deficiency *per se* influenced the caesarean section rate, or that rhGH therapy would have reduced it. The median maternal height in our cohort was 1.64 (1.40 to 1.68) m and therefore an explanation of small maternal height causing an increased incidence of pelvic disproportion is unlikely. Only the shortest patient had pelvic disproportion which resulted in caesarean section.

Hypertension during pregnancy and pre-eclampsia are relatively common (32, 33), and the incidence in

our cohort is not excessive. Post-partum haemorrhage has an incidence of 3–4% (34), and this is in agreement with the one case reported in our study. The psychological well-being of subjects during pregnancy was not formally assessed; however, there was an equal spread of patients who perceived the pregnant state as one of improved or reduced well-being.

It might be predicted that maternal well-being and morbidity would be similar in GH-deficient subjects and normal subjects, since during pregnancy the placenta increasingly becomes the major source of circulating maternal GH (14, 20, 21), and regulation of GH secretion appears to be independent of the hypothalamus (35). Maternal IGF-I and IGF-II levels have been shown to increase from below normal into the normal range during the second half of pregnancy, in three patients with GH deficiency (15). The increase in IGFs was independent of maternal pituitary GH production. Clearly there will be a period from conception to about the 15th week of pregnancy, before significant increases in placental GH production occur, during which time potentially adverse effects of pituitary GH deficiency might become manifest. Our data suggest that these are not clinically significant. We cannot, however, assess the impact of GH deficiency on conception, fertility and well-being in the post-partum period. Although GH is not essential for fertility (36), GH may improve the outcome of specific fertility therapy (37).

In conclusion, the fetal and maternal outcome of pregnancy is not adversely affected by GH deficiency, and therefore replacement with rhGH during pregnancy is probably not essential. This might be due to the alternative source of GH (placental GH) available to these patients during the second half of pregnancy.

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