Pregnancy outcomes in women with growth hormone deficiency

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Objective: To study pregnancies in a large group of patients with growth hormone deficiency and hypopituitarism; and to investigate potential factors determining pregnancy outcomes and pregnancy complications.
Design: We analyzed pregnancies reported in KIMS, the Pfizer International Metabolic Database, of adult patients with growth hormone deficiency treated with growth hormone.
Setting: Outpatient clinics.
Patient(s): A total of 201 pregnancies were reported: 173 in female patients and 28 in partners of male patients.
Intervention(s): Growth hormone replacement therapy (GHRT) was prescribed according to the local clinical practice.
Main Outcome Measure(s): Pregnancy outcomes (live births, gestational week at delivery, and birth weight), pregnancy complications, and their relationship to use of GHRT during pregnancy were analyzed with regression models.
Result(s): Two-thirds of women underwent fertility treatment to achieve pregnancy. Growth hormone replacement therapy was stopped before pregnancy in 7.5% of the female patients, as soon as pregnancy was confirmed in 40.1%, and at the end of the second trimester in 24.7% of the patients, whereas 27.6% continued GHRT throughout pregnancy. Birth of a healthy child was reported in 79% of the female pregnancies, nonelective abortions occurred mainly in the first trimester, and one fetal malformation (cystic hygroma) was diagnosed in the second trimester. Pregnancy outcomes and pregnancy complications were not related to GHRT treatment patterns, method of conception, or number of additional pituitary deficiencies.
Conclusion(s): These data on pregnancy outcomes in a large group of women with hypopituitarism revealed no relationship between GHRT regimens and pregnancy outcomes. (Fertil Steril® 2015;104:1210–7. ©2015 by American Society for Reproductive Medicine.)
Key Words: Growth hormone, hormone replacement therapy, pituitary deficiency, pituitary tumors, pregnancy

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Physiologic replacement for growth hormone deficiency (GHD) is recommended during both childhood and adulthood, because growth hormone (GH) not only promotes growth but also influences body composition, metabolism, cognitive functioning, psychological well-being, quality of life, and cardiovascular mortality (1–5). Nevertheless, GH replacement therapy (GHRT) in women with GHD is not specifically approved for use during pregnancy.

The endocrine milieu of pregnancy is characterized by dynamic changes in maternal hormones paralleled by the development of the placenta, which acts as an endocrine organ. Its syncytiotrophoblast layer tonically secretes a GH variant called placental growth hormone (PGH) (6). During pregnancy, PGH continuously increases, starting from nearly undetectable levels and peaking at week 36, reaching concentrations (20–40 ng/mL) comparable to those in acromegaly (7). It binds with

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high affinity to GH receptors but with low affinity to PRL receptors, gradually replacing pituitary GH and controlling production of maternal insulin-like growth factor I (IGF-I) (8). The rise in PGH is accompanied by a sharp decline of pituitary GH, which is no longer detected in maternal serum after the 24th week of gestation (7).

In this context, the benefit and safety of GH replacement to women with GHD at the time of pregnancy remains unclear. This topic has been addressed in few studies of limited sample size. A retrospective study of 25 women with GHD, who underwent pregnancy without GHRT, concluded that unsubstituted GHD during pregnancy is not detrimental to the fetus (9). Another publication described four GHD women who stopped GHRT immediately after confirmation of pregnancy and remained off treatment throughout the pregnancy. They had no pregnancy complications and gave birth to healthy babies of normal height and weight (10). In a case report, physiologic GH replacement until there was evidence of sufficient PGH production also led to a normal pregnancy and a healthy fetus (11). This regimen of maintaining GHRT during the first trimester, gradually decreasing it during the second trimester and discontinuing it during the third trimester was reported to lead to successful outcomes in 12 pregnancies (12). In addition, replacement with human GH during pregnancy did not suppress the physiologic increase in PGH (13). Taken together, these publications are of interest but do not establish whether GHRT is safe before and during pregnancy and call for further reports in larger studies.

The aim of this study was to evaluate pregnancy outcomes in relation to the etiology and extent of pituitary disease, and in relation to patterns of GHRT during pregnancy, in a large group of patients with GHD included in KIMS (the Pfizer International Metabolic Database).

MATERIALS AND METHODS

KIMS was a large, prospective, pharmacoepidemiologic surveillance study of hypopituitary adults with GHD from 800 outpatient clinics at medical centers in 31 countries, performed between 1994 and June 2012. The KIMS protocol was approved by the institutional review boards, as required by local regulations in each participating country. Before registration in the database, written informed consent was obtained from patients, according to country regulations. We searched this database for reports of pregnancies during the period between patient entry in KIMS and September 2011, aiming to obtain information on pregnancy outcomes before the KIMS closure in 2012.

After identifying patients and pregnancies, we extracted background data regarding gender, diagnosis and treatment of pituitary disease, pituitary deficiencies, medical history, and comorbidities. In addition, the following pregnancy-related data were extracted: date when pregnancy was reported, approximate date of conception, method of conception (whether with or without fertility treatment), maternal age and body mass index (BMI) at conception, IGF-I standard deviation score (SDS) at conception (last value reported before conception), GH replacement dose at conception and during pregnancy, replacement of pituitary deficiencies and other concomitant medications at conception and during pregnancy, expected date of delivery, and pregnancy complications (defined as gestational diabetes, hypertension, preeclampsia, vaginal bleeding, and other). Pregnancy outcomes of interest were [1] child outcome (spontaneous abortion, induced abortion, healthy live birth, stillborn, Apgar score, congenital malformations), [2] gestational age of birth/abortion, and [3] birth weight.

To capture missing data, study-specific questionnaires were designed and prefilled with the available information already extracted from the database, then sent to local site investigators, who were asked to verify the data and add any missing information to the questionnaires. In total we prefilled 1.153 observations, and of those the investigators changed the recording of 68 observations.

Growth hormone replacement therapy before and during pregnancy was prescribed according to local clinical practice. Growth hormone replacement therapy regimens during pregnancy were classified into three main categories: discontinuation of GHRT before or at confirmation of pregnancy, partial continuation of GHRT during the pregnancy (GHRT during the first and second trimesters of pregnancy), and GHRT during the whole pregnancy. This classification was based on data extracted from KIMS visits, safety reports, and adverse events reports.

The IGF-I SDS was determined centrally. Between 1994 and October 1997, measurements of serum IGF-I were performed at Kabi Pharmacia, Stockholm, Sweden, and thereafter at Sahlgrenska University Hospital, Gothenburg, Sweden, using the following assay methods: until November 2002, radioimmunoassay after acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostic); until September 2006, chemiluminiscence immunoassay (Nichols Advantage system); and after September 2006, Immulite 2500 (DPC Siemens). For each assay, age- and gender-specific reference ranges expressed in μg/L were used to calculate IGF-I SDS. Between-assay reference ranges and consistency of IGF-I SDS values were validated internally. The algorithm formulas used were as follows: between 1994 and 1997, SDS = (ln (IGF-I) − (5.95–0.0197 × Age))/0.282; between 1997 and 2002, SDS = (ln (IGF-I) − (5.92–0.0146 × Age))/0.272; and after 2002, as reported by Brabant et al. (14).

Descriptive statistics were presented as proportions, mean and SD, or median and range, depending on the type of variable. Analyses assessing proportions and ratio of proportions of outcome of a healthy child and pregnancy complication, respectively, by some selected covariates were conducted using simple and multiple log-linear Poisson working regression models for repeated observations with model-robust standard error estimates (15). The outcome measure was proportions, and parameter estimates in the model present the ratio of proportions (relative proportions). The correlation structure was assumed to be autoregressive of order 1. On the basis of clinical and research experience, we selected the following covariates for further analysis: etiology of pituitary disease, number of additional pituitary hormone deficiencies