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Placental and Pituitary Growth Hormone Secretion during Pregnancy in Acromegalic Women

ALBERT BECKERS, ACHILLE STEVENAERT, JEAN-MICHEL FOIDART, GEORGES HENNEN, AND FRANCIS FRANKENNE

Endocrinologie Expérimentale et Clinique (A.B., G.H., F.F.), Neurochirurgie (A.S.), and Biologie Générale (J.-M.F.), Centre Hospitalier Universitaire, B-4000 Liege, Belgium

ABSTRACT. It is now well established that during the second half of normal pregnancy, the human placenta secretes its specific GH variant (placental GH) in increasing amounts up to delivery. During the same period, pituitary GH secretion is progressively suppressed. The present study was aimed at clarifying the physiology of GH secretion in pregnant acromegalic women. Two young women remained acromegalic despite transsphenoidal removal of their pituitary adenoma. Increased basal levels of GH and insulin-like growth factor-I (IGF-I) as well as paradoxical GH release after TRH injection were noted. Both women became pregnant and delivered term babies without any complication. In both patients, pituitary GH remained elevated during the entire pregnancy, contrary to the situation in normal women. Paradoxical GH release after TRH treatment was also present, whereas no response was observed in five normal control subjects. GH pulsatility studies revealed a highly pulsatile secretory pattern of pituitary GH, in contrast to that in normal woman, whose placental GH is secreted tonically. Tissue placental GH concentrations were within the range of levels in normal placentas. An increase in serum IGF-I in late pregnancy was also similar to that observed in normal pregnancy.

These findings confirm that increased IGF-I levels are not pituitary GH dependent in late pregnancy. They add new evidence that adenomatous somatotrophs lack an IGF-I-dependent feedback regulation present in normal somatotrophs. (*J Clin Endocrinol Metab* **71:** 725–731, 1990)

HUMAN placenta has been shown to express the GH-V gene and to produce placental GH, which can be detected in blood and is distinguishable from pituitary GH on the basis of its specific pattern of reactivity with two anti-GH monoclonal antibodies (MAbs) (1). Placental GH is composed of two forms of 22 and 25 kilodaltons (K) mol wt, respectively; the latter is probably glycosylated (2). Recent sequence data (3) have clearly established that both forms are GH-V gene products (4, 5).

During the first trimester, pituitary GH is the only measurable GH in maternal serum. It is secreted in a highly pulsatile pattern (6, 7). From 15–17 weeks up to term, serum pituitary GH is progressively replaced by increasing levels of placental GH, displaying a fairly constant, rather than episodic, 24-h secretory profile. Simultaneously, the pituitary has been shown to be unresponsive to GH secretagogues (8–13). Hence, placental GH could well be the main stimulator of IGF-I secretion in late pregnancy and should account for the elevated maternal IGF-I levels during that period. Since IGF-I is a highly potent inhibitor of somatotrophs (14, 15), it is likely to be responsible for the inhibition of the maternal pituitary GH during pregnancy.

Acromegaly rarely occurs in women of childbearing age (16). Moreover, fertility is low in acromegalic women. For these reasons, the outcome of pregnancy in acromegalic women has seldom been reported. Until recently no specific method capable of overcoming interferences due to circulating human placental lactogen (hPL) were available to assess GH secretion under these conditions.

The present study was undertaken to clarify the pathophysiology of GH secretion in pregnant acromegalic women compared to that in normal women.

Subjects and Methods

Patients

Two acromegalic patients were studied. They had already undergone transsphenoidal adenomectomy (17). Although clinical remission occurred after surgery in both patients, they still presented with high basal GH and insulin-like growth factor-I (IGF-I) serum levels as well as a paradoxical rise in GH after TRH injection, typical of acromegaly. In both cases, computed tomographic (CT) scans failed to demonstrate a recurrence of the adenoma.

The first patient (28 yr old) became pregnant 2 yr after the operation. The second patient became pregnant for the first

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Address requests for reprints to: Dr. Albert Beckers, Endocrinogie Expérimentale et Clinique, Centre Hospitalier Universitaire, B35 B-4000 Liege, Belgium.
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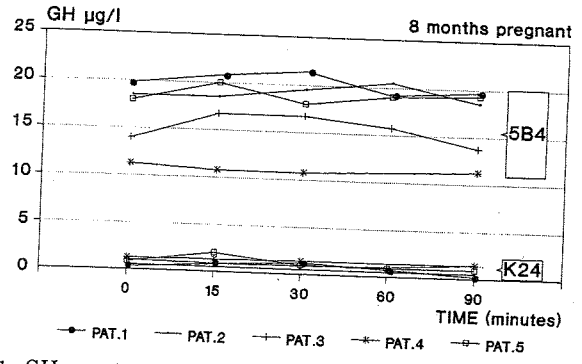


FIG. 1. GH secretory response to TRH in five normal women in late pregnancy measured using two MAb-based RIAs, one recognizing pituitary and placental GH (5B4) and the other recognizing only pituitary GH (K24).

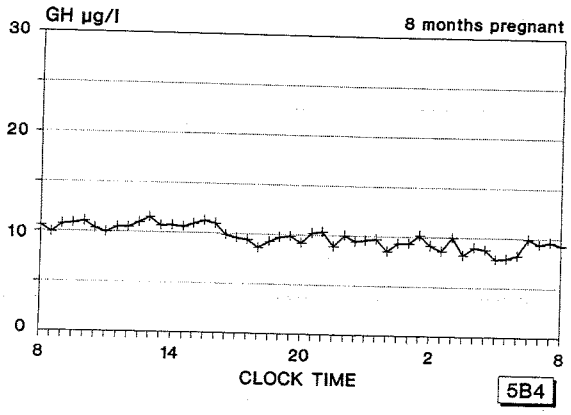


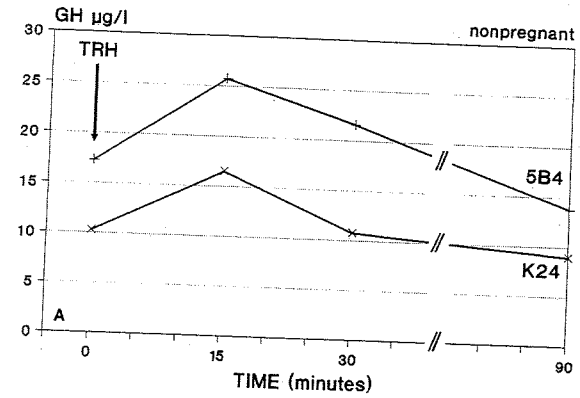
FIG. 2. Twenty-four-hour GH concentration profile in the serum of a normal woman in late pregnancy, as measured using a RIA recognizing both pituitary and placental GH (5B4 antibody).

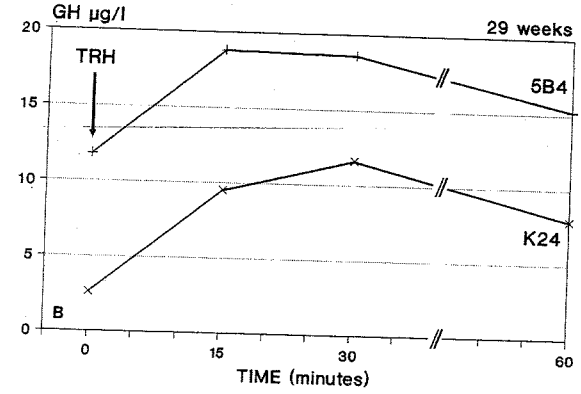
time 2 yr after the operation and delivered a term baby, but no information on that pregnancy was available. The second pregnancy, which occurred 5 yr after the operation, was followed during the present study. The pregnancies neither influenced clinical symptomatology, which remained mild, nor induced local adenoma recurrence, as studied by CT scan performed after delivery. Visual field studies performed during pregnancy failed to reveal any defect. The three children resulting from these pregnancies were normal.

As a control study, TRH stimulation tests were performed in 5 normal pregnant women (24–38 yr old) between 36–38 weeks of pregnancy. The pulsatility of GH secretion was examined in 1 control pregnancy in the present study and in 6 previously reported controls (7). The patient described here was 23 yr old and was investigated during the 37th week of pregnancy. GH content was measured in extracts from 20 term placentas obtained from normal pregnancies, as described previously (6). The 20 normal women age ranged in age from 19–34 yr.

Methods

Endocrine study. The studies were performed only after being approved by the local ethical committee and receipt of the patient's written consent. Pituitary and placental GH responses





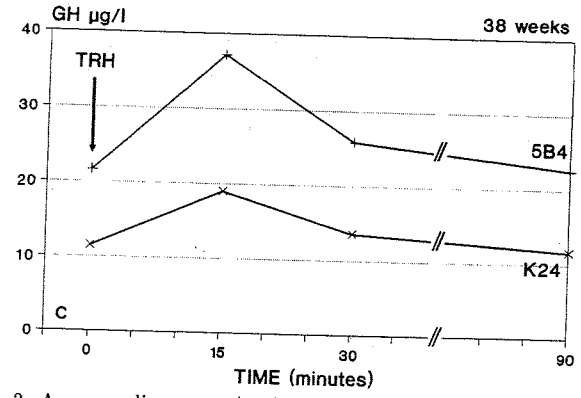


FIG. 3. Acromegalic woman (patient I). GH secretory response to TRH before pregnancy (A) and during pregnancy (B, week 29; C, week 38) using two MAb-based RIAs, one recognizing pituitary and placental GH (5B4) and the other recognizing only pituitary GH (K24).

to a 200-µg iv bolus dose of TRH were determined before pregnancy and during the second half of pregnancy (weeks 29–38) in both cases. In the second patient, pituitary and placental GH secretory rhythms were determined during the third and eighth months of pregnancy. After admission to the hospital an indwelling cannula was inserted into a forearm vein at 0800 h, and 2 mL blood were drawn every 30 min for 24 h. The serum was stored at −20 C until assayed. In both patients, IGF-I levels were measured before and during pregnancy, whereas hPL was measured in late pregnancy.

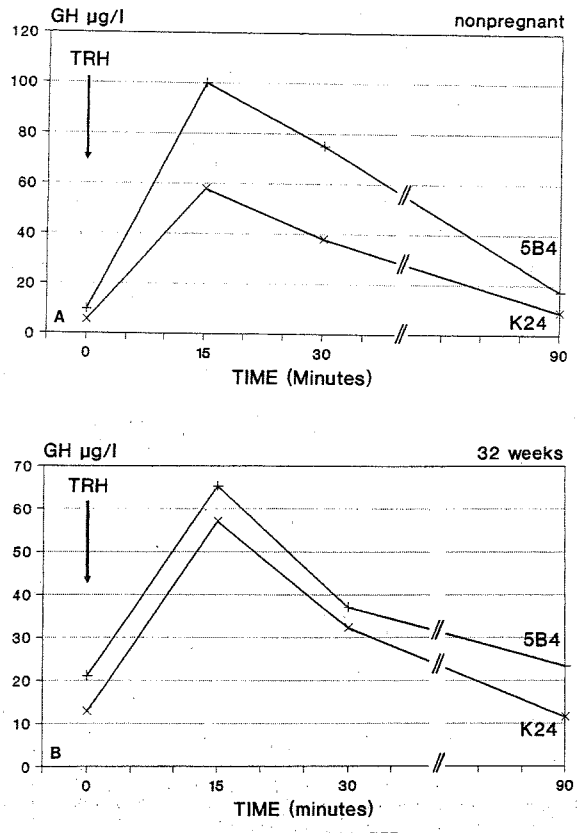


FIG. 4. Acromegalic woman (patient II). GH secretory response to TRH before pregnancy (A) and during pregnancy (B; week 32) using two MAb-based RIAs, one recognizing pituitary and placental GH (5B4) and the other recognizing only pituitary GH (K24).

GH pulsatility. Significant GH peaks were identified with the Pulsar program (18) in connection with the MLAB (19) system using a Digital DEC-20 computer.

Assays. IGF-I plasma levels were assayed using a commercial kit (Nichols Institute, San Juan Capistrano, CA). Pituitary and placental GH levels were determined using two RIAs described previously (2, 6, 20) and using distinct anti-GH monoclonal antibodies, coded 5B4 and K24. The immunochemistry of the two MAbs and the characteristics of the related assays have previously been reported (6). Briefly, the affinity constants (K_a) of the binding reaction with the 22K hGH were 5×10^9 M^{-1} and 1.02×10^{11} M^{-1} for the K24 and 5B4 MAb, respectively. Sensitivities of the assays were 1 μg/L (K24 RIA) and 0.25 μg/L (5B4 RIA). The 5B4 MAb was found to be directed toward the N-terminal epitope and to recognize all known pituitary as well as placental GH variants. The K24 MAb reacted with a more internally located epitope and recognized the 22K pituitary GH, but not the placental variant. Placental GH could, therefore, be distinguished from the pituitary 22K GH by its lack of reactivity with the K24 MAb. Serum GH concentrations were measured in 53 normal nonpregnant subjects. The mean basal serum GH level was 4.0 ± 0.8 μg/L for the 5B4 RIA and 2.4 ± 0.6 μg/L ($P < 0.01$) for the K24 RIA. The ratio of the values obtained from either system ranged from 1.1–2 (5B4 *vs.* K24 RIA values) in subjects whose K24-assayable serum GH

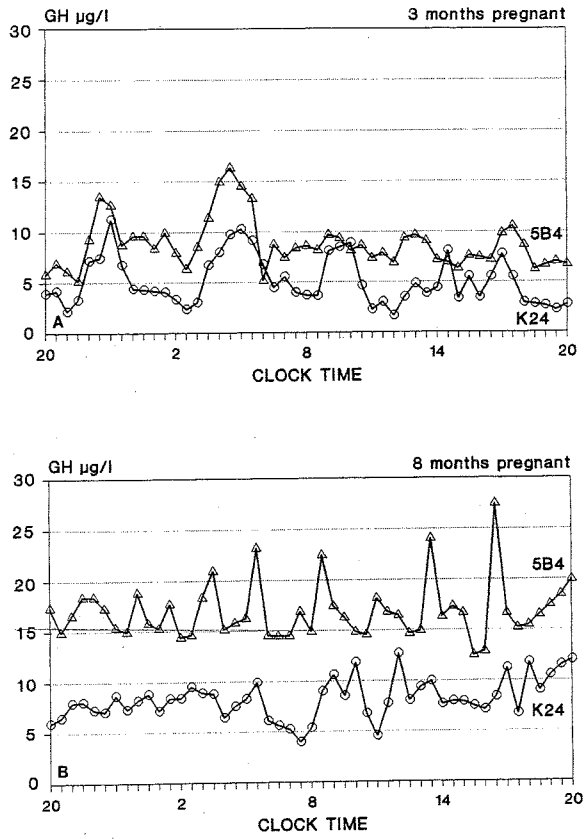


FIG. 5. Acromegalic woman (patient II). Twenty-four-hour GH profile in the serum of an acromegalic woman during pregnancy (A, month 3; B, month 8) measured using two MAb-based RIAs, one recognizing pituitary and placental GH (5B4) and the other recognizing only pituitary GH (K24).

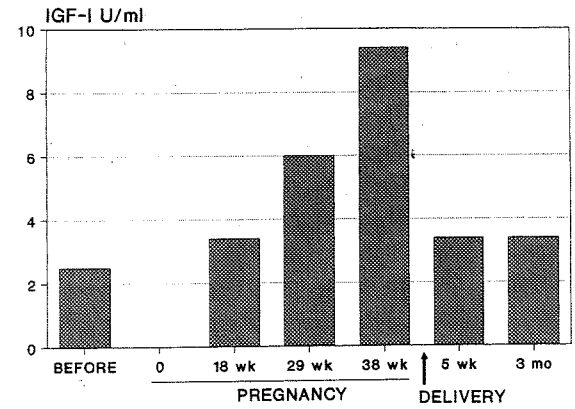


FIG. 6. IGF-I levels in an acromegalic woman (patient I) while nonpregnant and during pregnancy.

level was above 1 μg/L. hPL was unable to compete with [^{125}I] 22K GH for binding to both MAbs even at the highest physiological dose of 10 μg/mL.

All analyses in an individual subject were performed in a single assay. The assays were calibrated against the hGH 66/217 International Reference Preparation (WHO Medical Research Council, London, United Kingdom), and the results

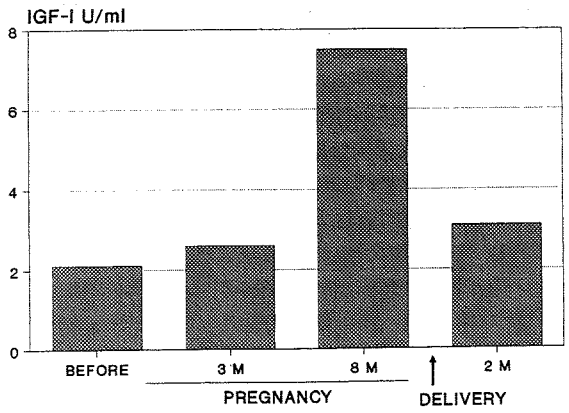


FIG. 7. IGF-I levels in an acromegalic woman (patient II) while nonpregnant and during pregnancy.

were expressed as micrograms per L. The intra- and interassay variations for the GH RIAs were 3% and 10%, respectively.

Placental extract contents in GH were measured as described previously (6). hPL has been measured by RIA, using a rabbit anti-hPL antiserum, at a 1:250,000 final dilution. Bound-free separation was achieved by a 20-min incubation with 1 mL preprecipitated goat second antibody (PPA, UCB-Bioproducts, Braine-L'Alleud, Belgium), followed by centrifugation at 2,000 × *g* for 20 min. Highly purified hPL used for labeling and standard doses were obtained from UCB-Bioproducts and calibrated against the WHO Medical Research Council 73/545 International Reference Preparation. The inter- and intraassay coefficients of variation were, respectively, 15% and 8%, and the cross-reactivity of pituitary hGH in this assay was 0.1%.

Statistics. Ratios of the serum GH values at 3 and 8 months using the 5B4 and K24 assays (5B4/K24 ratio) were statistically compared using *t* test, Kruskall-Wallis test, and one-way analysis of variance.

Results

Normal women (Figs. 1 and 2)

In late pregnancy, the bolus injections of TRH in normal women did not elicit any significant qualitative or quantitative modification of serum GH immunoreactivity (Fig. 1). As previously described (6), the recorded 5B4 MAb (+) and K24 MAb (−) GH immunoactivity pattern accounts for the presence of placental GH and the absence of pituitary GH during that period. The mean maternal serum IGF-I level in late pregnancy was 5.7 + 1.9 U/mL (mean ± SD; n = 5) compared to 1.08 ± 0.56 (n = 18) in nonpregnant women. During that period, the study of GH pulsatility (7) (Fig. 2) failed to reveal any peak GH secretion.

Acromegalic subjects (Figs. 3–7)

While they were nonpregnant, the bolus TRH injection in both patients resulted in a paradoxical rise in the serum GH concentration (Figs. 3A and 4A), as often seen in acromegaly. The 5B4 MAb (+) and K24 MAb (+) GH immunoactivity pattern was that of pituitary GH.

In late pregnancy, basal GH levels similar to those in normal women were measured with the 5B4 antibody, but the 5B4 MAb (+) and K24 MAb (+) immunoactivity pattern accounted for the presence of pituitary instead of placental GH as the main serum GH variant. TRH remained an active pituitary GH secretagogue (Figs. 3, B and C, and 4B), triggering high amplitude responses in both pregnant patients.

The 24-h serum GH pattern recorded for patient II in early and late pregnancy (Fig. 5) shows a high level of pulsatility, typical of pituitary GH. Indeed, in early pregnancy, 8 significant peaks [mean amplitude (±SD), 5.1 ± 1.9 μg/L] and 6 significant peaks (mean amplitude, 4.5 ± 2.9 μg/L) were calculated from the data yielded by the K24 and 5B4 RIAs, respectively. In late pregnancy, 8 peaks (mean amplitude, 4.2 ± 1.8 μg/L) and 5 peaks (mean amplitude, 8.1 ± 2.6 μg/L) were found using K24 and 5B4 RIAs. It appears that the mean 5B4/K24 ratio was 2.17 at 8 months *vs.* 1.98 at 3 months. This could indicate the presence of placental GH [5B4 (+) and K24 (−)] beside pituitary GH [5B4 (+) and K24 (+)], but this difference was not statistically significant. Whether placental GH was also present together with the pituitary variant in the serum of the patient was, therefore, not evident from concentrations derived from the 5B4 and K24 values. Since an immunoactivity pattern of the placental GH type [5B4 (+) and K24 (−)] was found in extracts of the placentas obtained at delivery (patient I, 50 μg/kg; patient II, 188 μg/kg), it is concluded that placental GH is indeed produced in these acromegalic subjects and present in placental tissue (and probably in serum) in amounts similar to those found in 20 normal control women (range, 40–500 μg/kg).

In both patients IGF-I levels were stable and slightly above the normal range (while nonpregnant and during the first half of pregnancy; Figs. 6 and 7). During the second half of pregnancy serum IGF-I became 2–3 times higher, following the same pattern as in normal pregnant women.

hPL levels were similar to those recorded in late normal pregnancy (5.6 and 5.2 μg/mL for patients I and II, respectively).

Discussion

The recent discovery of placental GH allows the opportunity to gain new insights regarding GH physiology during pregnancy. The present work was aimed at studying placental and pituitary GH in pregnancies associated with disorders of pituitary GH secretion.

The two patients described here were operated upon

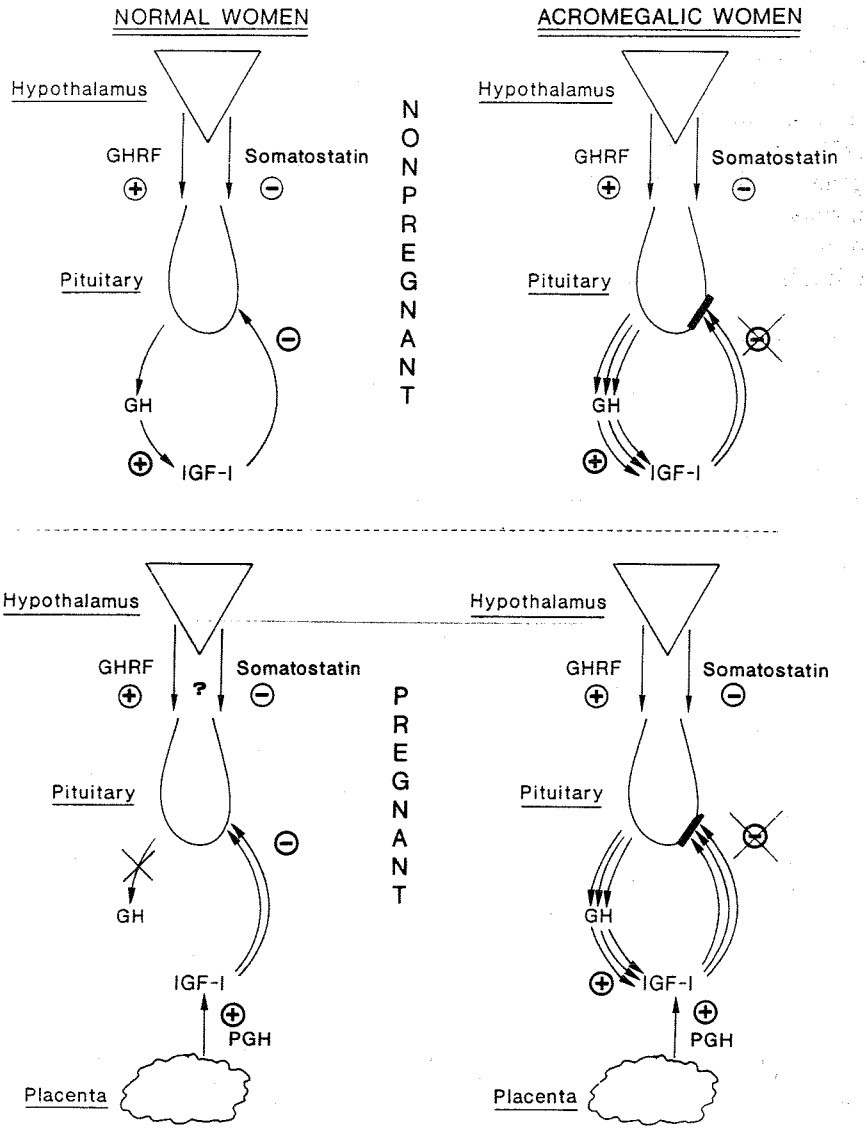


FIG. 8. Proposed model for regulation of the secretion of pituitary and placental GH in normal and acromegalic women.

for GH-producing pituitary adenoma. However, lack of normalization of GH and IGF-I levels as well as persistance of a paradoxical release after TRH were consistent with persistent hypersecretion of GH secondary to tumor.

The novel finding in this study was the demonstration that pituitary GH secretion persisted during the entire pregnancy in acromegalics unlike during normal pregnancy.

The pituitary GH level was not significantly different during pregnancy from that during nonpregnancy in both patients. This suggests that the adenomatous somatotrophs are resistent to the factors that are responsible for the inhibition of pituitary GH secretion in normal pregnant women. Paradoxical GH release after TRH administration is known to occur frequently in acromegalic patients. Such a response occurred before and during pregnancy in both patients. This paradoxical GH responsiveness to TRH was not altered by pregnancy, while in control pregnant women, TRH did not change either placental or pituitary GH levels.

Moreover, the pulsatile secretory pattern of pituitary GH was maintained in late pregnancy in our acromegalic woman, while placental GH measured in late normal pregnancy is secreted in a nonepisodic mode, as shown previously (7) and in the study of the control women.

These data provide evidence that the regulation of GH secretion by adenomatous somatotrophs is not fundamently modified by pregnancy. More specifically, the persistance of pulsatile secretion demonstrates that some hypothalamic regulation of the somatotrophs is still present. IGF-I levels were elevated in the two patients while nonpregnant. This fits well with a typical acromegalic state. Interestingly, during the second half of their pregnancies and despite the apparent stability of pituitary GH secretion, serum IGF-I levels increased in both pa-

tients as in normal pregnant women (21). Thus, it appears that this rise in serum IGF-I levels is specific to pregnancy and independent of the maternal somatotrophs. This has already been shown by Merimee *et al.* (22) in the case of a pregnant patient lacking the GH-N gene and in whom IGF-I levels increased from low to normal values during pregnancy. This strengthens our previous hypothesis of placental GH being the main stimulator of IGF-I secretion in late pregnancy (23), even if a possible contribution of hPL cannot be ruled out.

On the other hand, IGF-I is a potent inhibitor of GH secretion that can override the effects of GHRH. Considering its activity and serum concentrations, IGF-I is, thus, likely to play a major role in the inhibition of pituitary GH secretion in normal pregnant woman. The persistence of GH secretion by the adenomatous somatotrophs is consistent with the lack of IGF-I effects on adenomatous cells. These findings consolidate data from Goodyear *et al.* (24) which indicate that *in vitro* IGF-I failed to inhibit GH secretion by pituitary adenomatous cells.

Our data are compatible with a model (Fig. 8) of normal pituitary GH secretion inhibited in late pregnancy by the rise of maternal IGF-I serum concentrations due to placental hormone secretion (probably human placental GH) blocking the somatotrophs and of adenomatous somatotrophs lacking IGF-I-dependent negative regulatory mechanisms.

In conclusion, a mild acromegalic state does not appear to be an obstacle or a risk factor for normal pregnancy. Pituitary GH can remain elevated during the third trimester of pregnancy in acromegalics unlike in normal women. Pregnancy did not modify the paradoxical GH response to TRH injection recorded in both acromegalic patients when nonpregnant. In addition, the pulsatile pattern of pituitary GH secretion was also maintained, opposite to the nonepisodic pattern of placental GH in normal pregnancy.

Our data provide further evidence that high IGF-I levels in late pregnancy are not due to pituitary GH and that adenomatous somatotrophs can be characterized by the lack of IGF-I-dependent negative feedback regulation.

Acknowledgments

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