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Case report

Placental growth hormone and IGF-I in a pregnant woman with *Pit-1* deficiency

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Summary

The respective contributions of pituitary and placental GH to circulating IGF-I in pregnant women have not been well established. We measured the serum concentrations of placental growth hormone (PGH) and IGF-I in a woman with pit-1 deficiency before, during and after pregnancy, resulting in the birth of a healthy child (not pit-1 deficient). Both PGH and IGF-I concentrations were below the assay detection limit before and after pregnancy. During pregnancy, PGH and IGF-I levels increased steadily; the concentrations of PGH and IGF-I in late pregnancy were comparable with levels previously measured in normal pregnancies. PGH and IGF-I concentrations were strongly correlated throughout pregnancy ($r = 0{\cdot}90$; $P = 0{\cdot}002$). PGH was undetectable in cord serum, whilst the IGF-I concentration was within the normal range. The findings of this case study corroborate the notion that PGH is the prime regulator of maternal serum IGF-I during pregnancy.

Introduction

Placental growth hormone (PGH) is encoded by the hGH-V gene, which forms part of the hGH gene locus on chromosome 17 (q22 to q24), consisting also of the hGH-N gene and 3 chorionic somatomammotrophin (hCS-L, hCS-A and hCS-B) genes. The hGH-N gene is expressed in the anterior pituitary, whereas the hGH-V and the hCS genes are expressed in the syncytiotrophoblast of the placenta.

PGH is secreted in a nonpulsatile manner. Whereas the concentrations of PGH gradually increase during pregnancy, pituitary GH concomitantly falls to undetectable levels. PGH is thought to replace pituitary-derived GH during pregnancy; the somatogenic activity of PGH appears to be mediated by the production of IGF-I, similarly to pituitary-derived GH. Indeed, the rise in PGH concentrations is correlated with that of IGF-I in normal pregnancies, and both PGH and IGF-I levels fall rapidly after delivery (Caufriez *et al*., 1990; Mirlesse *et al*., 1993; Alsat *et al*., 1997).

Pituitary transcription factor 1 (*pit-1*) is a transcription factor necessary for the expression of the hGH-N, the PRL and the TSH genes in the pituitary (Pfäffle *et al*., 1999), and for the expression of the hGH-N but not the hGH-V gene in peripheral blood mononuclear cells (Melen *et al*., 1997). *Pit-1* messenger RNA and protein have also been shown to be present in the human placenta (Bamberger *et al*., 1995), and rat *pit-1 has* been reported to bind to the distal site of the hGH-V gene (Nickel *et al*., 1991). In this case study, we longitudinally measured PGH and IGF-I concentrations in a *pit-1* deficient woman before, during and after her second pregnancy.

Patient and methods

The woman concerned has been described previously (de Zegher *et al*., 1995). Briefly, this Caucasian patient is heterozygous for a point mutation in codon 271 of the *pit-1* gene, with a C to T substition replacing an Arg (CTT) by a Trp (TTT). GH was administered temporarily before the age of 19, and final height is 149·5 cm. The woman is also hypothyroid; during her first pregnancy, thyroid replacement therapy was suboptimal, and mother and child (who was also *pit-1* deficient) were found to be severely hypothyroid at delivery/birth (de Zegher *et al*., 1995).

The 34-year-old patient was seen 7 and 2 months before her second pregnancy, and at regular intervals during pregnancy. Body weight increased from 61 kg before pregnancy (body mass index: 27·3 kg/m^2) to a maximum of 73·7 kg at 35 weeks. The pregnancy was characterized by oedema and paresthesiae in both hands from 12 weeks onwards, which improved thereafter to worsen again from 35 weeks. Pedal oedema was seen from 29 weeks onwards. Blood pressure was normal throughout pregnancy. Based on circulating thyroid hormone concentrations, L-T_4 therapy was increased gradually from 75

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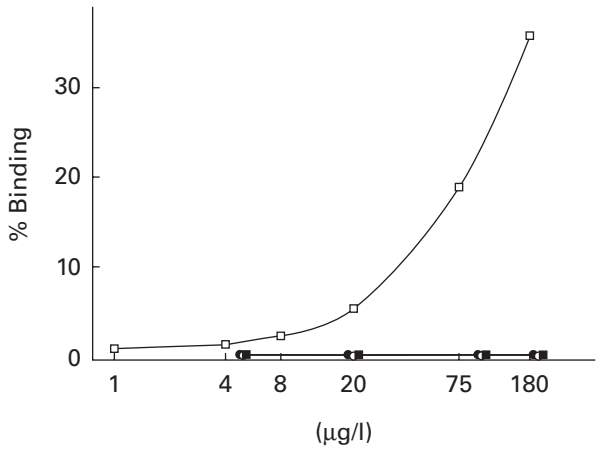

Fig. 1 Typical standard curve of the PGH two-site immunoradiometric assay for serum samples, using recombinant human PGH (□) as the standard, and monoclonal antibodies E8 and 7C12. There is no cross-reactivity in this assay with hGH (●), hPRL (○) or hPL (■) (< 0·001%). Conversion to molar units: 10 μg/l = 0·448 nmol/l. This standard curve was provided by A. Igout.

to 125 μg/day before conception (to attain high-normal free T_4 levels in anticipation of pregnancy) and further to a maximum of 150 μg/day during pregnancy. The patient agreed orally that an additional blood tube be obtained for the purpose of this study, each time blood was sampled to monitor L-T_4 therapy. There was no evidence of noncompliance with L-T_4 therapy. At 15 weeks of pregnancy, the patient underwent an amniocentesis, and the molecular findings indicated that the fetus was not carrying the maternal *pit-1* mutation. A healthy girl was born by elective repeat caesarean section at 38·6 weeks, with birth weight 3230 g (between 50th and 75th percentile, according to the Flemish reference charts), length 49 cm and head circumference 34 cm. Cord blood was sampled from the umbilical artery after cord clamping. Because lactogenesis failed after the first pregnancy (PRL levels were undetectable), breast feeding was not attempted. The patient was seen 9 weeks after delivery, and the L-T_4 dose was lowered again.

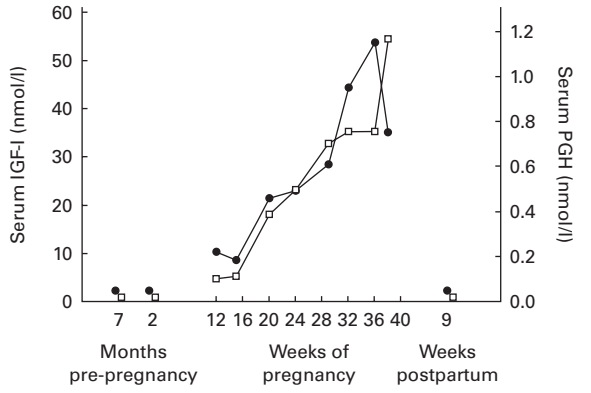

Fig. 2 Serum PGH (□) and IGF-I (●) concentrations in a patient with *pit-1* deficiency before, during and after pregnancy. PGH was undetectable before and after pregnancy, while IGF-I concentrations were far below the detection limit of the assay. During pregnancy, there was a steep rise in both PGH and IGF-I concentrations, with a strong correlation ($r = 0{\cdot}90$; $P = 0{\cdot}002$) between both parameters.

PGH was measured using a two-site immunoradiometric assay. Recombinant human PGH was used as the standard (Igout *et al*., 1993), and monoclonal antibodies E8 and 7C12 were used in a ^{125}I-labelled sandwich immunoassay (Igout & Hennen, 1997). The molecular mass of PGH is 22 320 Da (Igout *et al*., 1993). In this assay, the cross-reactivity of hGH, hPRL and hPL is < 0·001% (Fig. 1). The intra-assay coefficients of variation were 5·1, 3·0 and 5·5%, for samples with PGH concentrations of 20·5, 49·5 and 73·5 μg/l (low, medium and high), respectively; the interassay coefficients of variation were 5·5, 5·0 and 7·9%, respectively. The detection limit is about 0·2 μg/l (9 pmol/l) for serum samples. After acid ethanol extraction, IGF-I was measured by radioimmunoassay using recombinant human IGF-I (rhIGF-I) as the standard and a polyclonal antiserum raised in guinea pigs, as described previously (Verhaeghe *et al*., 1992, 1993). The detection limit of the IGF-I assay is about 50 pg/tube, or 35 μg/l (4·6 nmol/l) for routine serum samples.

Results and discussion

Figure 2 demonstrates that the serum concentrations of PGH and IGF-I were undetectable and far below the detection limit, respectively, in this *pit-1* deficient woman, both before (two time points) and after pregnancy. For IGF-I, the results were 7 and 3 μg/l before pregnancy, and 1 μg/l after pregnancy (the detection limit of routine assay is 35 μg/l); PGH was undetectable in the three samples. There was a steady increase in the levels of PGH and IGF-I in the course of pregnancy. The maximum level of PGH was comparable with previous data in normal pregnancies (Mirlesse *et al*., 1993). For IGF-I, the maximum concentration was 53·7 nmol/l (411 μg/l), which is 3 SD above the mean previously measured with the same assay in 36 nonpregnant women of 30–40-year-old (31·3 ± 7·6 nmol/l, mean ± SD) (Bouillon *et al*., 1995). Mirlesse *et al*. (1993) reported that mean IGF-I levels rose from 20 to 26 nmol/l (150–200 μg/l) in the first half of pregnancy to 43·4 nmol/l (332 μg/l) at term. Thus, the IGF-I concentrations in late pregnancy in this patient are in line with previous findings in normal pregnancies; consequently, the rise in IGF-I levels during early pregnancy was much steeper compared with normal pregnancies. Interestingly, the patient developed symptoms of oedema and paresthesiae in both hands at 12 weeks when IGF-I levels started to rise, and worsened at

35 weeks when IGF-I values were maximal. Oedema and paresthesiae (carpal tunnel-like symptoms) are known side-effects of the use of rhIGF-I therapy (Jabri *et al*., 1994); rhIGF-I has been shown to increase forearm blood flow (Copeland & Nair, 1994). PGH and IGF-I concentrations were strongly correlated during pregnancy ($r = 0{\cdot}90$; $P = 0{\cdot}002$; $n = 8$), a finding that confirms the notion that PGH regulates maternal serum IGF-I concentrations during pregnancy (Caufriez *et al*., 1990; Mirlesse *et al*., 1993).

The IGF-I concentration in cord serum was 9·7 nmol/l, which is within the normal range (mean ± 1 SD of 52 girls at 38 weeks: 8·4 ± 3·0 nmol/l) (Verhaeghe *et al*., 1993). PGH was undetectable in cord serum, confirming previous data (Frankenne *et al*., 1988).

In conclusion, serum PGH levels and IGF-I levels increased steadily during pregnancy in a woman with *pit-1* deficiency, and there was a strong correlation between both. This case study shows that PGH is the prime regulator of maternal serum IGF-I during pregnancy.

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