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## Maternal Plasma Concentrations of Insulin-Like Growth Factor-I (IGF-I) and Human Placental Lactogen (hPL) in Twin Pregnancies

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**Abstract.** Maternal plasma IGF-I and hPL concentrations were examined in 10 singleton pregnancies and in 11 twin gestations near term. hPL concentrations were higher in the twin pregnancies ( $14.4 \pm 2.4 \mu\text{g/l}$  vs  $6.9 \pm 0.9 \mu\text{g/l}$ ,  $P < 0.02$ ). In contrast, plasma IGF-I concentrations were similar in the singleton and twin pregnancies ( $533 \pm 45 \mu\text{g/l}$  vs  $572 \pm 60 \mu\text{g/l}$ , respectively). IGF-I concentrations failed to correlate with hPL concentrations in either group separately or when all subjects were considered together. These data do not support the hypothesis that maternal IGF-I secretion is an hPL-dependent process.

**Key words:** Twins, Insulin-like growth factor-I, Human placental lactogen

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### INTRODUCTION

In the nonpregnant state, circulating concentrations of IGF-I are thought to primarily reflect human growth hormone (hGH) dependent production by the liver and perhaps other tissues. Plasma concentrations of IGF-I increase during pregnancy [4], but the mechanism underlying this change and the site(s) of the presumed increase in IGF-I production remain to be determined. It has been proposed that hepatic IGF-I secretion is enhanced during pregnancy in response to increasing circulating concentrations of

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hPL, which is similar in structure to hGH [4]. In this study, we hypothesized that the higher circulating hPL concentrations known to characterize multiple pregnancies [8] might be associated with corresponding elevations in circulating IGF-I concentrations.

## MATERIALS AND METHODS

### Patients

Ten women with singleton pregnancies and 11 women with twin pregnancies were studied. All women were between 37 and 40 weeks from the last menstrual period and were free of concurrent medical problems. None of the women were taking medications other than prenatal vitamins and iron. The mean ages of the two groups of gravida were similar:  $26.7 \pm 1.9$  yr vs  $29.0 \pm 2.9$  yr for the singleton and twin group, respectively.

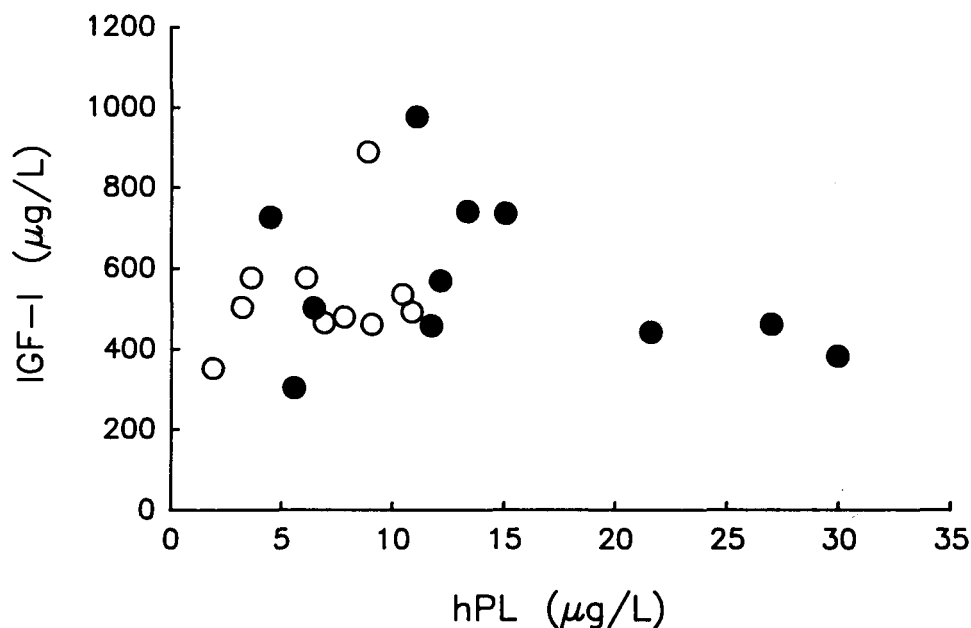
### Protocol

Each woman underwent a single phlebotomy during waking hours. Blood was collected into EDTA treated tubes and promptly centrifuged. Plasma was stored at  $-20^{\circ}\text{C}$  until assay. Subsequently, plasma concentrations of hPL were determined using a commercially available radioimmunoassay kit (Amersham Corporation, Arlington Heights, IL). All samples were assayed in triplicate in a single assay. The intraassay coefficient of variation is 9.4%. Plasma IGF-I concentrations were measured by radioimmunoassay after acid incubation and solid phase extraction to remove binding proteins. The details of the extraction step have been previously described [7]. Non-equilibrium immunoassay was performed after the method of Furlanetto et al. [3], using a 1:1400 dilution of polyclonal rabbit antiserum provided by the National Institutes of Health and  $^{125}\text{I}$ -labeled recombinant human [Thr<sup>59</sup>] IGF-I from Amersham Corporation (Arlington Heights, IL). Recombinant human IGF-I (Bachem, Torrence, CA) served as standard. All samples were assayed in duplicate and at least two dilutions of each sample were tested. The intraassay coefficients of variation of the assay for standards containing 130, 200, and 440 pg/tube are 6.5%, 3.9%, and 2.6%, respectively. The interassay coefficients of variation for the same standards are 6.9%, 8.2%, and 4.3%, respectively.

The study protocol had previously been approved by the Hospital Research Committee of Northwestern Memorial Hospital and by the Institutional Review Board of Northwestern University. All women provided informed consent prior to entering the study.

### Statistical Analysis

Differences between the two groups were assessed by means of two-tailed group T tests. Correlations between dependent variables were assessed by calculating Spearman Rank correlation coefficients. P values less than 0.05 were considered to be significant. Data are presented as mean  $\pm$  SE.



**Figure.** Serum IGF-I and hPL concentrations in subjects with singleton pregnancies (open circles) and with twins (solid circles).

## RESULTS

Maternal plasma hPL concentrations were higher in the twin than in the singleton pregnancies ( $14.2 \pm 2.4 \mu\text{g/l}$  vs  $6.9 \pm 0.9 \mu\text{g/l}$ ;  $P < 0.02$ ). Maternal plasma IGF-I concentrations were similar:  $533 \pm 45 \mu\text{g/l}$  vs  $572 \pm 60 \mu\text{g/l}$  in the singleton and twin pregnancies, respectively. IGF-I and hPL values failed to correlate (Figure) in either group separately (singletons:  $r = 0.30$ ; twins:  $r = 0.30$ ) or when all subjects were considered together ( $r = 0.09$ ). Moreover, IGF-I concentrations failed to correlate with either (total) newborn or placental weight (data not shown).

## DISCUSSION

The hypothesis that hPL is an important regulator of maternal IGF-I production during pregnancy stems primarily from two findings. First, hPL is structurally similar to human growth hormone (hGH) and has some hGH-like activity [6]. Second, circulating maternal concentrations of hPL and IGF-I are correlated when measured over a wide range of gestational ages [4]. Both rise steadily throughout gestation and fall precipitously after delivery. Because such a pattern of temporal change is typical of many of the biochemical, as well as clinical, changes which accompany pregnancy, the possibility that the observed correlation does not reflect a causal relationship is particularly high.

In order to eliminate such noncausal parallelism as a possible source of artifactual correlation, we chose to study all our subjects at approximately the same gestational age (at or near term). Furthermore, we attempted to exploit the documented increase in circulating concentrations of hPL in women carrying twins in order to elucidate a relationship between hPL and IGF-I concentrations.

As expected, the hPL concentrations in the twins group were double those of the singleton group. In contrast, however, the plasma IGF-I concentrations were quite similar, and no correlations between hPL and IGF-I values were detected.

In our opinion, these findings render the hypothesis that hPL is an important stimulator of maternal IGF-I release less likely. This interpretation should be viewed with caution, however, for at least two reasons. It is possible that at a particularly high concentration of circulating hPL, a maximal maternal production rate of IGF-I is achieved. If the majority of our subjects had hPL concentrations which exceeded this value, a causal relationship between the two hormone concentrations might thus be masked. Nevertheless, such a mechanism would certainly be unusual in a physiologic setting such as a pregnancy. In addition, it is possible that immunoreactive IGF-I values may be poor reflectors of bioactivity because specific binding proteins of IGF-I, which are known to modulate the effect of IGF-I on target tissues, are altered in pregnancy [5].

Recently, a GH-like peptide of placental origin has been identified [2]. It now appears that 85% of circulating GH activity during pregnancy, as determined by a radioreceptor assay, is attributable to this GH variant; in contrast, the percentage attributable to hPL is 12% [1]. To the extent that maternal IGF-I production is dependent on specific binding to GH receptors, these data likewise suggest that hPL is a relatively unimportant modulator of maternal IGF-I production. The physiologic significance of alterations in the GH/IGF-I axis which occur during pregnancy remains to be elucidated.

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