Human Chorionic Gonadotropin (hCG) in Early Pregnancy – A Review of the Evidence

Key Points

- Levels of hCG in serum and urine rise rapidly and predictably during the first days of pregnancy[6,8-13,19]
- Levels of hCG are related to gestational age[14,15,16]
- Levels of hCG are similar between women at least up to a week after hCG is first detected [6,13,18]
- In early normal pregnancy, hCG levels are sufficiently similar to allow the identification of normal, abnormal and multiple pregnancies[4,11,19,20,21,23, 26-32]

Introduction

Human chorionic gonadotropin (hCG) is produced in the earliest stages of pregnancy. During early pregnancy it plays a role in survival of the corpus luteum [1] and in stimulating the thyroid gland[2], and it also appears to have a significant role in the implantation of the blastocyst and protection of the embryo against immune attack at the fetal/maternal boundary. The hormone is initially produced by the embryo and, therefore, also acts as a marker for its presence[3].

Levels of hCG following conception have been the subject of a great deal of research over the last twenty years, but with differing objectives. The main thrust of research has been directed at patients undergoing *in-vitro* fertilisation (IVF) or assisted conception since early results indicated that levels of hCG could be used as a marker for pregnancy outcome. This marker has the potential for predicting likely pregnancy outcome in both assisted conception and natural conception pregnancies at an earlier time and more predictably than other means of monitoring pregnancy. To a lesser degree the levels of hCG have been investigated for their potential in estimating length of gestation. HCG levels are also being investigated alongside other biochemical and physical markers for use in predicting genetic abnormality in pregnancy.

This review provides a brief summary of research conducted in the area of levels of urinary and serum hCG in the early (i.e. up to ~50 days post-conception) stages of pregnancy over the last twenty years.

Levels of hCG in Early Pregnancy

Key Points

- Levels of hCG rise rapidly and predictably in the early days of pregnancy[6,8,9-13,19]
- hCG is detectable at least 6 days after estimated day of conception in urine and serum[4-8]
- The increase is described as log quadratic[6,10,11]
- Levels of hCG are related to gestational age[14-16]

HCG levels rise rapidly in the earliest days of pregnancy and can be detected very early on in a pregnancy. The day that hCG is reported to be first detected depends upon the method of estimating conception and on the sensitivity of the assay for hCG. Several studies have shown hCG detection in maternal urine 6 or more days after estimated day of fertilization[4-6]. Lenton[8] first detected hCG in plasma on day 8 after the LH surge (measured by standard RIA) but in only 5.3% of cases and in a recent prospective study by Cole[7], hCG detection in urine was detected as early as 4 days following ovulation (LH peak measure. However, these analyses rely on extremely sensitive measurements made in the region of the assay curve displaying high coefficients of variation, so some spread in first day of detection would be expected. For example, the Immunolite assay used by Cole only has a sensitivity of 1mIU/ml hCG, so measurements this early in pregnancy would be challenging the analytical capability of the assay.

The rate of increase of hCG levels during the first few days has been measured and reported in varying ways. A steep rise in serum hCG is characteristic of pregnancy around the peri-implantation period[9]. The increase was described as a log quadratic trajectory[6,10] in spontaneous pregnancies; and also in a retrospective cohort analysis of 455 IVF pregnancies. A plateau was reached earlier in assisted conceptions than in natural conceptions although the rate of rise was similar[11]. One report concerning naturally conceived pregnancies described the rise as log linear[12]. A 50% increase was reported in 1 day and 124% in 2 days and the rate of increase was reported to slow down 24 hours after oocyte retrieval in IVF pregnancies[11]. In naturally conceived pregnancies, the median slope for a rise was 1.5 (representing a 50% increase) after 1 day, 2.24 (124% increase) after 2 days, and 5.0 after day 4[12]. The rate of increase has also been described by doubling time.

In an early study, doubling time was reported as 1.3 days[8]. In a study of 120 IVF pregnancies and 16 spontaneous pregnancies, where serum beta-hCG was measured on days following ovarian aspiration/rupture, doubling times were 1.6 days in the IVF pregnancies and 1.4 days in spontaneous pregnancies[13]. In a study of 143 natural pregnancies, where serum beta-hCG levels were related to day of ovulation, the doubling time increased between days 10-20 and 21-30 in normal pregnancies[10]. The average rate of increase has also been referred to as a fold increase by Nepomnaschy. He reported a 3-fold increase in urinary hCG between the first day of detection and the second, and a decrease thereafter to 1.6 fold by day 6 and 7 from day of first detection[6].

Our findings, based on the daily collection of urine samples prior to conception until six weeks post-conception, with LH surge as the marker for ovulation, found the hCG rise to be extremely similar to these observations (34). Levels each day were significantly different from the previous day, at the 95% confidence level, up to day 21 after LH surge. There was a 30-fold increase in mean urinary hCG between days 8 and 9, a 5-fold increase between days 9 and 10, a nearly 3-fold increase between days 10 and 11, a doubling between days 11 and 12, and a progressively slower rate of increase thereafter. After 21 days, the daily differences were not significantly different.

A study by McChesney looked at the different isoforms of hCG in early pregnancy and concluded that certain variants fluctuate markedly during early pregnancy, whereas other forms were more consistent. As such, different hCG assays can give very different profiles in early pregnancy depending on the forms of hCG it detects. This means that concentrations/doubling times reported by one group may be different to those by another[33].

It should also be noted that in early normal pregnancy, hCG levels are considered sufficiently similar to allow the identification of abnormal and multiple pregnancies[4,11,19-21,23,26-32]. This demonstrates that there is a defined range in which hCG levels should fall at any given gestational age in a normal pregnancy.

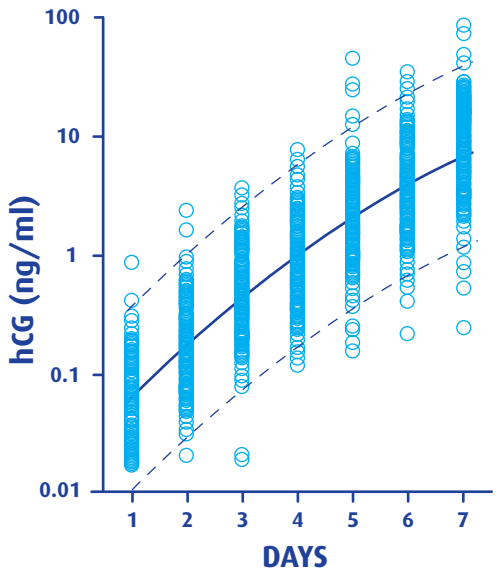
Levels of hCG are highly similar between women

Key Point

- The levels of hCG in early pregnancy are highly similar between women depending on point of reference[6,13,18]

The levels of hCG have been reported to be consistent among normal pregnancies. Nepomnaschy[6] described the average profile of hCG and its variability during the 7 days following estimated implantation in naturally conceived pregnancies. Early morning urines were collected from 142 clinical pregnancies prior to conception up until 8 weeks pregnancy and frozen at the volunteer's home. The mean rise in hCG levels among women was consistent when related to the day of first detection of hCG, at least for the first week. Figure 1 demonstrates this similarity.

Figure 1



Predicted hCG excretion patter and observed values during the first week of detection for 142 clinical pregnancies. Circles represent individual data points, the central solid line represents the hCG trajectory predicted in the regression equation and the broken lines represent the 95% probability band for the model.

Day 1 = day of detection (hCG >0.015 ng/ml)

Source: Nepomnaschy *et al.* 2008
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Table 1 Daily Mean hCG concentrations in the first morning urine during the first week following detection calculated for 142 clinical pregnancies

Days*	*n*	Geometric Mean (n g/ml)	95% CI
1	141	0.05	0.05-0.06
2	142	0.17	0.15-0.20
3	140	0.40	0.35-0.47
4	137	0.91	0.78-1.07
5	137	1.94	1.63-2.31
6	136	3.99	3.40-4.69
7	133	6.76	5.66-8.07

*Day 1 = day of detection (hCG >0.015 ng/ml)

Table 1 shows the mean levels of hCG and confidence intervals for each day during the first week of pregnancy.

Source: Nepomnaschy *et al.* 2008
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Despite the consistency seen in the mean rise in hCG concentrations, the study identified that individual hCG profiles vary markedly. Unfortunately the assay used for detection of hCG in this study did not have sufficient precision to properly evalulate sources of variation as it had an intra-assay variability of 15-21% (in-house IRMA assay).

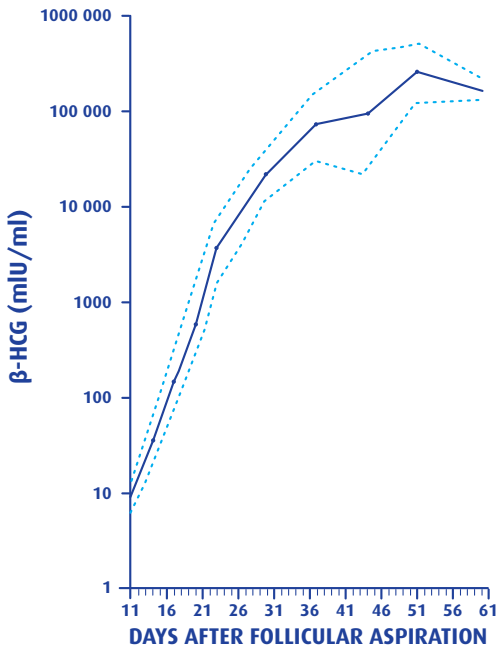
IVF pregnancies may not be the obvious place to find evidence for uniformity of hCG rise, because by their nature, they reflect pregnancies in which conception has usually been problematic. Therefore levels may not necessarily be comparable to natural conceptions. However, this type of study does have the advantage of having greater precision in calculating gestational age in relation to hCG, as embryo implantation can be considered a fixed time point.

In a study on hCG levels in 12 pregnancies achieved by IVF, various glycoforms of hCG levels were

measured in urine normalised to creatinine by immunometric assays. Highly similar profiles were observed in the early stages of normal pregnancy for all types of glycoforms measured. Note that this study found a statistically significant difference in levels of hCG between normal pregnancies and early pregnancy loss[18].

In another study of pregnancies achieved by IVF[13], hCG levels in serum measured on days after follicular aspiration also showed very similar profiles with little statistical variation among 48 normal and singleton pregnancies, the results of which are shown below.

Figure 2



Serum β–human chronic gonadotrphin (hCG) concentrations in normal singleton IVF–embryo transfer pregnancies. Solid line represents mean values and dashed lines represent ± SD.

Source: Zegers-Hochschild *et al.* 1994
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These studies confirm that hCG levels are statistically highly similar in normal pregnancies in the early days of pregnancy and only fall below normal levels when the viability of the pregnancy is threatened.

Absolute levels of hCG and gestational age

Key Point

- Levels of hCG predict gestational age[14-16]

Levels of hCG are sufficiently robust to be used to estimate gestational age. In a study in 16 spontaneous pregnancies, the calculated doubling times from day of ovulation (estimated from the rise in basal body temperature) revealed a significant correlation between doubling times, hCG concentration and gestational age both within groups and in individual pregnancies[14]. In 99 normal pregnancies, quantitative beta-hCG in serum measured by radioimmunoassay, accurately established the age of pregnancies up to 3 weeks post-conception, and with an accuracy of ±4 days from the 3rd to the 8th week of gestation indicating highly similar levels among women. In the same study results of urinary beta-hCG measurements were not found to be useful for pregnancy evaluation and/or gestational aging[15]. It should be noted though, that the urinary beta-hCG excretion profile in pregnancy is different to that of intact hCG used in standard home pregnancy tests. In addition error was introduced because different criteria were used to estimate conception, which were based on the information that the women provided (LMP, remembered sexual intercourse, or known ovulation).

Three gestational age bands were revealed from measurement of serum hCG levels in 29 pregnant women. Each had a linear increase in hCG, which could be translated into doubling times and percentage increase over time[16].

Summary

The levels of hCG in serum and urine have been studied extensively over the last twenty years. Studies have shown that levels of hCG rise rapidly during the first days of pregnancy and are statistically highly similar between women during early normal pregnancy. Levels of hCG in normal pregnancy are sufficiently similar that levels of hCG that are outside the normal range predict abnormal pregnancy. Levels are sufficiently similar to allow thresholds of absolute levels of hCG to be drawn up to predict pregnancy outcome and gestational age. Overall it is clinically accepted that levels of hCG are highly consistent and reliable during early pregnancy and only fall outside normal ranges when the viability of a pregnancy is threatened or multiple conceptus are present.

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