Analysis of human chorionic gonadotrophin (hCG) levels in normal and failing pregnancies

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Introduction and purpose of study

- Levels of hCG increase following conception, and are usually detectable in the urine between 6 and 10 days after fertilisation[1,2,3]
- There is approximately a 1 in 4 chance that the pregnancy will end in early loss
- In early pregnancy loss, hCG levels usually do not increase as expected[4]
- Serum hCG measurement is often used for assessment of pregnancy viability, but the optimum number and timing of measurements is unknown[5]
- Urine hCG levels closely mirror those in the serum, thus provide a non-invasive monitoring method.

The purpose of this study was to examine daily urinary hCG concentrations to assess pregnancy viability.

Methods:

- This was a prospective study of 129 women (aged 18–45 years) recruited preconception to collect daily urine samples (for hormone analysis) for complete menstrual cycles, and for up to 28 days after the day of their expected period if they became pregnant
- Miscarriages were classified into early losses (< 6 weeks, n=18) and clinical losses (> 6 weeks, n=24)
- Quantitative luteinising hormone (LH) (to determine the surge day) and hCG testing were conducted using a validated quantitative automated immunoassay system (AutoDELFIA, Perkin Elmer)
- The day following the LH surge was used as a reference for the start of pregnancy
- Longitudinal models were created for each of the three groups in order to profile hCG
- Cox proportional hazards models were used to identify miscarriage risk factors (demographic and hCG)
- SAS version 9.2 and SATA version 13 were used for the statistical analysis.

Results

Volunteer demographics grouped by pregnancy outcome are summarised in Table 1.

Table 1: Study population demographics

Pregnancy outcome	Viable	Miscarriage
Age, years		
Mean (SD)	29.95 (4.15)	32.34 (4.60)
Median (range)	29 (20)	32(20)
Ethnicity, n (%)		
White	75 (88.24)	34 (77.27)
[Hispanic or Latino]	*7 (8.24)*	*7 (15.91)*
Asian	4 (4.71)	2 (4.55)
Black or African American	3 (3.53)	7 (15.91)
Mixed	3 (3.53)	1 (2.27)
Self-reported average menstrual cycle, days		
Mean (SD)	29.94 (2.95)	28.66 (3.21)
Range	24 – 39	19 – 37
Time trying to conceive, months		
Mean (SD)	4.36 (5.83)	4.55 (5.98)
Range	0 – 48	1 – 36

Summary plots of the hCG concentration by viable pregnancy and miscarriage plots are shown in Figure 1.

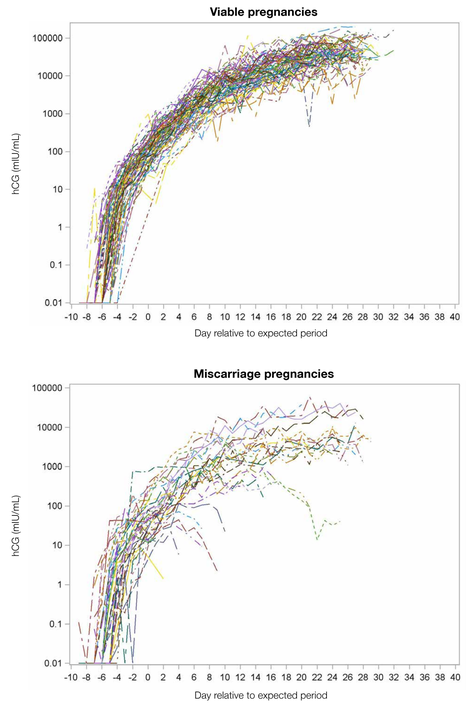

Figure 1: hCG profiles of pregnancy outcomes

A longitudinal model was fitted to each of the three groups (viable, early loss and clinical loss) which allowed random intercepts and slopes. A random quadratic day term was also included in the model to account for the curvature in the profiles. An unstructured covariance structure was assumed.

Figure 2 displays the fixed effects profiles for the three groups showing that the early pregnancy loss group has a markedly different profile to the other two groups; these exhibit a steep rise in the log hCG concentration before pregnancy loss occurs and the hCG concentration decreases. Those who either suffered a clinical pregnancy loss or had a viable pregnancy exhibited a steadier rise in the log hCG concentration before plateauing. Clinical pregnancy losses tend to plateau at a lower hCG concentration than viable pregnancies.

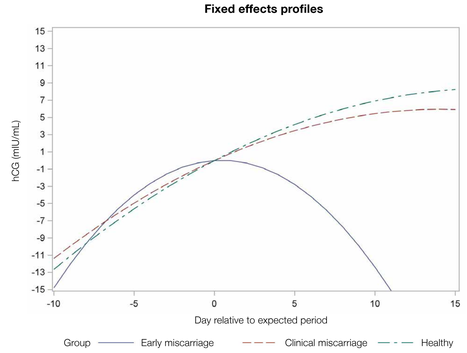

Figure 2: Fixed effects profiles

Additionally, a Cox proportional hazards model was constructed using the 'Collet Procedure' to identify miscarriage risk factors, using demographic and hCG data. Table 2 provides the model estimates, indicating that the length of time from the LH surge to the hCG concentration reaching 25 mIU/mL is a significant prognostic factor when determining likelihood of miscarriage. For example, for an increase of 1 day, there is a 44% increase in the risk of miscarriage; hazard ratio 1.44 (95% confidence interval 1.25 to 1.66).

Covariate	P-value	Hazard ratio	95% Confidence interval
Age	0.806	0.98	0.80 to 1.19
Time from the LH surge to hCG reaching 25 mIU/mL	<0.001	1.44	1.25 to 1.66
Longest cycle length	0.184	0.92	0.80 to 1.04
Time dependent			
Age	0.094	1.12	0.98 to 1.27

Table 2: Cox proportional hazards model estimate

Conclusions

- **Urinary hCG profiles in viable pregnancies are highly consistent, as shown in Figure 1**
- **Early pregnancy loss urinary hCG profiles differ, making it possible to identify prior to examination of any clinical symptoms**
- **Further studies would be needed to understand the exact dynamics, but our findings suggest an algorithm based on hCG concentration and ovulation day may be possible**
- **A significant predictor in early pregnancy loss is the characteristic of the first appearance hCG following conception**
- **Clinical pregnancy losses could not be consistently differentiated from viable pregnancies, prior to the onset of loss.**

References

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Declaration of Interest

This study was funded by SPD Development Company Ltd., a wholly owned subsidiary of SPD Swiss Precision Diagnostics GmbH. Sarah Johnson and Lorrae Marriott are employees of SPD Development Company Ltd.

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