Article

Age and a single day-14 β-HCG can predict ongoing pregnancy following IVF

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Abstract

The current study was undertaken to investigate the use of beta human chorionic gonadotrophin (β-HCG) concentration and other significant factors to predict the likelihood of an IVF pregnancy progressing to detection of cardiac activity by ultrasound, and to create data tables which can be used for patient counselling. A retrospective data analysis was undertaken of 1374 IVF cycles performed from January 1997 to July 2007, resulting in 662 pregnancies. Maternal age ($P = 0.0005$), day-14 ($P < 0.001$) and day-16 ($P < 0.001$) post-oocyte aspiration β-HCG concentrations were found to be significant in predicting pregnancy outcome. Multiple logistic regression modelling revealed that the most accurate predictive model used a single day-14 β-HCG concentration and maternal age. Day-14 and day-16 β-HCG concentrations were highly correlated, with the addition of a day-16 concentration adding no additional predictive value. Ongoing pregnancy rates were proportional to day-14 β-HCG concentration and inversely proportional to maternal age. The multiple pregnancy incidence increased proportionally with the initial β-HCG concentration. Thus, for the counselling of patients following IVF, a single day-14 post-oocyte-aspiration β-HCG concentration and maternal age are most predictive of the pregnancy continuing to detection of cardiac activity by ultrasound.

Keywords: *β-HCG, human chorionic gonadotrophin, IVF, maternal age, pregnancy outcome*

Introduction

Over 125,000 cycles of IVF were performed in the USA in 2004, resulting in 36,000 deliveries (Centers for Disease Control and Prevention [CDC] *et al.*, 2006). Patients who undergo IVF are often plagued by stress and anxiety related to their infertility and subsequent treatment. The emotional burden of undergoing IVF can be significant, with 56% reporting that going through IVF 'put their life on hold', was an 'ordeal' and interfered negatively with their job and lifestyle (Hammarberg *et al.*, 2001).

Women undergoing IVF report that they experience the highest level of psychological stress at the stage of the pregnancy test, with 81% reporting that the period of waiting for the result was extremely or very stressful (Yong *et al.*, 2000). The time between the first pregnancy test and confirmation of a viable intrauterine pregnancy by ultrasound can also be emotionally stressful, with 46% of patients reporting this waiting time as being extremely or very stressful (Hammarberg *et al.*, 2001).

Results are conflicting as to whether stress and anxiety result in a poor IVF outcome. Some studies have shown that anxiety is related to a poorer outcome in IVF (Klonoff-Cohen *et al.*, 2001; Smeenk *et al.*, 2001). However, others have shown no adverse effect on outcome (Milad *et al.*, 1998; Anderheim *et al.*, 2005). Without question, however, the overall result of these stressors can result in significant emotional strain. Studies have reported that 26–64% of those patients who had an initial IVF failure discontinue IVF treatment due to the emotional and psychological burden (Hammarberg *et al.*, 2001; Olivius *et al.*, 2004).

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The prediction of success following IVF has always been a desire of both clinicians and patients. Accurate prediction of IVF success may ease some of the stress and anxiety that patients endure. Many studies have aimed to identify methods to predict the success of a pregnancy achieved after IVF. Serum markers such as progesterone and oestradiol (Yamashita *et al.*, 1992), activin and inhibin (Hauzman *et al.*, 2004), pregnancy-associated protein-A (Coddington *et al.*, 1989), CA-125 (Hauzman *et al.*, 2005), hyperglycosylated human chorionic gonadotrophin (Sutton-Riley *et al.*, 2006) and beta human chorionic gonadotrophin (β-HCG) (Homan *et al.*, 2000; Papageorgiou *et al.*, 2001; Chung *et al.*, 2006; Porat *et al.*, 2007) have been studied in an effort to forecast pregnancy outcome. β-HCG has become the most frequently studied of these serum markers and has been demonstrated as being the most predictive as well (Yamashita *et al.*, 1992; Qasim *et al.*, 1996; Homan *et al.*, 2000; Porat *et al.*, 2007). The rate of rise in β-HCG from soon after implantation through to early pregnancy has been established (Chung *et al.*, 2006; Lohstroh *et al.*, 2007), and the concentration of β-HCG soon after implantation has been shown to have a direct correlation with pregnancy outcome (Qasim *et al.*, 1996; Poikkeus *et al.*, 2002; Urbancsek *et al.*, 2002; Kumbak *et al.*, 2006). Prior studies have also related outcome to both single β-HCG concentrations as well as multiple serial measurements. (Yamashita *et al.*, 1992; Guth *et al.*, 1995; Chen *et al.*, 1997; Bjercke *et al.*, 1999; Homan *et al.*, 2000; Papageorgiou *et al.*, 2001; Zayed *et al.*, 2001; Alahakoon *et al.*, 2004; Sutton-Riley *et al.*, 2006; Porat *et al.*, 2007).

Many of the prior studies have also had a limited number of IVF cycles in their analysis or have used a heterogeneous population combining IVF cycles with intrauterine insemination and natural conception cycles (Bjercke *et al.*, 1999). Various end-points have also been used in describing an ongoing pregnancy, e.g. using end-points at completion of the first trimester, 20 weeks or live birth (Chen *et al.*, 1997; Zayed *et al.*, 2001; Papageorgiou *et al.*, 2001; Alahakoon *et al.*, 2004; Kumbak *et al.*, 2006). Issues may arise after the embryonic stage, resulting in miscarriage, which are likely to be unrelated to and unpredicted by early biomarkers, such as those due to premature rupture of membranes, intra-amniotic infection or cervical incompetence.

In relating β-HCG to pregnancy prediction, most previous studies have either used complicated logarithmic and quadratic predictive equations or analysed data using receiver operating characteristic (ROC) curves which give a cut-off point with a corresponding sensitivity and specificity. These studies give broad generalizations for interpreting β-HCG concentrations, but limit the clinical utility of applying this data to an individual patient for counselling purposes, unless that patient's β-HCG concentrations happen to be near the cut-off point.

The objective of this study was to investigate the use of β-HCG concentration along with other significant factors to predict the likelihood of an IVF pregnancy, with the definition of an ongoing pregnancy as one in which cardiac activity is detected by ultrasound. It is known that the miscarriage rate in an asymptomatic person after this point is approximately 5% in spontaneously conceived cycles and 7.5–12% in cycles conceived by IVF (Siddiqi *et al.*, 1988; Makrydimas *et al.*, 2003; Tummers *et al.*, 2003; Tong *et al.*, 2006).

Once significant outcome predictors are determined, this data could be used to more accurately and easily assist in individualizing the counselling of patients during that stressful period between implantation and subsequent ultrasound.

Materials and methods

A waiver of consent and appropriate University of Louisville institutional review board approval were obtained. A retrospective data analysis was performed for all IVF cycles completed at the study centre from January 1997 to July 2007. Cycles varied in the stimulation protocol used, based on physician preference, patient and clinical scenario. Only cycles utilizing fresh multi-cell embryos (day 3) or blastocysts (day 5) were considered, as these are representative of 73.5% of all cycles nationwide (Society for Assisted Reproductive Technology [SART] and the American Society for Reproductive Medicine [ASRM], 2004). Donor egg cycles were excluded to reduce the confounding issue of donor versus recipient age. Frozen-embryo cycles were also excluded in order to form a more homogeneous data set. All cycles and transfers were managed and performed by one of seven attending physicians.

As part of the study centre's routine protocol, serum quantitative β-HCG concentrations are taken on days 14 and 16 post-oocyte aspiration. If the day-14 β-HCG test is positive, a second β-HCG concentration is taken 48 h later (day 16), in part to assist in predicting a viable intrauterine pregnancy or to aid in evaluating for a possible ectopic pregnancy. An ultrasound was then performed at 6–7 weeks' gestational age to verify cardiac activity and number of gestational sacs. Often additional β-HCG concentrations were drawn according to physician and patient desire for reassurance or to follow a falling concentration. Serum analysis was performed using one of two analysers utilizing a chemiluminescence technique, calibrated to the World Health Organization Third International Standard 75/537. A change in analysers occurred in November 1997, from a Beckman Coulter Access Analyser (Beckman Coulter Inc., Pasadena, CA, USA) to an Immulite 1000 Analyser (Siemens Medical Solutions, Malvern, PA, USA).

An ongoing pregnancy for this study was defined as one which progressed at least to the point of detection of cardiac activity by ultrasound. Pregnancies defined as not ongoing were ectopic pregnancies and those that had falling β-HCG concentrations which ultimately became negative, an empty gestational sac on ultrasound (anembryonic) or a fetal pole with no cardiac activity visualized (missed abortion). Multiple gestations were defined by having more than one embryo with cardiac activity.

Data analysis using multiple logistic regression modelling was performed using Stata 9.2 (StataCorp, College Station, TX, USA). Initial analysis of the data considered multiple possible prognostic and confounding factors, assessing each individually and in multiple combinations for their significance. These factors included patient age, day-14 β-HCG concentration, day-16 β-HCG concentration, the type of transfer (day-3 embryo versus blastocyst), number of embryos/blastocysts transferred, the two different β-HCG

analysers used, intracytoplasmic sperm injection (ICSI) versus conventional fertilization and whether it was the patient's first or subsequent IVF cycle.

Once the significance of each of these factors was determined, the fitting of several logistic regression models was performed utilizing various combinations of the significant factors. This allowed for the determination of the significance of each predictive factor individually as well as in varying combinations to predicting an ongoing pregnancy.

Results

There were 1511 IVF cycles using fresh embryos or blastocysts performed from January 1997 to July 2007, resulting in 799 pregnancies, defined by a positive β-HCG on day-14 following egg aspiration (52.9% overall implantation rate). Because of incomplete data or non-uniform β-HCG analysis (i.e. not drawn on days 14 or 16), 137 cycles were excluded. In all, 587 patients underwent 1374 cycles yielding 662 pregnancies that were included in the final analysis.

Analysis of the factors thought to impact pregnancy outcome was first undertaken using the chi-squared test to compare proportions and Student's *t*-tests to compare continuous data in order to determine the significance of a factor in outcome prediction. The difference in age between the groups was strongly significant ($P = 0.0005$), as was the difference in the day-14 and day-16 β-HCG concentrations ($P < 0.001$ and $P < 0.001$, respectively) (**Table 1**). Both the day-14 and day-16 β-HCG concentrations were found to have no significant correlation with age ($r^2 = 0.0026$ and $r^2 = 0.0007$, respectively) (data not shown).

The stage of embryo transferred showed an overall significant difference in outcome between day-3 embryos and blastocysts (68.7% versus 77.9% ongoing pregnancy, $P = 0.03$).

The ongoing pregnancy rates were not significantly different between those that were fertilized by conventional IVF methods and those that underwent ICSI (71.1% versus 70.2%). The β-HCG values also did not differ significantly by fertilization method. There was also no significant difference in the ongoing pregnancy rate based on the number of embryos transferred, calculated using the chi-squared test of independence.

Cycles were separated to determine if a patient's first IVF cycle or subsequent repeat cycles would show any difference in success rate. Of the 587 patients, 73 ultimately had a second IVF cycle during the studied time period, and two underwent a third cycle. No difference was found in the success rate between a first IVF cycle and subsequent cycles. Those in their first IVF cycle had an ongoing pregnancy rate of 70.0% compared with 76.0% of those in repeat cycles.

The potential confounding effect from using different β-HCG analysers was examined. The success rates for the two different assays were found to be very similar. Day-14 β-HCG concentrations did not significantly differ for the two different assay methods, nor did the day-16 β-HCG concentrations.

Table 1. Initial prognostic factors for pregnancies ongoing versus not ongoing following IVF/ICSI.

Prognostic factor	*Pregnancies* *Total* *(n = 662)*[a]	*Ongoing* *(n = 468)*[b]	*Not ongoing* *(n = 194)*[b]	P-*value*
Age (years)	32.8 ± 4.1	32.5 ± 4.0	33.7 ± 4.1	0.0005
Day-14 β-HCG (mIU/ml)	125.7 ± 97.4	153.0 ± 94.1	60.1 ± 70.4	<0.001
Day-16 β-HCG (mIU/ml)	295.3 ± 247.5	368.0 ± 244.0	120.1 ± 148.9	<0.001
Type of embryo				
Day-3 embryo	517 (78.1)	355 (68.7)	162 (31.3)	0.03
Blastocyst	145 (21.9)	113 (77.9)	32 (22.1)	
IVF cycle				
First IVF cycle	587 (88.7)	411 (70.0)	176 (30.0)	NS
Repeat IVF cycles	75 (11.3)	57 (76.0)	18 (24.0)	
Fertilization method				
Conventional IVF	387 (58.5)	275 (71.1)	112 (28.9)	NS
ICSI	275 (41.5)	193 (70.2)	82 (29.8)	
Embryos transferred				
1	21 (3.2)	14 (66.7)	7 (33.3)	NS
2	260 (39.3)	189 (72.7)	71 (27.3)	
3	244 (36.9)	177 (72.5)	67 (27.5)	
4	115 (17.4)	75 (65.2)	40 (34.8)	
≥5	22 (3.3)	13 (59.1)	9 (40.9)	

Values are mean ± SEM or *n* (%).
[a]Percentages reflect proportions within column for total pregnancies.
[b]Percentages reflect proportions within row for ongoing and not ongoing pregnancies.
HCG = human chorionic gonadotrophin; ICSI = intracytoplasmic sperm injection; NS = not statistically significant.

The day-14 and day-16 β-HCG concentrations were found to be highly correlated. This relationship is shown in **Figure 1** (r = 0.880, P < 0.0001, r^2 = 0.774), with each data point representing an individual IVF cycle.

Four ectopic pregnancies occurred in the 662 documented pregnancies, one with a blastocyst transfer and three with day-3 embryos, yielding an ectopic rate of 0.6%. The mean day-14 and day-16 β-HCG concentrations of these ectopic pregnancies were 31 and 82 mIU/ml, respectively, with an average rise of 179% over the 2-day period.

Table 2 lists the comparison of the four different logistic regression models used for the prediction of an ongoing pregnancy, with the odds ratio (OR), associated 95% confidence interval (CI) and P value. The models analysed used varying combinations of the initial significant predictive factors: age, day-14 and day-16 β-HCG concentrations. In each model, age has an OR of 0.91, indicating that for each increase in age of 1 year, there is a 9% decrease in the chance of a successful pregnancy outcome. Both the day-14 and day-16 β-HCG components of the models show an OR of 1.01–1.02. Thus, a 1-unit increase in the day-16 β-HCG concentration is associated with an increase in the odds of success by a factor of 1.01 (or 1%). Since odds ratios are multiplicative, a 10-unit increase in day-16 β-HCG concentration is associated with an increase in the odds of a successful pregnancy outcome by a factor of 1.01^{10} = 1.10 (10% increase). The similar OR for both day-14 and day-16 β-HCG concentrations reinforces the correlation between the two, as previously mentioned.

Out of 662 patients, the full model, age + day 14 + day 16, correctly classified ongoing versus not ongoing pregnancies in 555 patients (83.8%), age + day 14 correctly classified 562 patients (84.9%), age + day 16 correctly classified 552 patients (83.4%) and day 14 + day 16 correctly classified 562 patients (84.9%). The disagreement between any two of the four models ranged from only 3–9%.

Figure 2 displays the results of the data by age group. These graphs show the proportions of pregnancies progressing to the point of detection of cardiac activity based on age group and the initial day-14 β-HCG concentration. This figure was created by calculating the percentage of cycles ongoing within each β-HCG concentration quintile. Each point represents the mean of the quintile group. When the β-HCG concentrations were divided into deciles, similar graphs were produced but with larger standard errors. The proportion of multiple pregnancies for a given day-14 β-HCG concentration is also shown. As can be seen, there is a declining probability of an ongoing pregnancy with increasing age. The peak percentage of ongoing pregnancies also declines with age, as does the percentage for a given β-HCG concentration. These same relationships hold true for the probability of multiple gestations as well.

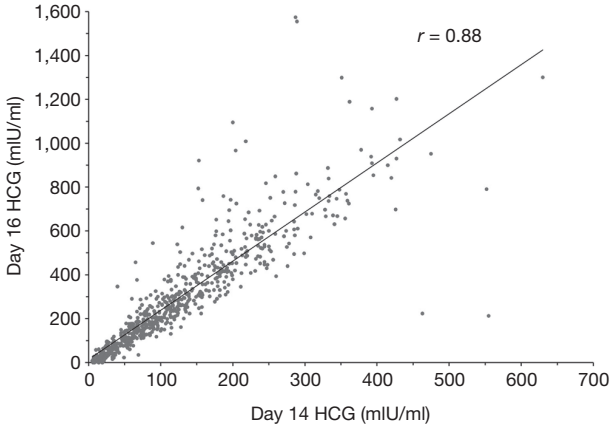

Figure 1. Correlation of β-HCG concentrations obtained 14 and 16 days after oocyte retrieval (r = 0.880).

Table 2. Comparison of four models used for the prediction of an ongoing pregnancy with associated odds ratio of each component.

Model	*Age*	*Day-14 β-HCG*	*Day-16 β-HCG*
Age + day-14 + day-16 β-HCG (full model)	0.91 (0.87–0.96) 0.001	1.01 (1.00–1.02) 0.01	1.01 (1.00–1.01) <0.001
Age + day-14 β-HCG	0.91 (0.87–0.97) 0.001	1.02 (1.02–1.03) <0.001	NA
Age + day-16 β-HCG	0.91 (0.86–0.96) <0.001	NA	1.01 (1.01–1.02) <0.001
Day-14 + day-16 β-HCG	NA	1.01 (1.00–1.02) 0.006	1.01 (1.00–1.01) <0.001

Values are odds ratio (95% confidence interval) P-value.
HCG = human chorionic gonadotrophin; NA = not applicable.

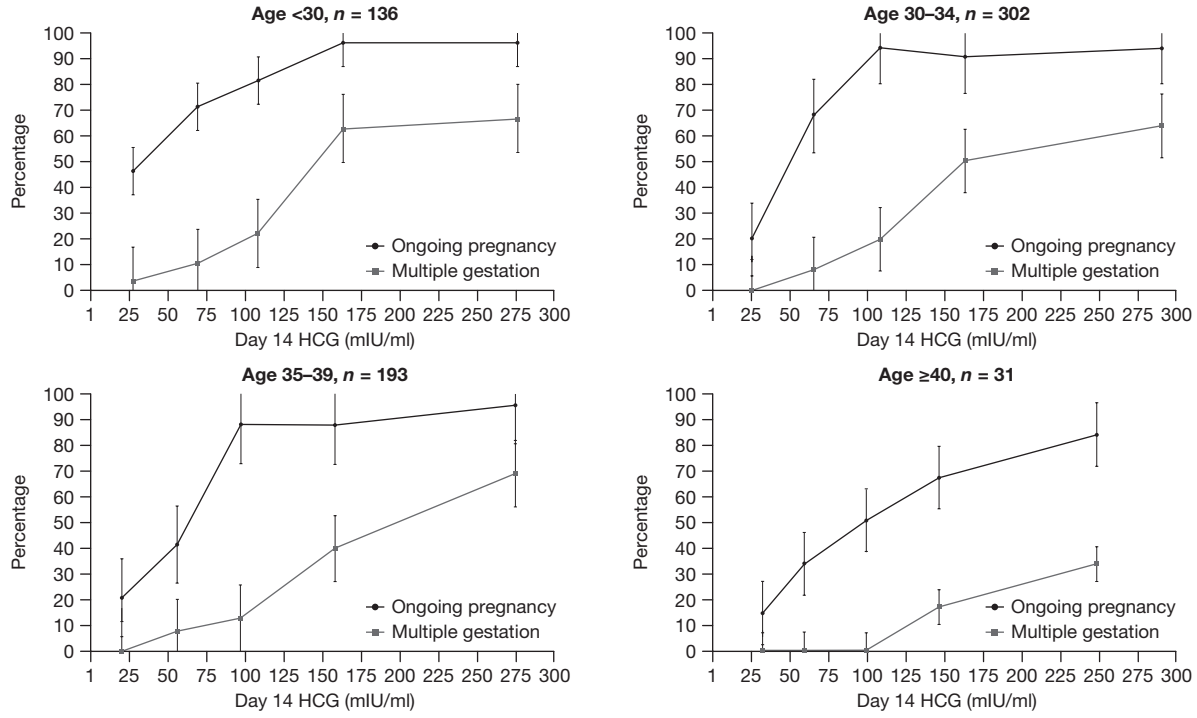

Figure 2. Day-14 β-HCG concentration and chance of an ongoing pregnancy and of its being a multiple gestation.

Discussion

Prediction of pregnancy outcome is desired by every patient who conceives during fertility treatment. However, this has been found to be uniformly difficult due to multiple factors. The large number of IVF cycles analysed in this study, though retrospective in nature, permitted more accurate determination of significant predictive factors, analysis of possible confounding factors and prediction of pregnancy outcome.

Overall, 48.8% of the cycles analysed resulted in a pregnancy, with 70.7% of those pregnancies continuing until at least the detection of cardiac activity by ultrasound.

The maternal age, day-14 β-HCG concentration and the day-16 β-HCG concentration were found to be strong predictors of successful pregnancy continuation. The difference in age between those pregnancies that were ongoing and those that were not was strongly significant ($P = 0.0005$), as was the difference within the day-14 and day-16 β-HCG concentrations ($P < 0.001$). This significance indicates that these variables may be predictive of implantation success.

Analysis of success based on the stage of embryo development revealed a significant difference in outcome. However, it should be noted that the difference in outcome between these two stages became significant only during the last 2 years of data collection (74 total cycles, $P = 0.003$). There was no significant outcome difference seen within the first 8 years (591 total cycles) (data not shown).

A Cochrane Library database review showed no difference in the clinical pregnancy rate in cycles conceived with day-3 embryos compared with blastocysts (Blake *et al.*, 2005). The study centre's early data confirmed these findings; however, within the past 2 years, there has been a clear benefit in blastocyst transfer compared with day-3 embryo transfer resulting in ongoing pregnancy rates of 48.9% versus 86.2%, respectively ($P = 0.003$). This benefit in blastocyst transfer has been mirrored in more recent studies (Papanikolaou *et al.*, 2005, 2006). This recent significance may reflect ongoing changes in the culture technique of blastocysts. The development of culture media that more closely matches the needs of a developing embryo has been an area of continued research and has likely contributed to this success. The higher pregnancy rate could also be attributed to selection bias. At this study centre, usually only those with at least four good-quality embryos on day 3 are allowed to be cultured to day 5 before being transferred, thereby possibly selecting those with higher quality embryos or those that would be inherently more successful.

No significant difference in outcome based on fertilization method was found. Although recent SART data shows slightly higher pregnancy success rates with conventional fertilization techniques compared with ICSI, these data show no difference between the two groups in ongoing pregnancy rate or β-HCG concentration (CDC *et al.*, 2006).

Although the differences in the number of embryos transferred were not statistically significant, there was a small but non-significant trend to have multiple pregnancies with larger numbers of embryos transferred. Within this study's data, singleton pregnancies accounted for 61.3% of cycles (average 2.7 embryos transferred), twins 31.9% (average 2.8 embryos transferred), triplets 6.6% of cycles (average 3.1 embryos transferred) and a single quintuplet set accounting for 0.2% of all cycles (4 embryos transferred).

The results from these data may be criticized due to the fact that multiple embryo transfer was and still is the norm in the USA. One may theorize that, by transferring multiple embryos, there may be instances in which more than one embryo implant, with subsequent early loss of one or more embryos. This could theoretically cause discrepancies in the β-HCG rise, thereby possibly distorting the data; however, confirming this theory is not easily possible. It is believed to be an infrequent occurrence, due to both the short testing interval as well as by the high correlation in the day-14 and day-16 β-HCG concentrations. Further studies, likely to be performed outside the USA, would be necessary to thoroughly confirm the data's significance in the setting of single-embryo transfers.

This study also discounted the influence of cycle, whether the studied cycle was an initial IVF cycle or a subsequent cycle, on the outcome of the pregnancy, and the potential confounding influence of two different β-HCG analysers, as neither of these factors showed clinical or statistical significance.

The primary analysis tested several models for their predictive value in an attempt to find the strongest model and identify the relative contributions of the significant predictive factors: age, day-14 β-HCG concentration and day-16 β-HCG concentration. The results listed in **Table 2** demonstrate that each of these variables is strongly predictive of an ongoing pregnancy. The odds ratios for age are fairly consistent, confirming that increased age is associated with a lower likelihood of pregnancy success. Describing the predictive value of the two β-HCG predictors is more difficult due to their aforementioned strong direct correlation. However, with similar OR within each model, the day-14 and day-16 β-HCG concentrations seem to be equally significant.

The day-14 and day-16 β-HCG concentrations were found to be highly correlated (**Figure 1**). Judging from the similar correct predictive ability and the strong correlation between the day-14 and day-16 β-HCG concentrations, they can be considered equal predictive factors and, thus, proxies for one another. Thus, the two concentrations have equal predictive value and could be used interchangeably, and considering them together offers little additional benefit. The several outlier points are thought to possibly be due to multiple pregnancies that subsequently spontaneously reduced to a lower number of ongoing embryos.

Although several of the studied mathematical models were found to have equal value in predicting pregnancy success, the simplest and most accurate model used only maternal age and a single day-14 serum β-HCG measurement. As previously mentioned, the addition of a second β-HCG measurement 2 days later added no additional predictive information over that provided by the day-14 measurement.

A review of these data revealed that the average IVF patient had 2.6 β-HCG measurements for the purpose of trending and possible prediction of pregnancy outcome. By forgoing one subsequent measurement, each patient would be saved US$225 in laboratory fees. Of ongoing cycles, 99% had initial day-14 concentrations >23 mIU/ml. In this study, 64 cycles had day-14 β-HCG concentrations below 23 mIU/ml, of which only five were ongoing (8%). However, for these 64 pregnancies, there were 101 additional β-HCG concentrations obtained to follow the concentrations, at a total cost of US$22,725. No ongoing pregnancy had a day-14 β-HCG concentration <12 mIU/ml.

The ectopic rate (0.6%) was similar to that reported in the 2004 SART data (0.7%) (CDC *et al.*, 2006) as well as by other programmes (Jun and Milki, 2007; Keegan *et al.*, 2007), although it is lower than the previously reported rates of 2–5% occurring in IVF cycles (SART and ASRM, 2004). It has been previously shown that ectopic pregnancies cannot be distinguished by the use of β-HCG concentrations at this very early stage (Poikkeus *et al.*, 2002). Continual follow up with β-HCG concentrations in an effort to rule out an ectopic pregnancy has not been found to be cost efficient even in the setting of a much higher ectopic rate. Therefore, in the absence of symptoms suggesting an ectopic pregnancy (vaginal bleeding, pain), sequential following of β-HCG concentrations is not justified (Mol *et al.*, 2002).

Figure 2 shows a graphical representation of the chance of an ongoing pregnancy based on age group and initial day-14 β-HCG concentration. The odds of achieving a multiple pregnancy for a given initial day-14 β-HCG concentration is also expressed within each age group. IVF success has been shown to be related to the patient's age, with the success rate decreasing with increasing age. Success rates begin to decline after age 30, with sharper rates of decline after ages 35 and 40 (CDC *et al.*, 2006). Given these trend-points, the cut-off points of 30, 35 and 40 years of age were used to stratify the data into clinically relevant groups.

As expected, ongoing pregnancy rates consistently increased across all age groups as the day-14 β-HCG values increased. This is in agreement with previous findings (Guth *et al.*, 1995). Ongoing pregnancy rates also declined consistently as age increased, with ongoing rates declining from 78.1% for those aged 30 years or less to a low of 48.4% for those 40 years or older. As β-HCG values increased, the rate of multiple pregnancies increased as well.

The data presented in **Figure 2** will be useful for counselling patients as to the chance of success during the stressful period following the result of their first β-HCG concentration. These data will provide patients with a reasonable estimate of their chance of having an ongoing pregnancy as well the chance of a multiple gestation.

Although implementation of these results could reduce the expense of IVF treatment by limiting the number of unneeded β-HCG concentrations, it is unlikely that clinicians will abandon this routine as patients often want the concrete numbers obtained from laboratory results rather than just reassurance that the pregnancy is progressing normally.

This counselling information will undoubtedly ease some of patients' anxiety during the time interval from the initial β-HCG concentration to their subsequent ultrasound 4 weeks later, and hopefully provide patient reassurance in this high-stress situation.

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