the Forecast of Weekly β-HCG and Progesterone for Early Pregnancy

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Abstract

Background: Serum beta human chorionic gonadotropin (β-HCG) and progesterone levels are both monitored to assess the status of early pregnancy. Deviations from the expected levels of these hormones may indicate abnormal pregnancy. However; the relationship between progesterone levels and the magnitude of weekly β-HCG increases, as well as their combined predictive value for pregnancy outcome, is still debated. This study evaluated the predictive value of weekly serum β-HCG multiplication and progesterone levels on early pregnancy outcomes.

Methods: This retrospective study reviewed patients with pregnancy confirmed by β-HCG in our hospital. Weekly β-HCG and progesterone levels were analyzed and ultrasonography was performed as necessary to determine outcomes at 13 weeks gestation.

Results: There were 277 viable intrauterine pregnancies, 102 spontaneous abortions, and 59 ectopic pregnancies. At weeks 5-8, β-HCG was multiplied by 6.76, 6.21, 2.11, and 0.68 respectively. Logit models were established with the logarithm of HCG (LHCG) and progesterone as independent variables to predict viable intrauterine pregnancy. The sensitivity, specificity, and overall accuracy for the models were 85.9% and 90.25%, 44.72% and 72.04%, and 70.77% and 83.6%, respectively. When progesterone was ≥10 ng/ml, the sensitivity and specificity for predicting viable pregnancy were 90.25% and 72.04%, respectively. When progesterone was <10 ng/ml, the sensitivity and specificity for predicting ectopic pregnancy and complete abortion were 94.2% and 81.57%78.86%, respectively. Progesterone values were significantly different for viable pregnancy, abortion, and ectopic pregnancy ($p<0.0001$). A joint progesterone and LHCG model to predict viable pregnancy had 88.8% sensitivity, 75.2% specificity, and 83.8% overall prediction accuracy.

Conclusion: Weekly β-HCG multiplication and progesterone levels can predict early pregnancy outcomes individually or jointly.

Background

Serum human chorionic gonadotropin (HCG) and progesterone are the most common hormones monitored after conception. HCG can be detected in maternal serum within 1 day after implantation of fertilized eggs [1]. Progesterone (P) is produced by the corpus luteum graviditatis in early pregnancy and synthesized by placental syncytiotrophoblasts after 8-10 weeks of pregnancy.

Most gynecologists believe that in normal intrauterine pregnancy, serum HCG should double every 2 days [2]. Deviation from this rule may indicate abnormal pregnancy, abortion, or ectopic pregnancy. For cases where the initial HCG value is <1500, 1500-3000, and >3000 mIU/ml [3], the predicted minimum 2-day increases are 49%, 40%, and 33%, respectively. Viroj [4] believed that progesterone monitoring is cheaper and advocated combined monitoring of HCG and progesterone to predict threatened abortion. However, Jee [5] showed that progesterone is of little importance in predicting outcomes of in vitro fertilization pregnancy.

The magnitude of HCG increase and the relationship between progesterone and pregnancy outcomes have recently been the focus of clinicians' attention,because they wanted to understand the relationship between early pregnancy outcomes and development trends of HCG and progesterone value,Therefore, this study reviews the relationships between β-HCG weekly multiplication, progesterone changes, and early pregnancy outcomes.

Methods

A total of 438 patients with pregnancy confirmed by serum β-HCG in the gynecology clinic of our hospital from July 2016 to July 2017 were included.All patients had regular periods, and were not using progesterone to achieve pregnancy. **Inclusion criteria** Patients with a history of trophoblastic disease, recurrent miscarriages, multiple pregnancy, uterine malformation, irregular menstruation, embryo transplantation, thyroid dysfunction, diabetes**,** kidney or liver diseases, hypertension, thrombosis, or autoimmune diseases such as systemic lupus erythematosus were excluded. Patient data was de-identified upon data collection.

Serum samples for β-HCG and progesterone were collected weekly at 8-11 am. The patients were monitored from 24 to 85 days after amenorrhea, in which 145 (33.10%) were detected once,110 (25.11%) twice,51 (11.64%) three times, and 132 (30.13%) for ≥4 times.All samples were processed by ELECSYS 2010 electrochemiluminescence fully-automatic immunoassay analyzer (Roche, Basel, Switzerland), with a matching Roche detection kit for serum β-HCG and progesterone. The HDI-4000 three-dimensional color Doppler ultrasound (Philips, Amsterdam, Netherlands) was used to perform two-dimensional vaginal ultrasonography. Vaginal B-mode ultrasonography was conducted to confirm the survival of intrauterine pregnancy embryos, ectopic pregnancy, missed abortion, and complete abortion. For patients with vaginal bleeding and/or abdominal pain, ultrasonography was performed weekly. For asymptomatic patients with serum β-HCG ≥100,000 mIU/ml, ultrasonography was performed to determine embryo survival and was repeated after 2 weeks for patients without fetal heartbeat. The women were followed until 13 weeks of pregnancy for early pregnancy outcomes.

Diagnosis of early pregnancy, complete abortion, missed abortion, and ectopic pregnancy was based on guidelines in Obstetrics and Gynecology, 9^{th} edition [1]. SPSS Statistics 22.0 statistical software (IBM, Armonk NY, USA) and R language were used for data analysis. One-way ANOVA analysis and multiple comparison tests were used to compare the mean values of various sub-samples. A polynomial regression model based on nonparametric regression was established to investigate the nonlinear curve variation characteristics of HCG and P-values relative to the amenorrhea time (adt). A logit regression model was used to investigate the prediction effect on pregnancy outcomes.

Results

The 438 patients included in the study were aged 18 to 37 years, (average 27.78±3.75,mean±SD), had a gravidity of 0 to 48(48% of the cases were 0,42 % were 1 or 2,6 % were 3,4% were 4), and a menstrual

cycle of 23 to 37 days (average31.23±4.77).There were 277 viable intrauterine pregnancies, 102 spontaneous abortions (10 complete and 92 missed abortions), and 59 ectopic pregnancies.

The amenorrhea time was recorded as adt,the logarithm of β-HCG was taken and recorded as LHCG. Considering LHCG as a dependent variable, a polynomial regression model was established for the adt. The best model is in the form of a cubic polynomial: $LHCG=a0+a1*adt+a2*adt^2+a3*adt^3+e$, where e is the random error term. The resulting fitted image is in Figure 1. The significant p-value of each estimation parameter is < 0.01, and $R^2 = 0.4431$.

The regression fitting equations for viable pregnancy, missed abortion, and ectopic pregnancy data with respect to adt were considered individually. The fitting formula for viable pregnancy data is $LHCG=22.4981+1.5111adt-0.0222adt^2+0.0001adt^3$(Figure 2). The p-values of each estimation parameter are <0.00001, indicating great statistical significance, and $R^2 = 0.7927$.

The gestational weeks were set as 4,5,6,7,8,9,10, and 11 weeks and was substituted into the above cubic polynomial model to obtain the corresponding predicted LHCG values, which were then reverted to the original β-HCG values. The predicted weekly β-HCG multiplication values were calculated as (β-HCG Value of Next Week - Value of Last Week)/Value of Last Week. The daily increment was calculated as Weekly Multiplication/7. (Table 1).

Table 1. Predicted values and multiplications of β-HCG in viable intrauterine pregnancy

The fitting formula for data on missed abortions is: $LHCG = adt + adt^2 + adt^3+e$. The significant p-value of each estimation parameter is <0.01, and $R^2 = 0.4493$ (Figure 3).

The predicted β-HCG values in different gestational weeks of missed abortion, the predicted 95% confidence intervals, weekly multiplications, daily multiplications, and daily increments are shown in Table 2.

Table 2. Predicted values and multiplications of β-HCG in missed abortion

ɔnal ː	4	5	6	7	8	9	10	11
ːed ˀ	314.5	2444.54	17623.5	54840.82	92086.17	104308.7	99642.1	100351.07
ːed nce al	222.10-446.75	2070.66-2885.93	15388.18-20183.53	48131.16-62486.02	78957.34-107398.23	85431.06-127358.47	76570.72-129666.36	58105.121-173313.96
ly ɑtion	6.76	6.21	2.11	0.68	0.13	-0.04	-0.01	
ˈ ɛnt	304.22	2168.42	5316.76	5320.76	1746.08	-666.66	101.28	
ˈ ɑtion	0.97	0.89	0.31	0.1	0.01	-0.00	0.00	

Gestational week	4	5	6	7	8	9	10
Predicted value	157.47	1587.30	10053.48	20220.27	21789.34	21225.66	31536.47
Predicted 95% confidence interval	52.41-473.1	922.28-2731.85	6900.04-14648.09	14667.52-27875.13	15237.61-31158.15	14189.92-31749.9	15195.96-65447.59
Weekly multiplication	9.08	5.33	1.01	0.08	-0.03	0.49	
Daily increment	204.26	1209.45	1452.4	224.15	-80.53	1472.98	
Daily multiplication	1.3	0.76	0.14	0.01	-0.003	0.07	

The best fitting curve for the ectopic pregnancy data is a quadratic curve: LHCG = adt + adt^2+e, R^2 = 0.06196, and the overall p-value for the F-test is 0.1422, with no significant correlation (Figure 4). The scatter plot shows little definite trend, and the fitting accuracy is very poor.

Pregnancy outcome (end) recorded as viable pregnancy (0) or other (1) was used as the two-value dependent variable, with LHCG as the independent variable to establish a logit model to predict viable pregnancy. p=P(end=1) was recorded, and the logit model was set as ln(p/1-p)=a0+a1*LHCG. The model

had 85.9% sensitivity(95%CI 81.3%-89.56%), 44.72% specificity(95%CI 37.25%-52.42%), and 70.77% overall accuracy. (Table 3)

Table 3. Prediction of pregnancy outcomes by HCG

Prediced of pregnancy outcomes	Clinical pregnancy outcomes	
	Abnormal pregnancy	Viable pregnancy
Abnormal pregnancy	72	89
Viable pregnancy	39	238

A logit model was established with Progesterone as the independent variable to predict viable pregnancy. p=P(end=1) was recorded, and the logit model was set as ln(p/1-p)=a0+a1*P. The model had 90.25% sensitivity(95%CI86.15%-93.26%), 72.04% specificity(95%CI 64.65%-78.42%), and 83.6% overall accuracy. (Table 4)

Table 4. Prediction of pregnancy outcomes by progesterone

Prediced of pregnancy outcomes	Clinical pregnancy outcomes	
	Abnormal pregnancy	Viable pregnancy
Abnormal pregnancy	116	45
Viable pregnancy	27	250

When progesterone was ≥10 ng/ml, the sensitivity, specificity, and total accuracy for predicting viable pregnancy were 90.25%, 72.04%, and 83.56%, respectively. When progesterone was <10 ng/ml, the sensitivity, specificity, and total accuracy for predicting ectopic pregnancy and complete abortion were 94.2%,78.86%,and 81.27%, respectively. (Table 5)

Table 5. Pregnancy outcomes measured with 10 ng/ml progesterone as the threshold

	Ectopic pregnancy	Complete abortion	Missed abortion	Viable pregnancy	Total
progesterone□10	55	10	51	27	143
progesterone≥10	4	0	41	250	295
Total	59	10	92	277	438

Progesterone was analyzed by one-way ANOVA according to three outcomes (single viable pregnancy = 0, missed or complete abortion = 1, ectopic pregnancy = 2) (Table 6). The F value was 154.853, with P<0.0001, indicating great statistical significance. A joint model of Progesterone and LHCG was established to predict viable pregnancy, with 88.8% sensitivity(95%CI 84.52%-92.04%),75.2% specificity(95%CI 67.92%-81.22%), and 83.8% overall accuracy (Table 7).

Table 6. Progesterone variance analysis of the three pregnancy outcomes

	cases	Average value	Standard deviation	Standard error	95% CI	
					Lower limit	Upper limit
Viable pregnancy	277	26.60	10.70	0.64	25.33	27.86
abortion	102	14.41	8.52	0.84	12.74	16.09
Ectopic pregnancy	59	4.90	4.10	0.53	3.83	5.97
Total	438	20.84	12.50	0.60	19.67	22.01

Table 7. Joint prediction of pregnancy outcomes by β-HCG and progesterone

Prediced of pregnancy outcomes	Clinical pregnancy outcomes	
	Abnormal pregnancy	Viable pregnancy
Abnormal pregnancy	121	40
Viable pregnancy	31	246

Discussion

Serum β-HCG contributes to the diagnosis and prediction of pregnancy, and continuous β-HCG measurement can monitor for abortion or ectopic pregnancy. For women with irregular menstrual periods or ovulation changes, the approximate gestational weeks can be calculated based on the initial β-HCG value. For example, according to the fitting curve of the study, if β-HCG is 2500, the possible gestational age is 5 weeks.

However, the increase curve of β-HCG has not been reported consistently. BarnHart [7] reported that the β-HCG of normal intrauterine pregnancy increases by 1.81, 3.28, and 10.76 at 1, 2, and 4 days respectively, with the lowest increases of 24% and 53% at 1 and 2 days. Seeber [8] reported a minimum β-HCG increase in intrauterine pregnancy of 35% over 48 hours. In this study, for viable pregnancies at weeks 4-9, the predicted β-HCG values were 314, 2444, 17623, 54840, 92086, and 104308 mIU/mL, respectively, with weekly multiplications of 6.76, 6.21, 2.11, and 0.68. The β-HCG peaked at 8 weeks and then gradually decreased.

Despite these variations in reporting, β-HCG is still the best index to diagnose pregnancy and predict continuous pregnancy. In an in vitro fertilization-embryo transfer study [5], the prediction accuracy of HCG was better than that of progestin (P=0.015). Monitoring of serum β-HCG [9] on the 15th day after the transfer of a cleavage stage embryo (3 days post in vitro fertilization) showed that when β-HCG was <500 mIU/ml, the rates of biochemical pregnancy, ectopic pregnancy, and missed abortion were all higher than when β-HCG was 501-1000 mIU/mL. The number of viable pregnancies was significantly reduced in the low β-HCG group. An additional study demonstrated that a ratio of HCG 48h/0h <11% was related to early pregnancy loss [10], while a ratio >75% was related to 100% surviving pregnancy.

A slow increase or decrease of β-HCG is related to ectopic pregnancy and abortion. In one study, a slow increase was seen in 80% of ectopic pregnancies and 35% of abortions [11]. There was no significant difference in daily HCG increase between the two groups, with (210±30 mIU/ml) in the ectopic pregnancies and (311±55 mIU/ml) in the abortions. The concentration of HCG decreased in the remaining

cases, with a significantly greater decrease in the abortions than in the ectopic pregnancies (578±28 vs 270±52 mIU/ml daily).

In this study, the logit model with LHCG（LHCG =-22.4981 + 1.5111 adt-0.0222 adt^2 + 0.0001adt^3） as the independent variable to predict viable pregnancy had 85.9% sensitivity, 44.72% specificity, and 70.77% overall accuracy. The predicted value, weekly multiplication, and daily multiplication of β-HCG in different gestational weeks of missed abortion were significantly lower than those of viable pregnancy. The daily β-HCG increases in missed abortion and viable pregnancy at 5-8 weeks were 130% and 97%, 76% and 89%, 14% and 31%, and 1% and 10%, respectively. Due to the low initial β-HCG level, the β-HCG level in the missed abortion group increased by 130% at 5 weeks of pregnancy, but was significantly lower than that in viable pregnancy at 6 weeks, and the β-HCG peak value was also relatively low.

However, the initial β-HCG in viable pregnancy was higher than that in disadvantaged pregnancy. The β-HCG level at 5 weeks in viable pregnancy was 2444mIU/mL, and the increase rate every two days was 178% (89% per day). The accuracy rate of predicting viable pregnancy was 85.9%, because some patients with missed abortion had a very good HCG increase rate, although the embryo stopped developing. The early pregnancy increase rate of the β-HCG regression curve was relatively high in viable pregnancy, compared to that of the missed abortion regression curve, and the ectopic pregnancy regression curve demonstrated a very small growth rate or even a decrease.

The variation in the regression curves for these groups was found to be clinically important. Even with symptoms of threatened abortion such as minor vaginal bleeding, if β-HCG conformed to the weekly multiplication curve of viable pregnancy, the possibility of viable intrauterine pregnancy was high, and the frequency of ultrasonography could be reduced.

The significance of progesterone to early pregnancy outcomes is controversial. Huang [12] studied the progesterone level during pregnancy weeks 4 to 6. The women were divided into high and low (< 25 ng/mL) progesterone groups. There was no statistical difference in pregnancy outcomes between the two groups. However, Huang's study may have used a progesterone threshold that was too high. Maged [13] showed that serum progesterone was significantly lower in the abortion group than in the continuous pregnancy group (8.7±1.85 vs 26.3±7.2 ng/ml, P<0.001). Progesterone <11.5 ng/ml predicted abortion with an overall accuracy of 99.8%. Puget [10] found that the sensitivity, specificity, and positive and negative predictive values of a 6.2 ng/ml progesterone level in diagnosing early pregnancy loss were 20%, 100%, 100%, and 65.2%, respectively. Ver Haegen reported that when the threshold was 10 ng/mL [14], the sensitivity for predicting infeasible pregnancy was 66.5%, and the specificity was 96.3%. If the progesterone level was low, the probability of non-viable pregnancy increased to 99.2%. Mehmet found 75% sensitivity and 78% specificity for identifying abnormal pregnancy when progesterone is <15 ng/mL [15]. The sensitivity and specificity of identifying abortion were 91% and 89%, respectively.

The conclusions of this study are similar: with progesterone ≥10 ng/ml, the sensitivity, specificity, and overall accuracy for predicting viable pregnancy are 90.25%, 72.04%, and 83.6%, respectively. With

progesterone <10 ng/ml, the sensitivity, specificity, and overall accuracy for predicting ectopic pregnancy and complete abortion are 94.2%, 78.86%, and 81.27%, respectively. Progesterone values in viable pregnancy (26.6±10.7ng/ml), missed abortion (14.41±8.52 ng/ml), and ectopic pregnancy (4.9±4.1ng/ml) were significantly different.

Serum β-HCG in normal intrauterine pregnancy doubles after 48 hours [16], and β-HCG in early tubal pregnancy is significantly lower than in normal intrauterine pregnancy. However, 1-2 weeks after uterine implantation of fertilized eggs, serum β-HCG levels in normal intrauterine pregnancy are similar to those in tubal pregnancy, so other biological indicators are needed to identify ectopic pregnancy [5]. In this study, we showed that progesterone can be a specific indicator of ectopic pregnancy, and is especially accurate when combined with the β-HCG increase curve.

Duan reported [6] that the serum progesterone and HCG values in inevitable abortion (13.76±5.52 ng/ml, 3647±2123 mIu/ml) are lower than those in normal intrauterine pregnancy (31.67±5.86 ng/ml, 13437±6256 mIu/ml) ($p<0.001$). Progesterone combined with β-HCG can predict inevitable abortion with a diagnostic accuracy of 85.7%.

The current research shows 88.8% sensitivity and 75.2% specificity of the combined progesterone and LHCG model for predicting viable pregnancy. The overall prediction accuracy of 83.8% was superior to HCG alone.

We conclude that when progesterone is ≥10 ng/ml, the amenorrhea time and gestational age can be estimated according to β-HCG. The weekly multiplications in first trimester viable pregnancy weeks 5-8 were 6.76, 6.21, 2.11, 0.68, and 0.13, respectively. If the weekly multiplication of β-HCG conforms to this rule, and progesterone is ≥10 ng/ml, 88.8% of the cases are viable pregnancies. If the weekly multiplication of β-HCG is lower than this rule and progesterone is <10 ng/ml, the possibility of ectopic pregnancy and missed abortion is extremely high. Timely vaginal ultrasound examination should be performed in combination with progesterone level monitoring for early identification of missed abortion or ectopic pregnancy.

One limitation of this study is that there was no assessment of other indicators that may be related to the prediction of pregnancy outcomes, such as estradiol. In future work, a triage model for early pregnancy diagnosis will be developed based on the current research results to minimize the risk to early pregnancy.

Conclusions

The innovative weekly combined examination of βHCG and progesterone in this study summarized the patterns of early β-HCG weekly multiplications, predicted values, and progesterone levels in different pregnancy outcomes. The sensitivity of the three methods (HCG, Progesterone, and their combination) were similar in predicting viable pregnancy, but the specificity of HCG alone was low, and the accuracy rate for predicting non-viable pregnancy was 44.72%. Therefore, monitoring of progesterone or HCG + Progesterone was superior to HCG alone.

Abbreviations

adt: adjust amenorrhea time

βHCG: beta human chorionic gonadotropin

LHCG: logarithm of HCG

P: progesterone

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Medical Ethics Committee of Maternal and Child Health Hospital of Hubei affiliated with Huazhong University of Science and Technology, and written informed consent was obtained from each participant.

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy concerns, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Not applicable.

Authors' contributions

YY was responsible for the design, writing and data collection of the paper. WW was responsible for recollecting and sorting out the data, while YMH was responsible for statistical analysis and the revision of the article.JD and XD were responsible for collecting data and revising articles.YW is responsible for guiding the implementation of the project. All authors read and approved the final manuscript.

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Figures

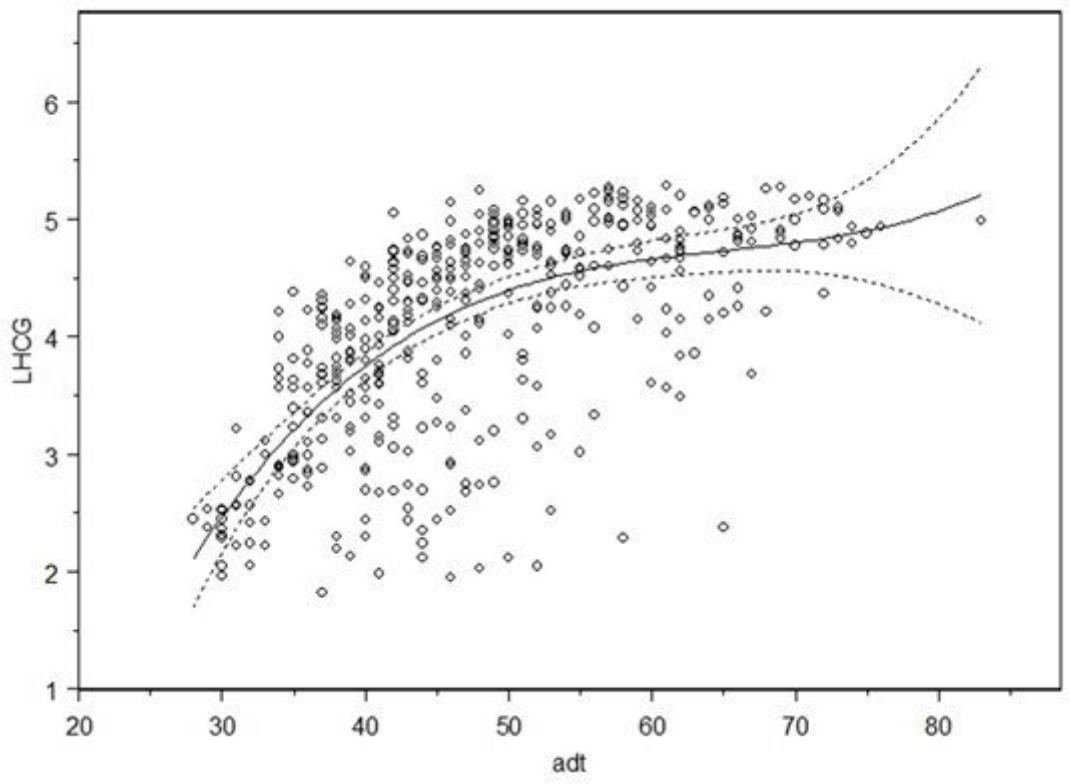

Figure 1

Regression model of LHCG and amenorrhea time. Curve-fitting equation: LHCG=-17.6965+1.2604adt–0.0189adt2+0.0001adt3,R2 = 0.4431

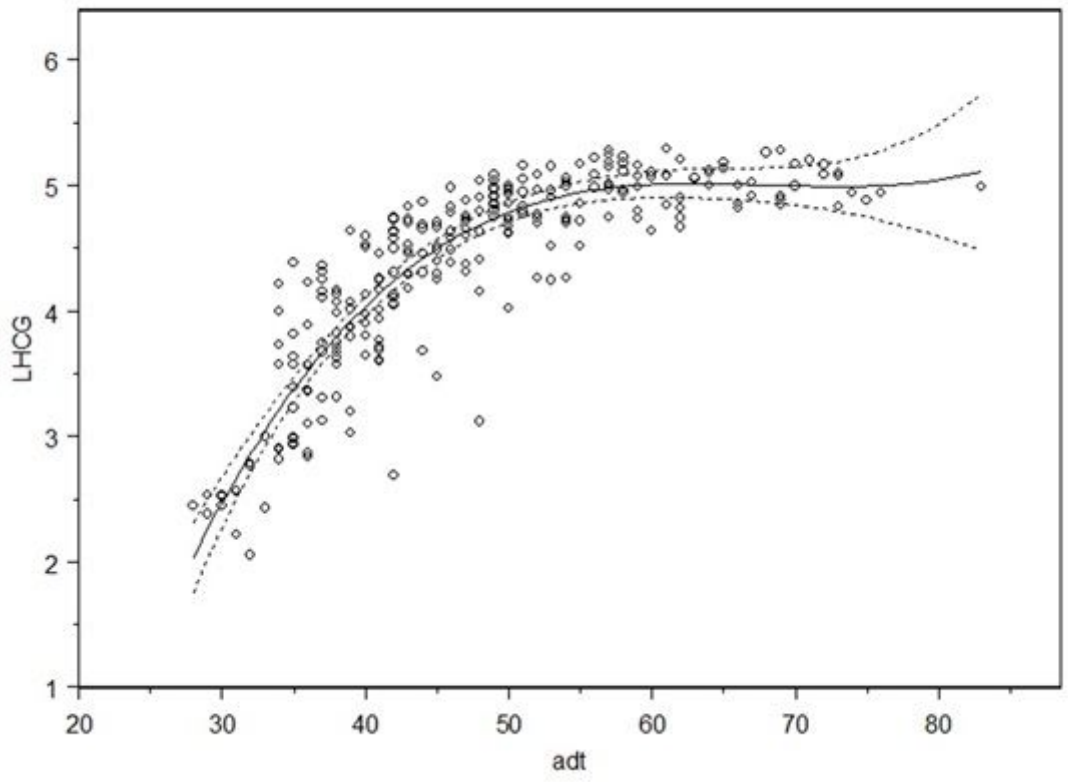

Figure 2

Regression model diagram of LHCG and amenorrhea time of viable pregnancy. Curve-fitting equation: LHCG =-22.4981+1.5111 adt-0.0222adt2+0.0001adt3 ,R2 = 0.7927.The solid line in the figure is a fitting curve, and the dashed lines on both sides are confidence intervals with a 95% confidence level.

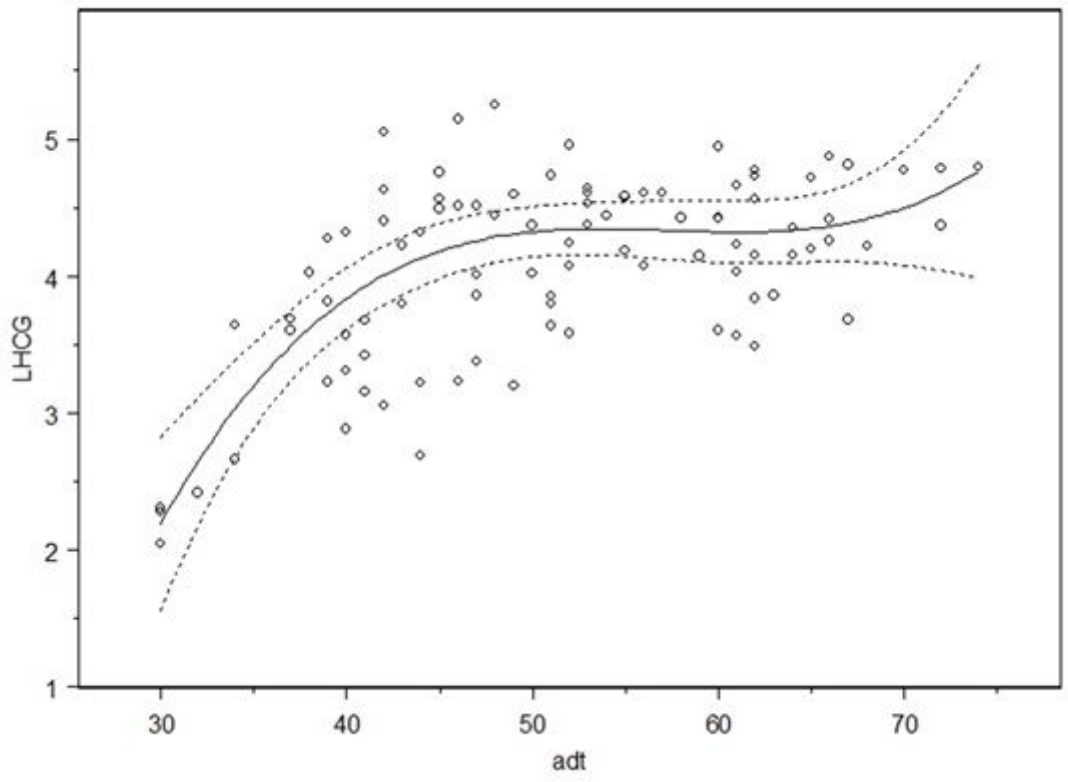

Figure 3

Regression model diagram of LHCG and amenorrhea time for missed abortion. LHCG =-37.3783 + 2.4976adt-0.0437adt2 + 0.0003adt3. R2 = 0.449

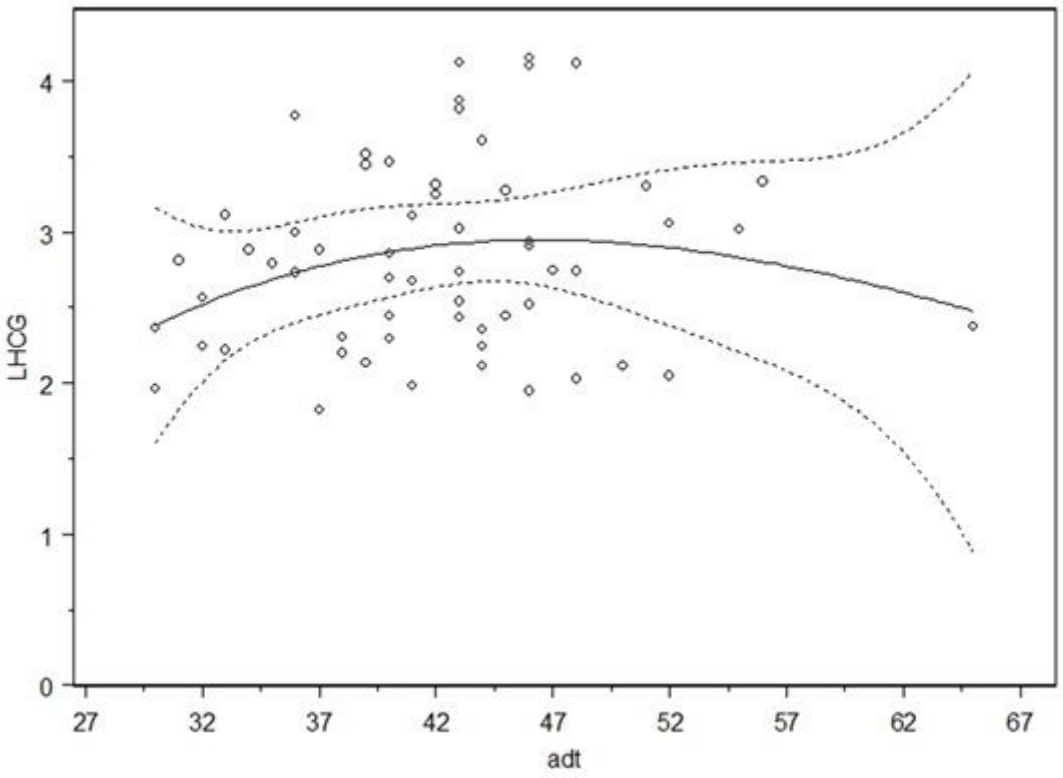

Figure 4

Regression model diagram of LHCG and amenorrhea time for ectopic pregnancy