

# Serum Progesterone and Serial Beta-hcG Levels in Predicting the Outcome of Early Pregnancies With Doubtful Viability: A Prospective Observational Research

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## Research Article

**Keywords:** Early pregnancy loss, viability, serial  $\beta$ -hCG, progesterone

**Posted Date:** September 16th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-842511/v1>

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# Abstract

**BACKGROUND:** To evaluate the doubling rate of maternal serum serial  $\beta$ -hCG and a single initial serum progesterone level to predict fetal viability before ultrasonography in women diagnosed with intrauterine pregnancy of undetectable viability.

**METHODS:** 336 pregnant women who applied to the outpatient clinic at Istanbul Okmeydanı City Hospital between March and December 2018 were evaluated on a "Prospective observational" basis. 236 women were excluded from the study for various reasons. The study was completed with 100 pregnant women diagnosed with intrauterine pregnancy (IUP) involving suspected fetal viability by transvaginal ultrasonography only, who met the inclusion criteria with CRL: < 7mm and mean gestational sac diameter: < 25mm. Serum  $\beta$ -hCG and progesterone were taken at the first admission. After 48 hours, control serum  $\beta$ -hCG was taken and the increase rates were calculated. Early pregnancy loss was diagnosed by (transvaginal) TV-USG performed after the days 7, 11 and 14. Patients were divided into two groups as fetal heart rate (FHR) positive (viable) and FHR negative (early pregnancy loss). Pregnancy results were compared with  $\beta$ -hCG increase rates and progesterone value. SPSS 22.0 software was used for statistical analysis and  $P < 0.05$  was accepted as statistically significant.

**RESULTS:** No statistically significant result was obtained between the viable and early pregnancy loss (FHR +/-) groups in terms of maternal age, previous pregnancy anamnesis, nationality, presenting symptoms, or ultrasound findings. According to the last menstrual period, the mean gestational age was  $45.1 \pm 14$  days in the viable (FHR+) group and  $51.3 \pm 14$  days in the Early pregnancy loss (FHR-) group, and this difference was found to be statistically significant. Estimation modality was developed in terms of viability with the serum progesterone values and increase rates of  $\beta$ -hCG. The study, which was conducted with a confidence interval of 95%, found the viability rate to be 70% with a  $\beta$ -hCG increase rate of 31%, 80% in the case of an increase by 49%, 90% in the case of an increase by 73%, 95% in the case of an increase by 97%, and 100% in the case of an increase by 181%. For progesterone, when the value was 5.9 ng/ml, the viability rate was 49%, and it was 69% at 10.5 ng/ml, 80% at 13.4 ng/ml, 90% at 18.0 ng/ml, 95% at 21.7 ng/ml, 99% at 29.3 ng/ml, and 100% at 37.5 ng/ml and above. In conclusion, the significant efficacy values of  $\beta$ -hCG increase and first progesterone level in predicting viability were found to be ROC AUC: [0.748 (0.621-0.874)] and ROC AUC: [0.796 (0.685-0.907)], respectively.

**CONCLUSION:** Either Serial  $\beta$ -hCG ratio or serum progesterone level can be used alone to predict pregnancy outcome in early pregnancy. With dissemination of similar studies, estimation modalities can be improved and TV-USG examinations can help shortening the waiting time for results to reduce anxiety of families, hospital admissions and health expenses.

## Introduction:

Early pregnancy loss is a frequently encountered problem in the reproductive period, which is the longest period of female life, and it is reported as the most common complication of pregnancy. It occurs in

about 10–15% of all clinically recognized pregnancies and affects one in every three women (1). Approximately 80% of all pregnancy loss cases occur in the first quarter (2).

Bleeding and pain are the most common reasons why women receive medical advice during their early pregnancy. This is an important cause of anxiety for women. Detection of intrauterine pregnancy (IUP) by Transvaginal Ultrasonography (TV-USG) following a positive  $\beta$ -hCG excludes ectopic pregnancy except heterotopic pregnancy, but especially during the follow-up of Pregnancy of Unknown Locations (PUL), pregnancy viability cannot be determined at the first visit when IUP is detected (3). When an IUP is detected, the second most important step is to determine viability. These one- or two-week follow-up visits may cause long-term anxiety for women, and these visits increase the cost and workload in the related healthcare facilities (4).

Serial measurements of serum hCG, the increase percentages, and serum progesterone measurement used for the same purpose as serum hCG in early pregnancies are highly important in differentiation of normal and abnormal pregnancies as well as in prediction of fetal viability. However, both involve significant differences in the literature (5). No cut-off value or predictive power of any of these markers could be determined for the definitive diagnosis of viability in IUPs.

The aim of this study is to compare maternal serum series  $\beta$ -hCG and a single serum Progesterone level with TV-USG for predicting fetal viability in women with intrauterine pregnancy and create a prediction modality using only serum markers.

## **Materials And Methods:**

Our study was carried out in the Obstetrics and Gynecology Clinic of Istanbul Okmeydani City Hospital on a single-center “Prospective observational” basis between March 2018 and December 2018. The study was commenced after obtaining the approval of the Ethics Committee for Clinical Research of Istanbul Okmeydani City Hospital under the protocol number 841 on 13/03/2018. The participants were informed verbally and in writing, and their written consents were obtained.

As a result of the Power analysis performed using the G\*Power software, taking the effect size for hCG ‘H48’ and Progesterone ‘P’ parameters as 0.1806 and SD: 17538, the minimum number of samples determined for Power:0.80 and  $\alpha$ :0.05 was determined as n:100 for each group. Inclusion criteria were defined as consent for participating in the study, being older than 18 years of age, diagnosis of intrauterine pregnancy by TV-USG, and early pregnancy with no fetal heartbeat detected / suspected (CRL < 7 mm, GS < 25 mm). Our study includes 336 pregnant women who applied to our outpatient clinic and accepted to participate in the study. 156 pregnant women who did not meet at least one of the inclusion criteria, and 28 pregnant women did not want to continue in the study, despite they initially agreed to participate in it, and 20 pregnant women having other reasons were excluded from the study. During the follow-ups, 32 pregnant women could not be reached and they were also excluded from the study. So, the study was completed with 100 pregnant women (Table-1). All women were evaluated by experienced obstetricians using ultrasound devices equipped with 6–12 MHz transvaginal transducer

and B-mode imaging. Pregnancy of Uncertain Viability (PUV) criteria in patients with intrauterine pregnancy confirmed by TV-USG were taken as no heart rate below CRL < 7 mm, and no embryo below GS < 25 mm (mean of three orthogonal measurements: mGSD). Anamnesis information such as maternal age, previous pregnancy anamnesis, nationality, admission symptoms, and ultrasound findings of the patients were noted at the first admission. Viability determination was performed by TV-USG on the days 7, 11, and 14, respectively. Pregnant women with fetal heartbeat detected, or diagnosed with fetal viability (Viable: FHR: +) were not invited to further controls. Pregnant women with undetectable fetal heart rate were held until the day 14 at the latest, and if no fetal heart rate could be detected still, they were diagnosed with “Early pregnancy loss” (Non-viable: FHR: -).

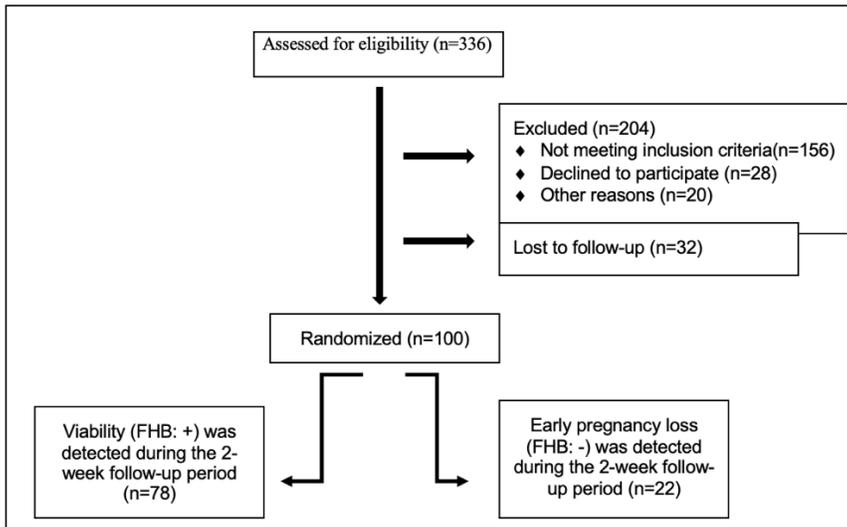
Serum  $\beta$ -hCG and progesterone were taken at the first admission. After 48 hours, control serum  $\beta$ -hCG was taken and the increase rates were calculated. Serum plasmic hCG and progesterone levels were measured with Roche hCG and Progesterone II Electrochemiluminescence Immunassay (ECLIA) in Roche Cobas e411 and e602 analyzers, respectively.

As a result, patients were divided into two groups as fetal heart rate positive group (FHR: +) and early pregnancy loss group (FHR: -). These results were interpreted with the percentage of serum  $\beta$ -hCG increase and Progesterone value at initial admission in the light of the literature. These two parameters were evaluated by means of Mann-Whitney u test and Wilcoxon test. However, z-scores and percentiles adjusted according to gestational week were used to calculate both  $\beta$ -hCG and serum progesterone levels. Thus, it was considered that the first progesterone level was not constant and  $\beta$ -hCG levels would decrease over time. Receiver Operating Characteristic (ROC) curve was used for the estimations, effect level and cutoff values of numerical parameters. SPSS 22.0 (Chicago, IL, USA) was used for statistical analysis.

## Results:

Our study includes 336 pregnant women who applied to our outpatient clinic and accepted to participate in the study. 156 pregnant women who did not meet at least one of the inclusion criteria, and 28 pregnant women did not want to continue in the study, despite they initially agreed to participate in it, and 20 pregnant women having other reasons were excluded from the study. During the follow-ups, 32 pregnant women could not be reached and they were also excluded from the study. So, the study was completed with 100 pregnant women (Table-1).

### Table-1: Consort Diagram



The Table-2 shows the age, pregnancy history, LMP (Last menstrual period), nationality, presenting symptom, previous mode of pregnancy, viability,  $\beta$ -hCG values (control at first admission and at hour 48) and percentage of increase, serum progesterone value at first admission, TV-USG findings and measurements of the patients participating in the study.

**Table-2:** Anamnesis, Ultrasound and Laboratory findings of the patients participating in the study

**All Cases**

	Min-Max	Median	Mean $\pm$ S.d./n-%
Age	18,0 - 42,0	29,0	28,8 $\pm$ 5,7
Gravida	1,0 - 8,0	2,0	2,6 $\pm$ 1,3
Parity	0,0 - 3,0	1,0	1,0 $\pm$ 0,9
Abortion	0,0 - 5,0	0,0	0,5 $\pm$ 0,8
Curettage	0,0 - 2,0	0,0	0,1 $\pm$ 0,3
Ektopic Pregnancy (-)			98 98,0%
(+)			2 2,0%
Last Menstrual Period ( Day )	21,0 - 116,0	44,0	46,4 $\pm$ 14,1
Nationality Turkish			97 97,0%
Foreign			3 3,0%
<b>Symptom</b>			
No			43 43,0%
Mens. delay / Pregnancy suspicon			19 19,0%
Bleeding / Spotting			21 21,0%
Waist / Groin pain			15 15,0%
Others			2 2,0%
Previously Pregnancy Nulliparous			32 32,0%
Vag. Delivery			34 34,0%
Cesarean Sect.			31 31,0%
Vag. Del. + C/S			3 3,0%
Viability Early Pregnancy Loss (FHB: -)			22 22,0%
Detected Viability (FHB: +)			78 78,0%
<b>BHCG (All cases)</b>			
First Examination	302 - 200727	18430	25880 $\pm$ 30951
Control	848 - 235654	28817	35962 $\pm$ 38268
Percentage Increase (%)	0,8 - 181,3	52,5	54,3 $\pm$ 36,2
<b>In-Group Change (p)</b>			
Progesteron	3,3 - 50,0	13,7	15,5 $\pm$ 8,3
USG mGSD (No CRL)			81 81,0%
CRL detected			19 19,0%

The mean age of all patients was 28.8±5.7, the mean number of Gravida was 2.6±1.3 and the mean Parity was 1.0±0.9. The most common presenting symptom was "Bleeding/Maculation" with 21% (n:21). 32% (n:32) of the women were nulliparous and 68% (n:68) were multiparous. The mean increase in beta HCG was 54.3±36.2% and the mean Progesterone value at first admission was 15.5±8.3. Fetal heart rate was positive (viability +) in 78% of women (n:78) and negative (early pregnancy loss) in 22% (n:22).

Table-3: Comparison of demographic characteristics and symptoms of patients with fetal heart rate positive (Viable) or negative (Early pregnancy loss)

	Early Pregnancy Loss (FHB: -)		Detected Viability (FHB: +)		P
	Mean ± S.d./n-%	Median	Mean ± S.d./n-%	Median	
Age	29,7 ± 5,0	30,0	28,5 ± 6,0	28,0	0,408 <sup>t</sup>
Gravida	3,1 ± 1,7	3,0	2,4 ± 1,2	2,0	0,144 <sup>m</sup>
Parity	1,2 ± 1,1	1,0	1,0 ± 0,9	1,0	0,610 <sup>m</sup>
Abortion	0,8 ± 1,0	0,0	0,4 ± 0,7	0,0	0,079 <sup>m</sup>
Curettage	0,1 ± 0,4	0,0	0,1 ± 0,3	0,0	0,864 <sup>m</sup>
Last Menstrual Period ( Day )	51,3 ± 14,0	49,0	45,1 ± 14,0	44,0	<b>0,040</b> <sup>m</sup>
Nationality	Turkish	21 95,5%	76 97,4%		0,530 <sup>x²</sup>
	Foreign	1 4,5%	2 2,6%		
<b>Symptom</b>					
No	10 45,5%		33 42,3%		0,984 <sup>x²</sup>
Mens. delay / Pregnancy	2 9,1%		17 21,8%		
Bleeding / Spotting	7 31,8%		14 17,9%		
Waist / Groin pain	3 13,6%		12 15,4%		
Others	0 0,0%		2 2,6%		

<sup>t</sup> t test / <sup>m</sup> Mann-whitney u test / <sup>x²</sup> Ki-kare test (Fischer test)

No significant statistical results were obtained in the comparison of maternal age, gravida number, parity number, nationality and presenting symptoms between the fetal heartbeat negative and positive groups. The difference between the gestational ages was found to be statistically significant only between the two groups according to their last menstrual periods (P: 0.040).

Table 4 : Comparison of serial β-hCG and percentage of increase between FHR +/- (Viable / Non-viable: Early pregnancy loss) groups

	Early Pregnancy Loss (FHB: -)	Detected Viability (FHB: +)	p
	Mean ± S.d.	Mean ± S.d.	
<b>BHCG</b>			
First Examination	16874 ± 16029	28420 ± 33644	0,090 <sup>m</sup>
Control	20031 ± 16602	40455 ± 41409	<b>0,012</b> <sup>m</sup>
Percentage increase (%)	32,5 ± 32,7	60,4 ± 34,9	<b>0,000</b> <sup>m</sup>
In-Group Change (p)	<b>0,000</b> <sup>w</sup>	<b>0,000</b> <sup>w</sup>	

<sup>m</sup> Mann-whitney u test / <sup>w</sup> Wilcoxon test

Between the fetal heartbeat positive and negative groups, the serum β-hCG value at first admission did show no statistically significant difference (P>0.05). The control β-hCG values obtained after 48 hours in both groups showed a significant increase (P<0.05) compared to the first admission. In the group with

fetal heartbeat positive, the increase rate between the two  $\beta$ -hCG values taken at 48 hour intervals was found to be significantly higher than the group without fetal heartbeat ( $P \leq 0.05$ ).

The Figure-1 shows the predictive power graph of serum  $\beta$ -hCG increase rates taken at 48 hour intervals in the likelihood of fetal heartbeat. According to the chart, the probability of fetal heartbeat was 70% while the rate of increase in  $\beta$ -hCG value was 31%, and the probability of fetal heartbeat was 80%, 90%, 95% and 100% while the rate of increase in  $\beta$ -hCG value was 49%, 73%, 97%, and 181%, respectively. Significant efficacy ( $p=0.000$ ) [0.748 (0.621-0.874)] of  $\beta$ -hCG increase was observed in predicting the groups with and without fetal heartbeat (Figure-2: ROC curve).

Table 5 : Comparison of serum Progesterone values between FHR +/- groups

	Early Pregnancy Loss (FHB: -)	Detected Viability (FHB: +)	p
	Mean $\pm$ S.d.	Mean $\pm$ S.d.	
Progesteron	9,9 $\pm$ 6,5	17,1 $\pm$ 8,1	<b>0,000</b> <sup>m</sup>

<sup>m</sup> Mann-whitney u test /

When the initial serum progesterone values of the groups with and without fetal heartbeat were compared, a statistically significant difference was found between the groups ( $P:0.000$ ). It was significantly higher in the FHR positive group compared to the negative group ( $P \leq 0.05$ ). (Table-5). Significant efficacy ( $p=0.000$ ) [0.796 (0.685-0.907)] of the progesterone value was observed in predicting the group with and without fetal heart beat. (Figure-3: ROC curve)

When the serum progesterone value was 5.9 ng/ml, the fetal heart rate was 49%, and when the serum progesterone value was 10.5 ng/ml or above, the fetal heart rate was 69%, 12 ng/ml and above 75%, 13.4 ng/ml and above 80%, 18.0 ng/ml and above 90%, 21.7 ng/ml and above 95%, 29.3 ng/ml and above 99% and 37.5 ng/ml and above 100%.

Table 6 : Comparison of TV-USG findings and measurements in FHR +/- groups

	Early Pregnancy Loss (FHB: -)		Detected Viability (FHB: +)		p
	Mean $\pm$ S.d./n-%	Median	Mean $\pm$ S.d./n-%	Median	
Only mGSD	19	86.4%	62	79.5%	0,468 <sup>x2</sup>
Ultrasonography detected (No CRL)					
CRL detected	3	13.6%	16	20.5%	
<b>USG measurement (mm)</b>					
mGSD	10,8 $\pm$ 4,7	10,0	11,8 $\pm$ 4,9	12,0	0,419 <sup>m</sup>
CRL	3,7 $\pm$ 2,1	3,2	3,4 $\pm$ 1,2	3,3	0,955 <sup>m</sup>

<sup>m</sup> Mann-whitney u test / <sup>x2</sup> Ki-kare test

There was no statistically significant difference in ultrasound findings between the two groups.

## Discussion:

Transvaginal ultrasonography has always been a classical method to predict pregnancy outcomes in cases where viability is suspected in patients with early pregnancy, but many publications have recently studied  $\beta$ -hCG and progesterone values, which are serum biochemistry markers. Using these parameters, 336 pregnant women were followed up in our study, in which we investigated whether they were related to the determination of early pregnancy outcome. The results of our study, which was completed with 100 pregnant women, were compared with the literature.

Advanced maternal age is known to be associated with the risk of fetal anomalies, early pregnancy loss and increased abortion rates (6, 7). Some studies show that maternal age is an important parameter for predicting fetal viability (2). Our findings regarding maternal age are not consistent with the literature. Although the mean maternal age was higher in the group diagnosed with early pregnancy loss compared to the group with fetal viability, this difference was not found to be statistically significant. The reason for this was that the mean age was close to each other and the mean age of the group with early pregnancy loss failed to meet the advanced maternal age criterion (> 35 years) mentioned in the literature.

As far as we know, this study is the first to include the evaluation of gravida and parity numbers in prediction of early pregnancy. The literature includes only a comparison of abortion rates and it is known that repeated abortions increase the risk of early pregnancy loss (6, 7). In the previous pregnancy anamnesis, no statistically significant results were obtained when the numbers of gravida, parity and optional curettages were evaluated according to the results of early pregnancy. Although the number of abortus had a 2 times more average in the group without heartbeat compared to the group with heartbeat, the difference between these two groups was not found to be statistically significant contrary to the literature. Although no significant results were obtained, we contributed to the literature by evaluating the previous pregnancy anamnesis in early pregnancy loss, except for the history of abortus.

In the literature, the probability of intrauterine cystic structure belonging to the gestational sac is 99.5% and the probability of false sac is 0.5% (8). In ectopic pregnancies, the rate of false sac was reported to be 10% (9, 10). In our study, 2 out of 100 patients were diagnosed with ectopic pregnancy. Considering that 81% of 100 patients had a gestational sac, the rate of false sac in patients with an observed gestational sac was 2.46%. This is highly above the 0.5% rate stated in the literature. Considering that only 10% of ectopic pregnancies have a false sac, it is interesting that such a high rate was found only in a study on intrauterine pregnancies. This led us to conclude that clinicians should be more careful in ultrasonography examination and understand the distinction between double decidual ring appearance and actual gestational sac.

This study includes a race question in a society against racism since it is thought that abort rates may be high due to the high number of Syrian asylum seekers in our country, poor living conditions and war stress. Although high rates of early pregnancy loss have been reported in African-Americans compared to other populations in the literature (6, 7), no literature data was found on races and or studies conducted in the Middle East. No statistically significant results were obtained in the comparison between

nationalities. The limited number of foreign patients participating in the study was considered as the reason for this.

Oh et al. (11) found that mGSD measured in pregnancies < 37 days and below according to LMP had no predictive value for fetal outcome later in pregnancy. In another study, it was emphasized that there was no predictive value of gestational age before 37 days according to LMP, and a definitely unsuccessful pregnancy was given as any pregnancy with no observed gestational sac on the day 46 (12). Fritz et al. (13) found that gestational age and hCG doubling time were correlated and therefore, gestational age was prognostic for fetal outcome. Napolitano et al. (14) stated that 30% of women had an uncertain or unreliable menstrual date and therefore the gestational age could not be determined correctly. In our study, a statistically significant efficacy of gestational age was observed between the groups with and without fetal heartbeat according to the last menstrual period. This was found to be consistent with the general literature (11, 13). However, the information that the predictive value of gestational age was not significant before 37 days in the literature contradicted the occurrence of a heartbeat in all 7 women (100%) diagnosed with pregnancy before 35 days in our study. Again, the information that the pregnancies detected after the day 46 mentioned in the literature were unsuccessful contradicted with the incidence of fetal heartbeat in 18 (60%) of the 30 women diagnosed with pregnancy after the 46th day. However, the fact that 15% of the patients did not know their last menstrual periods and 11% were incorrect makes this result contradictory, and Napolitano et al. confirmed the argument that the last menstrual periods of 30% of the women was unreliable and concluded that the gestational age should be determined ultrasonographically or biochemically by experienced physicians.

Early pregnancy loss is known to be common in patients with symptoms (1, 6). Although our study includes patients with a higher rate of symptoms in the group without fetal heartbeat (in the FHR negative group: 31.8% - positive group: 17.4%), this information was not found to be statistically significant. This was found to be inconsistent with the literature. The reason for this was construed as the fact that the study was conducted in a small population.

In the initial and 48-hour follow-up serum  $\beta$ -hCG controls, a statistically significant difference was found between the fetal heart rate positive group and the negative group. Claire et al. (1) found that serum  $\beta$ -hCG predicts viability with 100% sensitivity and 31% specificity when the doubling rate is 75% or more. Barnhart et al. (5) found the rate of determination of viability as 124% increase in 2 days. Bignardi et al. (12) found that the rate of determining viability with  $\beta$ -hCG doubled was 78% sensitive and 67% specific. As the main purpose of our study, the fact that hCG doubling rate provides prediction of viability is also consistent with many recent studies although the rates are different. What makes our study different is that the prediction of viability is mentioned by giving only certain ratios in the literature (1, 15), while in our study, a percentage is assigned to each patient in terms of viability at each increase rate of  $\beta$ -hCG (Figure-1). With this information, we believe that a clear rate will be provided to the patients during early pregnancy and that both the anxiety of the patients due to uncertainty will be reduced and their own anxiety will be reduced by physicians providing clear information and ratio to the patients. In addition to creating an early pregnancy prediction modality, our study examined the increase rates of  $\beta$ -hCG in the

ROC curve and determined high sensitivity cut-off values and confirmed that the  $\beta$ -hCG increase rate in recent literature could be used to predict early pregnancy outcomes. In our study, live pregnancy was achieved even with a low rate of  $\beta$ -hCG increase of 31%. Therefore, physicians should not diagnose pregnancy loss early, and early interventions should be avoided. The cut-off value determined in the 95% confidence interval was achieved with a minimum 97% increase in hCG at the hour 48. A 100% heart rate positivity was achieved with an increase of 181%.

Claire et al. (1) found 100% pregnancy failure where the progesterone value was 6.2 ng/ml or less. In a recent French guideline, an abnormal IUP or ectopic pregnancy was found to be associated with an initial serum progesterone value of 3.2 ng/ml or less (3). In our study, a significant statistical result was obtained when the initial progesterone values of the fetal heartbeat and non-fetal heartbeat groups were compared. This was found to be consistent with the general literature (1, 3). What makes our study different is that while the prediction of viability is mentioned in the literature only by giving certain ratios (12, 16), in our study, a percentage can be assigned to patients in terms of viability at each value of the initial serum progesterone (Figure-4). This information makes it possible to give a clear rate to the patients during early pregnancy, and reducing the anxiety of families caused by waiting for weeks. Furthermore, our study examined initial serum progesterone on the ROC curve and determined high sensitivity cut-off values and confirmed that serum progesterone in the literature could be used to predict early pregnancy outcomes. A successful pregnancy was achieved even at an initial progesterone value of 3.71 ng/ml. Therefore, the physicians are recommended to avoid early interventions. Besides, the cut-off value determined in the 95% confidence interval was provided at 21.7 ng/ml and above. A 100% heart rate positivity was achieved with values of 37.5 ng/ml and above. The reason why we found slightly higher cut-off values compared to the general literature is the low number of patients, which is also the limitation of our study .

The 22% early pregnancy loss rate obtained as a result of our study is higher than the EEC rate of 10–15% in the literature, but also lower than the EEC rate of 31% after implantation (1, 6, 7). Although our population was a heterogeneous group of healthy and symptomatic patients, the presence of symptomatic patients at a higher rate than the rate in the community was considered as the likely reason for the higher rate of our EEC rates than the literature statistics. The reason why our EEC rate was lower than the EEC rate observed after implantation was considered as the fact that patients with EEC were not evaluated without creating an intrauterine finding due to the inclusion of IUPs only with TV-USG in our population. Although the incidence of embryos was higher in the FHR positive group compared to the negative group, the incidence of gestational sacs or embryos between the FHR +/- groups was not statistically significant. This result is inconsistent with the literature because the literature states that the presence of embryos is more valuable than other ultrasound findings (yolk sac, GS) and it is among the good prognostic factors (2, 3). Pexster et al. (17) found variations up to 20% between the operators in CRL and mGSD measurement accuracy. It is possible to see many variations and cut-off values in the literature for diagnosis and definitions (18). Although our population is not as heterogeneous as the community and we do not study inter-operator variations, we think that ultrasound is a subjective

diagnostic tool. This is perhaps another reason why our ultrasound findings were not statistically significant in predicting early pregnancy outcomes.

## Conclusion:

In our study, the doubling ratio of serum hCG and the initial single value of serum progesterone were found to be highly significant in predicting early pregnancy outcomes in accordance with the literature. The difference of our study from the literature is that the patients are not given only a cut-off but a percentage in terms of viability at every increase rate of  $\beta$ -hCG and every value of serum progesterone. This prediction modality made a significant contribution to the literature. The probability of FHR was 70% while the  $\beta$ -hCG increase rate was 31%, and the probability of FHR was 80%, 90%, 95% and 100% while the  $\beta$ -hCG increase rate value was 49%, 73%, 97%, and 181%, respectively. When the progesterone value was 5.9 ng/ml, the probability of FHR was 49%, and 69% at 10.5 ng/ml, 80% at 13.4 ng/ml, 90% at 18.0 ng/ml, 95% at 21.7 ng/ml, 99% at 29.3 ng/ml, and 100% at 37.5 ng/ml and above. This information confirms that the doubling rate of serum  $\beta$ -hCG at the hour 48 and serum progesterone can be used to predict early pregnancy outcomes, and an estimation modality was created.

This study did not evaluate female anxiety or female satisfaction. However, there are observational findings that it provides psychological benefits. The limitation of our study was the small number of patients. Another limitation was that due to patients' previous pregnancy experiences and socio-demographic factors, patients who we predicted would be negative for FHR but could not demonstrate this ultrasonographically acknowledge this. In this study, prediction scores for early pregnancy outcomes incorporating clinical signs, biological markers, or ultrasound findings in early pregnancy outcomes were developed, but a few studies are not sufficient to set aside TV-USG. Furthermore, the superiority of serum  $\beta$ -hCG and serum progesterone levels to each other was not evaluated in our study. By disseminating similar studies on this subject and increasing patient participation, early pregnancy outcomes can be determined earlier and clearer rates can be found. Besides, TV-USG is an expensive examination tool for western countries, even if not for our country. Reducing subjectivity due to operators such as ultrasound and obtaining early results with diagnostic tools that do not require human interpretation can help reducing legal problems, families' anxiety, hospital admissions as well as health costs.

## Abbreviations

IUP : intrauterine pregnancy

CRL : Crown-rump Length

TV-USG : Transvaginal Ultrasonography

FHR : Fetal heart rate

FHR+ positive : Viable

FHR- negative : Non-viable, early pregnancy loss

PUL : Pregnancy of Unknown Locations

PUV : Pregnancy of Uncertain Viability

mGSD : mean of three orthogonal measurements Gestastional Sac Diameter

ROC : Receiver Operating Characteristic

LMP : Last menstrual period

## **Declarations**

### **Ethics approval and consent to participate**

Our study was carried out in the Obstetrics and Gynecology Clinic of Istanbul Okmeydani City Hospital on a single-center "Prospective observational" basis between March 2018 and December 2018. The study was commenced after obtaining the approval of the Ethics Committee for Clinical Research of Istanbul Okmeydani City Hospital under the protocol number 841 on 13/03/2018. The participants were informed verbally and in writing, and their written consents were obtained. The original of the document is available in the hospital archive. All methods were carried out in accordance with relevant guidelines and regulations.

### **Consent for publication**

We obtained approval from the Istanbul Okmeydani Prof.Dr. Cemil Tasci City Hospital Ethics Committee for the study. In accordance with the "Patient Rights Regulation" (Date: 01.08.1998; Issue: 23420), which was prepared in accordance with international standards, verbal and wet signed written consent was obtained from the patient under the title of "Consent to publish" in order to publish patient information and support public health. A wer signed copy of the document is attached.

### **Availability of data and material**

For this Research according to the "Patient Rights Regulation" 01.08.1998 dated and numbered 23420, patient information is allowed to be published with the permission of the patient. Ethics committee approval was obtained and documents regarding permission to publish were obtained from the patients and kept in the archive of Prof Dr Cemil Tascioglu City Hospital. Patient data and materials used in this research study are available in our hospital's electronic data warehouse and archive. The following links are available.

<https://cemiltascioglush.saglik.gov.tr/>

<https://cemiltascioglush.istanbulsaglik.gov.tr/hastaportal/#/?p=results>

## Competing interests

We declare that there is no conflict of interest between the authors. All authors are in agreement with the design, progress, evaluation and results of the study. Statement of Authorship form and Approval of The Responsible Authors form is attached.

## Funding

No resources or grants contributed to the completion of this study. The document is attached.

## Authors' contributions

From the authors; MY (*Corresponding author*), contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, and finally final approval of the version to be submitted. ENC; contributed by acquisition of data, analysis and interpretation of data. GD and OS helped us to the conception and design of the study. YO; contributed to the preparation and translation of the article. VM provided the final approval of the version to be presented. All authors have read and approved the manuscript. Approval of The Authors form is attached.

## Acknowledgements

No resources or grants contributed to the completion of this study.

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## Figures

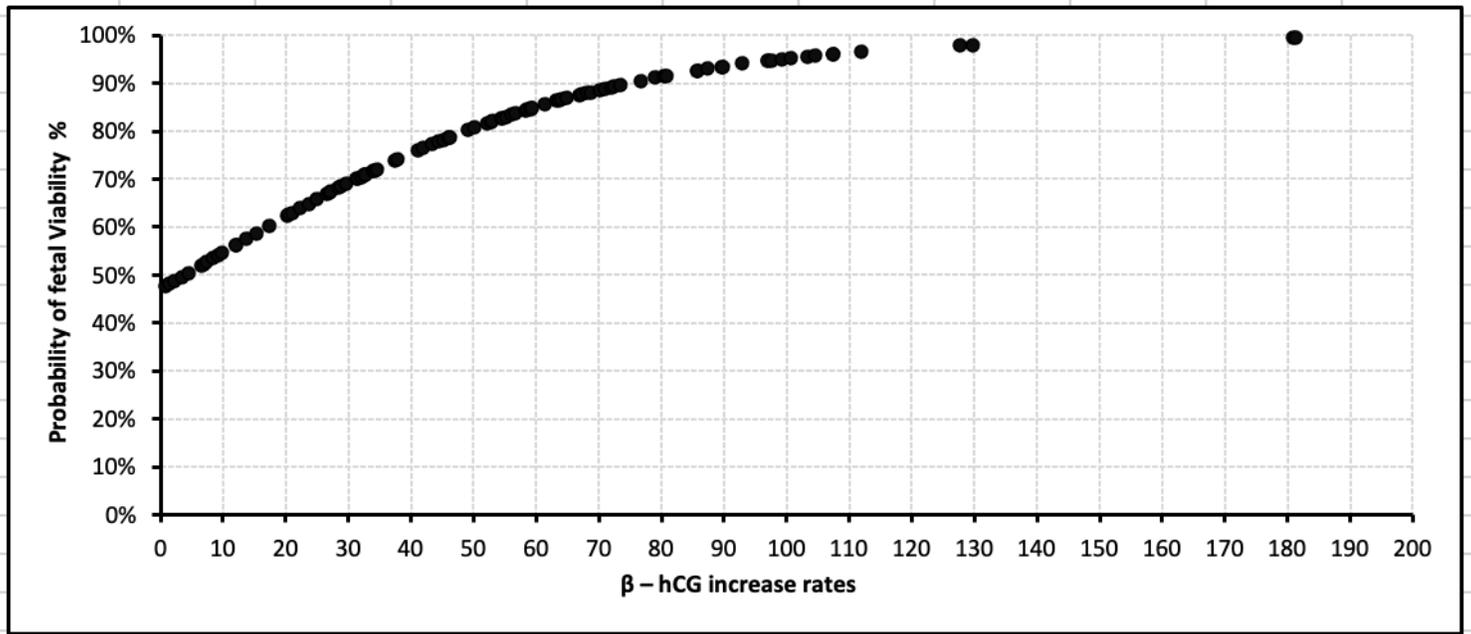


Figure 1

Chart of the likelihood of fetal heartbeat with serum  $\beta$ -hCG increase rates

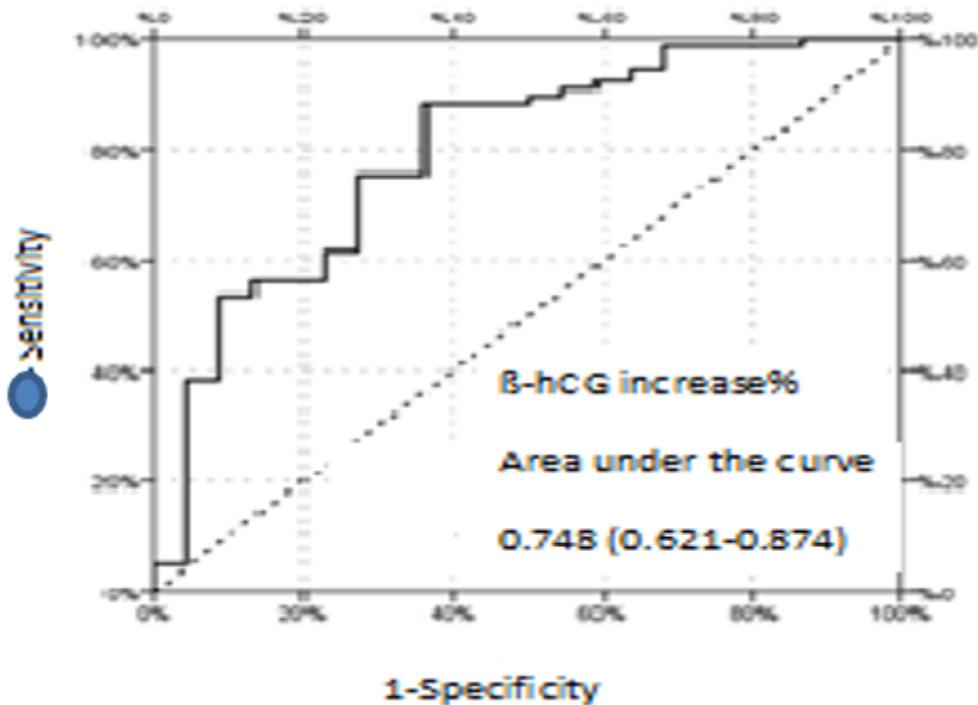


Figure 2

ROC analysis of  $\beta$ -hCG increase percentage in FHR +/- group prediction

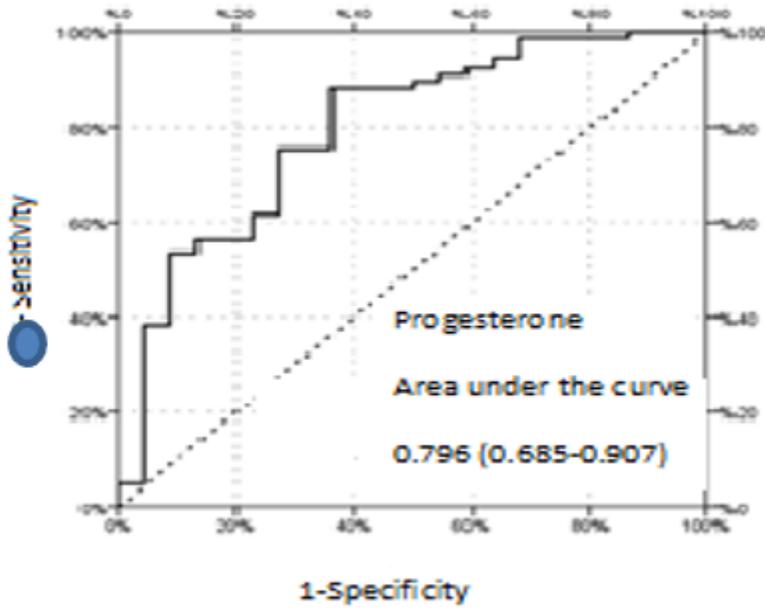


Figure 3

Serum Progesterone level ROC analysis in FHR +/- group prediction

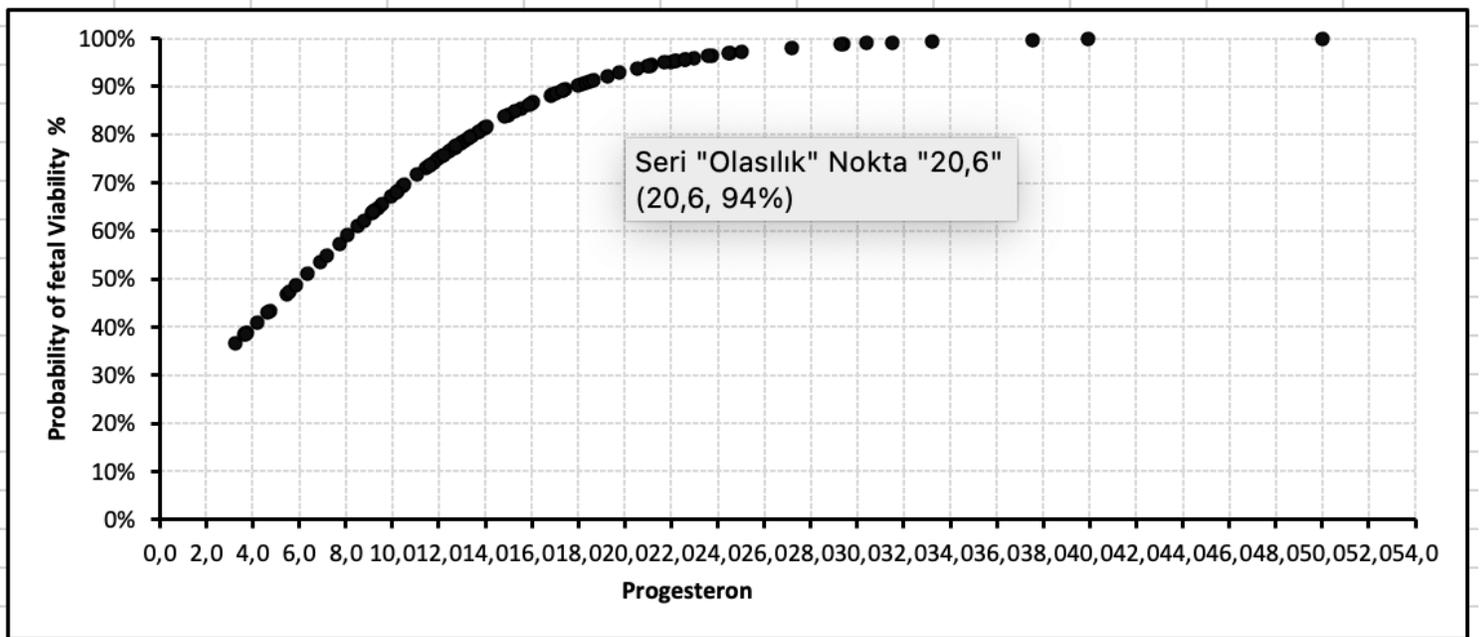


Figure 4

Chart of initial serum Progesterone value and probability of fetal heart rate