Original Article

Validity of Serum Progesterone Levels <20NG/ML as a Predictor of Spontaneous Miscarriage

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Abstract

Objective: To validate the serum progesterone levels <20ng/ml as a predictor of spontaneous miscarriage amongst women with threatened miscarriage during the first trimester of pregnancy.

Study Design: Cross Sectional Validation study.

Setting and duration: Outpatient department of obstetrics and gynaecology Military hospital, Rawalpindi from February-July, 2016 over a period of six months.

Methodology: All the women with singleton pregnancy presenting with threatened miscarriage during the first trimester were recruited in the study and followed for 4 weeks on weekly basis to determine whether the pregnancy is ongoing or ended up in spontaneous miscarriage (fetal demise). Descriptive statistics were used for quantitative variables and frequencies for qualitative variables. Independent sample t-test was applied to compare mean values of serum HCG and progesterone, and validity of serum progesterone was calculated at a cut off the level of <20ng/ml.

Results: Out of 93 pregnant women who participated in the study, 25 (26.8%) had a miscarriage till 4th week of follow up. Serum progesterone levels showed a significant difference between ongoing pregnancy group and miscarriage group (P-value<0.001). When the cut off value of serum progesterone was taken as < 20 ng/ml, the Sensitivity, Specificity, PPV and NPV was found to be 92.00%, 95.59%, 88.46% and 97.01% respectively.

Conclusion: The cut off the value of serum progesterone at <20ng/ml is a useful screening tool for the identification of pregnancy outcomes in women presenting with threatened miscarriage.

Keywords: Progesterone, cut-off level, threatened miscarriage.

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Introduction

Threatened miscarriage is defined by the National Library of Medicine, Medical Subject Headings (2012 MeSH), as viable pregnancy associated with vaginal bleeding through closed cervix with or without abdominal pain during first 20 weeks of pregnancy and it is a very common complaint in our day to day practice which not only causes anxiety to the couple but may also prove troublesome for the treating physician. If we know the possible pregnancy outcomes, it will help to individualize the patients for their management plan accordingly. [1]

The incidence of spontaneous miscarriage after an

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episode of threatened miscarriage is quite high, ranging up to 30-50% but this chance reduces if the fetal cardiac activity is observed on ultrasound. Around 2% of the cases who initially present with signs and symptoms of threatened miscarriage are diagnosed as having ectopic pregnancy so careful detailed evaluation is crucial for the appropriate management of these patients. Though threatened miscarriage is an alarming symptom, there is limited published literature on its prevalence and risk factors.[2] Even if the condition doesn't result in miscarriage and resolves ultimately, still there are chances of other complications [3] which includes the risk of suboptimal pregnancy outcome in the form of preterm delivery, low birth weight and unexplained intrauterine death.[4]

Ultrasound is probably the single best diagnostic test available for the viability of pregnancy, however, more than 30% of these women progress to spontaneous miscarriage regardless of initial confirmation of viability by ultrasound scan. Therefore, a biomarker with good sensitivity and specificity to successfully predict the outcome of pregnancy is of value. Many studies have examined biochemical markers such as serum human chorionic gonadotrophin (hCG), serum progesterone, activin A and inhibin A [5, 6] amongst which progesterone and β-hCG are considered reliable biochemical markers for predicting vthe iability of a pregnancy and its outcomes. [7] Progesterone is a steroid hormone secreted by the granulosa cells in the ovary which attributed to the physiology of pregnancy. This hormone plays a central role for preparing uterus for the blastocyst implantation, inhibition of contraction of the uterus, prevention of cervical dilatation and suppression of the maternal immune system. [6] Recent meta-analysis support a single measurement of serum progesterone to predict a viable pregnancy outcome [8,9] as serum progesterone levels are even low in those pregnancies which do not show any signs or symptoms of threatened miscarriage but end up on spontaneous miscarriage later on.

Despite strong evidence of its correlation with pregnancy outcomes in threatened miscarriage, it is not in clinical use widely which may be because of different cut-off levels which have been used in various studies for risk stratification. So, the current study has been designed to validate the serum progesterone levels <20ng/ml as a predictor of spontaneous miscarriage amongst women with threatened miscarriage during first trimester.

Methodology

After taking approval from hospital ethical committee, a total of 93 pregnant women visiting the outpatient department of obstetrics and gynaecology of Military hospital, Rawalpindi during the period of February 2016 to July 2016 were recruited in the study. Inclusion criteria included women with singleton pregnancy presenting with vaginal bleeding with or without abdominal pain during the first trimester of pregnancy. Detailed history and examination were conducted by a female researcher and then viability was confirmed by ultrasound. Ectopic pregnancy, blighted ovum, molar pregnancy, missed miscarriage, inevitable miscarriage or induced miscarriage were excluded from the study. All the women selected for the study were briefly described about the purpose of the study and written informed consent was taken prior to inclusion in the study.

A predesigned proforma was used to collect information regarding name, age, parity, gestational age (through last menstrual period and confirmed with ultrasound), serum progesterone levels and serum hCG levels. For laboratory tests, 5ml blood was collected from each participant for separating and centrifuging the serum, then radio-immuno assay (RIA) method was used to measure serum hCG and progesterone. All the women in the study were followed for 4 weeks on weekly basis to determine whether the pregnancy is ongoing or ended up in spontaneous miscarriage (fetal demise). The fetal demise was confirmed on ultrasound. Data were analyzed by SPSS version 20. Descriptive statistics were used to calculate mean with standard deviation for quantitative variables and frequencies along with percentages were calculated for qualitative variables. Independent sample t-test was applied to compare mean values of serum hCG and progesterone. A P-value less than 0.05 was considered significant.

Results

A total of 93 pregnant women fulfilling the inclusion criteria were included. Amongst these, 25 (26.8%) had a miscarriage and 68 (73.1%) were having ongoing viable pregnancy till 4th week of follow up.

The mean age of the women in ongoing pregnancy group was 28.2 ± 4.2 (range 22-35 years) which was significantly lower (<0.05) as compared with the spontaneous miscarriage group in which mean age was 30.3±3.6 (range 24-38 years). The median parity was same in both groups with a value of 3. There was

no statistically significant difference (P-value > 0.05) between the mean gestational ages of both groups. Table I

Table I: Comparison of different characteristics between ongoing pregnancy group and miscarriage group

Characteristics	Ongoing Pregnancy (n=68)	Miscarriage (n=25)	P-Value
Age of participants (years)			
Mean ± SD	28.25±4.28	30.36±3.67	0.021 *
Range	22 - 35	24 – 38	
Parity of the participants			
Median	3	3	------
Range	0 - 6	0 – 7	
Gestational age (weeks)			
Mean ± SD	11.55±4.35	10.64±3.84	0.337 **
Range	5 -18	4 – 16	
Antenatal Booking status			
Yes	49 (72%)	14 (56%)	0.1419 **
No	19 (28%)	11 (44%)	

** The difference is significant at 5% level of significance*
*** The difference is not significant at 5% level of significance*

On the basis of antenatal booking status, no statistically significant difference was found between both groups (P-value > 0.05).

The comparison of B-hCG and serum progesterone showed the statistically significant difference between ongoing pregnancy group and spontaneous miscarriage group (P-value < 0.001). The mean value of B-hCG among women in ongoing pregnancy group was 11865.0±5265.0 mIU/ml and in the miscarriage group it was significantly lower with a mean value of 5084.00±2089.00. Similarly, serum progesterone levels of women in a miscarriage group had a significantly lower value (12.9 ± 6.8) as compared with women who were in an ongoing pregnancy group. Table II

The validity of serum progesterone was calculated with two cut off values. When the cut off value was taken as <10 ng/ml, the validation parameters were found to be having a sensitivity of 72.0%, specificity 92.65%, positive predictive value (PPV) 78.26% and negative predictive value (NPV) of 90.0%. When the cut off value of serum progesterone was taken as < 20 ng/ml, the sensitivity, specificity, positive predictive value and negative predictive value was improved to 92.00%, 95.59%, 88.46% and 97.01% respectively. Table III

Table II: Comparison of B-hCG and serum progesterone between ongoing pregnancy group and miscarriage group

Characteris-tics	Ongoing Pregnancy (n=68)	Miscarriage (n=25)	P-Value
B-hCG (mIU/ml)	11865.0±5265.0	5084.00±2089.0	0.000 *
Serum Progesterone (ng/ml)	26.42 ± 4.76	12.96±6.89	0.000 *

** The difference is highly significant at 1% level of significance.*

Table III: Validation of serum progesterone levels with cut off value at 10 and 20 ng/ml for pregnancy outcomes

Validation Parameters	Serum Progesterone (ng/ml)	
	Cut Off < 10 ng/ml	Cut Off < 20 ng/ml
Sensitivity	72.00%	92.00%
Specificity	92.65%	95.59%
Positive Predictive Value	78.26%	88.46%
Negative Predictive Value	90.00%	97.01%

Discussion

Pregnancy loss rates among women with threatened miscarriage varies with respect to age, this rate is only 2% in women less than 35 years whereas the rate exceeds to 16% in women over the age of 35 years. Serum Beta-hCG and progesterone levels are good biochemical markers for predicting outcome in women with threatened miscarriage with good sensitivity and specificity whereas fetal cardiac activity and crown rump length are good ultrasonographic markers for the prediction of outcome in women with threatened miscarriage. [10, 11] About one fourth of all the pregnant women encounter threatened miscarriage and amongst these 12-57% end up in spontaneous miscarriage. Previous studies have concluded that heavy bleeding increases the risk of pregnancy loss as compared to spotting and light bleeding. [12, 13]

According to a recent meta-analysis, B-hCG levels and ultrasound findings are inadequate to assess the pregnancy outcome in patients presenting with threatened miscarriage but a single measurement of

serum progesterone level can be helpful for identification of pregnancy outcome in terms of miscarriage or pregnancy continuation. There are many cut off values of serum progesterone levels like any value less than 6 ng/ml will predict an almost 100% miscarriage. [14, 15] Previous studies have shown that the risk of fetal demise increases with increasing maternal age [16] which is in line with our results.

According to Al-Sebai MA et al, single serum B-hCG measurement in the diagnosis of early pregnancy failure has got some role which is in agreement with our results.[17]

A study conducted on pregnant women to find the outcomes of threatened miscarriage has shown that the single measurement of serum progesterone is very valuable in the immediate diagnosis of early pregnancy failure and also it predicts long-term prognosis of viability as serum progesterone levels were significantly low in non-continuing than threatened continuing pregnancies which support our findings. [18] Serum progesterone levels in women who ended up in miscarriage had a significantly lower value of 12.96 ± 6.89 as compared to those women who were in an ongoing pregnancy group. Similarly, the mean value of B-hCG among women in ongoing pregnancy group was 11865.0±5265.0 mIU/ml and in the miscarriage group it was significantly lower with a mean value of 5084.00±2089.00,

The validation parameters in literature also showed a high sensitivity and specificity of serum progesterone level in the identification of viable and non-viable pregnancies. A study conducted by Hanita et al found high sensitivity, specificity and positive predictive value of single serum progesterone test when its cut-off value was taken as <32.7 ng/ml for the prognosis of threatened miscarriage.[19] These results are in agreement with our study in which, when the cut off value was taken as <10 ng/ml, the sensitivity, specificity, PPV and NPV was low (72.0 %, 92.65%, 78.26%, 90.0%) whereas when the cut off value of serum progesterone was taken as <20 ng/ml the Sensitivity, Specificity, PPV and NPV were improved (92.00%, 95.59%, 88.46% and 97.01%).

It can be ascertained from this study that a single value of serum progesterone can be very helpful in determining the prognosis of the pregnancy among women presenting with threatened miscarriage. It may prove highly beneficial for deciding management plan and extending emotional support to the patients. But some caution would be necessary due to different cut off values recommended in the literature for screening out the non-viable pregnancies. The cut off values obtained through local population would be helpful in the management of threatened pregnancies.

Conclusion

Serum progesterone level can be used as a useful screening tool for the identification of pregnancy outcome in women presenting with threatened miscarriage during the first trimester. The analysis of serum progesterone level showed that the difference between ongoing pregnancy and miscarriage groups was highly significant. When the cut off value of serum progesterone was taken as < 20 ng/ml the Sensitivity, Specificity, PPV and NPV were found to be 92.00%, 95.59%, 88.46% and 97.01% respectively.

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