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Accuracy of Combined Maternal Serum Interleukin-8 and Salivary Estriol in Prediction of Preterm Labor

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Authors' contributions

This work was carried out in collaboration between all authors. Author GMS designed the study, wrote the protocol, and wrote the first draft of the manuscript, does the statistical analysis. Author GIK managed the literature searches, chemical analyses of the samples, authors HAE and SE managed the clinical examination of the patients with sampling the specimens. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To assess the accuracy of combined maternal serum interleukin and maternal salivary estriol levels in prediction of preterm labor in Egyptian pregnant females.
Study Design: Case control study.
Place and Duration of Study: It was conducted in El-Shatby University Hospital of Gynecology and Obstetrics, Alexandria, Egypt between 1st Jan to 30th September in the year 2012.
Methodology: We included 80 pregnant females of gestational age 28-36 weeks (40 females with preterm labor and 40 pregnant not in labor). Both groups were matched for the women's age and the gestational age. A questionnaire was completed; abdominal and vaginal examinations were done. Maternal serum and saliva were collected for measuring the serum interleukin-8 and salivary estriol levels using ELISA technique.

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Results: Using ROC curve analysis, the overall diagnostic accuracy of Salivary Estriol alone at cut off point 200 pg/ml in prediction of preterm labor was 58% (0.46-0.71). Sensitivity and specificity were 82.5% and 32.5% respectively. The diagnostic accuracy of combined Salivary Estriol and serum interleukin-8 in prediction of preterm labor was 68% (0.56-0.79). Sensitivity and specificity were 75%% and 60% respectively. Lastly, the maternal serum interleukin-8 had the following accuracy measures for prediction of preterm labor at cut off point 965 pg/ml. (Overall accuracy: 79% (0.69-0.89), sensitivity 92.5% and specificity 42.5%).
Conclusion: The maternal serum interleukin-8 is an effective and relatively non invasive and more accurate strategy for prediction of preterm labor at cut off point 965 pg/ml than salivary estriol. (Overall accuracy: 79%, sensitivity 92.5% and specificity 42.5%).

Keywords: Preterm labor; interleukin-8; salivary estriol; prediction.

1. INTRODUCTION

Preterm labor is defined as labor occurring before the completion of 37 weeks gestation (<259 days), It is a leading cause of neonatal morbidity [1,2]. Preterm birth includes preterm labor with intact membranes (PTL; ±40%), preterm premature rupture of membranes (PPROM; ± 40%), and indicated delivery because of deteriorating maternal or fetal health (± 20%) [3].

1.1 Burden of Disease due to Preterm Birth

Preterm birth is one of the most important issues in reproductive medicine. It complicates 10-15% of all pregnancies [4,5]. Its incidence has increased during the last decade. Main reasons are: (1) a higher incidence of multiple births due to fertility-enhancing drugs and procedures; (2) a tendency toward early (including preterm) induction or Cesarean section for pathological pregnancies; (3) an increase in registration of births near the borderline of viability; and (4) a more accurate estimated gestational age by the increasing use of early ultrasound [6]. It is among the top causes of death in infants worldwide.

1.2 Etiology of Preterm Birth

Preterm birth is a heterogeneous condition where up to 30 - 40% of all cases of preterm birth are due to elective delivery for a maternal or a fetal complication e.g. hypertension, diabetes, intra-uterine growth restriction [1]. The remaining 60 – 70% of preterm birth is likely due to covert or sub-clinical infective/inflammatory processes, cervical dysfunction, idiopathic (unknown), multiple gestations and possible social, nutritional, and environmental interactions [2].

The cause for preterm birth is in many situations elusive and unknown; many factors appear to be associated with the development of preterm birth, making the reduction of preterm birth a challenging proposition.

Spontaneous preterm birth (SPB), includes PTL and PPROM. The strategies to prevent or reduce SPB have not been effective until now. SPB is a syndrome produced by a wide variety of disease conditions operating through different pathogenic pathways and mechanisms [7]. With the recent advances in understanding the pathogenesis of SPB, a number of techniques have been proposed to predict SPB [7]. It is of clinical relevance to be able to predict SPB, if an intervention is available that is likely to improve outcome. Another reason to identify women at risk for a preterm birth is to allow appropriate maternal transport to a tertiary care center for the optimal care to be provided for the newborn.

The failure of traditional approaches to predict SPB is likely to be an inadequate understanding of the underlying heterogeneous pathogeneses of SPB, so the understanding of the pathogenesis has substantially improved the detection of the factors that help in predicting preterm labor. New biochemical fluid markers (cytokines, hormones and enzymes) might be relevant in the etiology of SPB.

1.3 Pathogenesis of Spontaneous Preterm Birth (SPB)

Cases of SPB result from four primary pathogenic processes that may occur either in isolation or in combination [8]. While each process follows a unique biochemical cascade, they share a common final biological pathway, involving the release of prostaglandins which generate uterine contractions and an increased expression of genital tract proteases which

promote cervical change and rupture of membranes (Fig. 1). To ascertain patients at risk, given these heterogeneous biochemical and biophysical pathways, a combination of pathogenic-specific markers will be needed.

Initial studies employing longitudinal sampling have demonstrated a rise in both plasma and salivary E3 two to five weeks before the onset of labor whether occurring at term deliveries or preterm. This increase in E3 may be used to diagnose threatened preterm labor in women at high-risk for spontaneous Preterm Birth [7,8].

The cytokines IL-1β,-6, -8 can be measured in maternal serum and cervical secretions. They play a role in inflammation-based spontaneous Preterm Birth. Lower genital tract IL-6 and IL-8 concentrations appear to be related to subsequent SPB. However, presently there are no consistent results regarding the usefulness in predicting spontaneous preterm birth.

1.4 Rational of the Study

In our community there were studies concerning the estriol, IL1 and IL6 only but no sufficient studies about IL8 or the combination of both of estriol and IL8. *While both were* involved in the pathogenesis pathway of preterm labor so estriol and IL-8 were assessed in our paper.

1.5 Research Hypothesis

The combination of maternal salivary estriol and serum interleukin-8 will be better predictor than either of them alone.

1.6 Limitations of the Study

The difficulty in following up pregnant cases till developing preterm labor causes limitation in doing follow up study design. We used case control study to evaluate the role of both factors in identifying cases of preterm labor, so we could use these markers in prediction of it.

Also, On sampling from the patients , the cases had symptoms of preterm labor like leucorrhea, abdominal pain but really not entered in true labor except after many days of admission; not the same day of collection of the specimens.

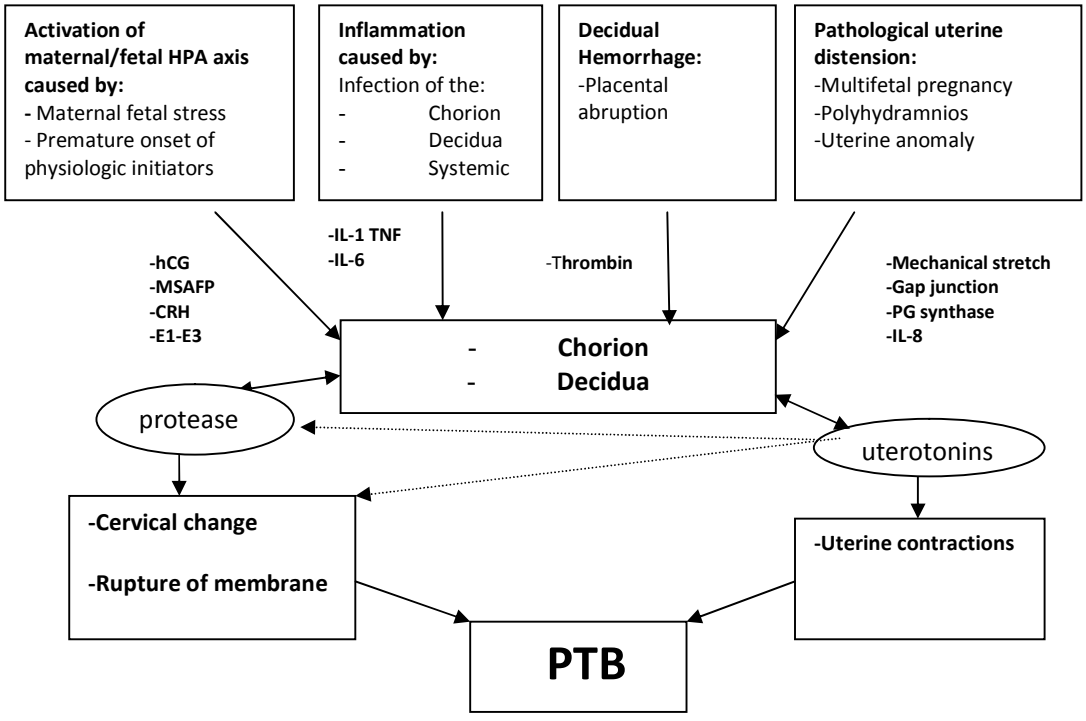

Fig. 1. Pathways of Preterm Birth (PTB) due to preterm Premature Rupture of the Membranes (PPROM) and/or Preterm Labor (PTL)

The other limitation was relatively small sample size which is limited due to the expensive price of the kits of both estriol and interleukin-8 (funded by the authors only) so we are in need for further research to establish these screenings as reliable, and limited specificity with large fund for larger sample size.

2. MATERIALS AND METHODS

2.1 Setting

The present study was conducted in El Shatby University Hospital of Gynecology and Obstetrics in Alexandria. It is the largest hospital of its kind in Alexandria, a tertiary care facility and a center of expertise in a maternity care and management of gynecological problems. It serves population of Alexandria city and nearby governorates (Matrouh and El-Beheira) with considerably high case load that warrants the accumulation of a sufficient number of cases during a reasonable period of time.

2.2 Study Design

Case Control study.

2.3 Study population

The Study population was pregnant females of gestational age 28-36 weeks (gestational age will be determined by dating from last menstrual period, fundal level and ultrasound) attending El-Shatby University Hospital of Gynecology and Obstetrics in Alexandria in the year 2012. The study population was classified into two groups the first group was healthy women not in labor (control) and the second group was women suffering from preterm labor (cases). Both groups were matched for the women's age and the gestational age.

2.4 Inclusion Criteria

All Pregnant females in gestational age between 28-36 weeks.

2.5 Exclusion Criteria

1- General maternal systemic diseases either medical or obstetrical
2- Local causes initiating preterm labor such as uterine myomas or uterine anomalies (bi-cornuate uterus or septate uterus), if any local cause is discovered postpartum, this case will be excluded.
3- Evidence of congenital anomalies
4- Intrauterine growth retardation

2.6 Sample Size Calculation

A minimum sample size of 38 for each group was calculated to achieve 80% power and to detect difference of 184 between the mean serum interleukin-8 levels of the null hypothesis (148±5) and the alternative hypothesis of (332±389) with a significance level of 0.05 [9].

2.7 Tools of Data Collection

After having approval from the ethical committee, Medical Research Institute, signed informed consents were obtained from all patients who agree to participate in the study.

Three tools were used to obtain relevant information: Interviewing questionnaire, clinical examination and investigations.

2.7.1 Interviewing questionnaire

An interview schedule was designed to collect relevant information from all eligible women enrolled in this study. The schedule included the following items: Personal history, menstrual History, obstetric History, Medical history and Present complaint

2.7.2 Examination

Complete clinical examination was done for the study subjects. General, abdominal and vaginal examination

2.7.3 Investigations

a- Abdominal sonography:
b- Biochemical analysis: for measuring the following:

1-Salivary estriol level by ELISA Technique (DiaMetra company, Italy).: Saliva sample was collected at any time of the day taking into cosideration the following Specific instructions: No teeth brushing before collection, At least 1hour was left after any food or drink before collecting the sample, Good clear sample shoyld be received (no contamination with food, lipstick or blood as in bleeding gums).

2- Serum interleukin-8 level by ELISA Technique (eBioscience company, North America): Blood samples were collected at any time of the day in a gel foam tubes for autoseparation and the sample was centrifuged for 15 minutes at 3000 rpm.

3. RESULTS

The study included 80 pregnant females presented to El-Shatby Maternity University Hospital, 40 healthy females (control) and 40 females with preterm labor (cases). The age of females ranged between a minimum of 18 years to a maximum of 35 years with a mean of 25.9±4.18 years. Both groups were matched for the female's age and the gestational age. Table 1 shows the association between the groups of cases and the socio-demographic characteristics. As regards female age, about 22.5% of the cases has age more than 30 years compared to 2.5% of the control. So, increased women's age was associated with a significant increased risk of preterm labor relative to those with younger age groups. (OR=5.6, CI= 1.34-23.5, p=0.024). Regarding the education, most of the cases (70%) were low educated (less than 12 years) versus 50% of the controls. This difference was not statistically significant. (OR=2.33, CI=0.94-5.7, p=0.06). Concerning the occupation, all the entire cases was not working (100%) compared to 97.5% of the control. This difference was not statistically significant. (OR=0.32, CI= 0.21-2.62, p=0.314).

Assessment of the diagnostic accuracy of Salivary Estriol alone, Serum interleukin-8 alone or the combination of both was done for prediction of preterm labor. We choose the cut off points of salivary estriol or interleukin-8 according to the highest sensitivity and highest specificity, It revealed the following results:

The role of salivary estriol in predicting preterm labor was presented in Table 2. It was shown that 82.5% of cases had salivary estriol more than 200 pg/ml compared to 67.5% of the controls. The risk of preterm labor was nearly two times among those with high salivary estriol levels more than 200 pg/ml than those with salivary estriol level less than or equal 200 pg/ml, but this was not statistically significant (OR =2.2, CI= 0.79-6.48, p=>0.05).

The role of interleukin-8 in predicting preterm labor was also demonstrated in Table 3, where 92.5% of cases had serum interleukin-8 more than 965 pg/ml compared to 57.5% of the controls. The risk of preterm labor was nearly nine times among those with high serum interleukin-8 levels more than 965 pg/ml than those with serum interleukin-8 levels less than or equal 965 pg/ml, this association was statistically significant (OR =9.11, CI= 2.4-34.57, p<0.05).

The role of combined salivary estriol at cut off 200 pg/ml and interleukin-8 at cut off 965 pg/ml in predicting preterm labor were shown in the same (Table 3). It clarified that 75% of cases had both tests positive versus 40% of the controls. The risk of preterm labor was nearly five times among those with positive tests than those with negative tests. This was statistically significant (OR =4.5, CI= (1.73-11.69), p<0.05).

Table 1. shows association between the groups of cases and the socio-demographic characteristics

Socio-demographic characteristics	Preterm labor				X^2 test (P)	OR (95% CI)
	No (control)		Yes (cases)			
	No	%	No	%		
Age:						
< 25 years®	16	40	14	35		
25-30 years	23	57.5	17	42.5	7.433	0.84 (0.32-2.18)
> 30 years	1	2.5	9	22.5	(0.024)*	5.63 (1.34-23.5)*
X ± SD years	25.5±3.4		26.2±4.8			
Range	19-35		18-35			
Education:						
< 12 years education ®	20	50	28	70	3.33	2.33
≥ 12 years education	20	50	12	30	(0.06)	(0.94-5.7)
Occupation:						
Non worker	39	97.5	40	100	1.03	0.32
Worker	1	2.5	0	0	(0.314)	(0.21-2.62)

*® is the reference group, *P is statistically significant (<0.05)*

Table 2. Salivary Estriol, serum interleukin-8 and combined both tests as predictors of preterm labor

Salivary estriol level **	Positive preterm labor by clinical examination		Negative preterm labor by clinical examination		Total no	OR (95% confidence interval))
	No	%	No	%		
Salivary Estriol > 200 pg/ml	33	82.5	27	67.5	60	2.2
Salivary Estriol ≤ 200 pg/ml	7	17.5	13	32.5	20	(0.79-6.48)
Total	**40**	**100**	**40**	**100**	**80**	
Serum Interleukin-8 level * **						
Interleukin-8 > 965 pg/ml	37	92.5	23	57.5	60	
Interleukin-8 ≤ 965 pg/ml	3	7.5	17	42.5	20	9.11
Total	**40**	**100**	**40**	**100**	**80**	(2.4-34.57)*
Combined salivary estriol and serum interleukin-8						
Both Tests are Positive	30	75	16	40	46	
One or Both tests negative	10	25	24	60	34	4.5
Total	**40**	**100**	**40**	**100**	**80**	(1.73-11.69)*

** P value is statistically significant (<0.05)*

*** Cut off point of salivary estriol 200pg/ml at highest sensitivity=83% and specificity=33%*

**** Cut off point of interleukin-8 965pg/ml at highest sensitivity=93% and specificity=43%*

Table 3. Diagnostic accuracy of Salivary Estriol alone, serum interleukin-8 alone and combinations of both tests in prediction of preterm labor

Parameters of diagnostic accuracy in predicting preterm labor	Value for the salivary estriol at cut off point 200 pg/ml	Value for serum interleukin-8 at cut off point 965 pg/ml	Value for combined salivary estriol at cut off point 200pg/ml & interleukin-8 at cut off point 965 pg/ml
Overall accuracy (95% C.I.)	58% (0.46-0.71)	79% (0.69-0.89)	68% (0.56-0.79)
P value	0.19	(0.00)*	(0.007)*
Sensitivity	82.5%	92.5%	75%
Specificity	32.5%	42.5%	60%

** P value is statistically significant (<0.05)*

Concerning the diagnostic accuracy of salivary estriol, serum interleukin-8 or both together in predicting preterm labor, (Table 3. and Fig. 2) illustrate the different parameters of diagnostic accuracy of at a cut off point 200 pg/ml for the salivary estriol (the cut off point of highest sensitivity (82.5%) and specificity (32.5%)), while the cut off for the serum interleukin-8 was 965 pg/ml (the cut off point of highest sensitivity (92.5%) and specificity (42.5%)). The overall accuracy of Salivary estriol in predicting preterm labor, was 58% (CI=0.48-0.71) which was not statistically significant (p=0.19). While it was 79% (CI=0.69-0.89) and 68% (0.56-0.79) for serum interleukin-8 and combined tests respectively which were statistically significant (p=0.00 and 0.007 respectively). It was shown that the overall accuracy of serum interleukin-8 were higher than the overall accuracy of salivary estriol alone or both combined, so serum interleukin-8 alone had high prediction rate of preterm labor (79%) than salivary estriol alone or both combined (58% and 68% respectively).

4. DISCUSSION

Preterm labor is a common serious clinical problem. It is a major determinant of neonatal mortality and morbidity and has long-term adverse consequences for health [10-12]. The highest rates occurred in Africa and North America, where 11.9% and 10.6%, respectively, of the births were preterm. Europe, where 6.2% of the births were preterm, had the lowest rate. [13].

Preterm birth rates available from some developed countries, such as the United

Kingdom, the United States and the Scandinavian countries, show a dramatic rise over the past 20 years [14,15]. Factors possibly contributing to but not completely explaining this upward trend include increasing rates of multiple births, greater use of assisted reproduction techniques. In developing countries, accurate and complete population data and medical records usually do not exist.

The current study was conducted in El-Shatby Hospital of Gynecology and Obstetric, a university hospital and a tertiary care facility providing health services to middle and low socioeconomic group of population of Alexandria and nearby areas. The study focused on the estimation of the accuracy estimates of the combined maternal serum interleukin-8 and Salivary estriol in predicting preterm labor among women presented with symptoms of preterm labor with or without premature rupture of membrane in comparison to the control group who were coming for antenatal care. Both groups were matched for the women's age and the gestational age. They had age ranged from 18-35 years with mean age of 25.9±4.18.

The study markers (Salivary estriol and Serum interleukin-8) were measured in the study sample with mean of salivary estriol (pg/ml) in the cases and controls 738.1±106.7 and 525.1±103.8 respectively. While the mean of serum interleukin-8 (pg/ml) in the cases and controls was 1136.1±126.8 and 986.7±118.8 respectively. Although this figure was obtained based on the study that occurred in only one hospital, yet this hospital provides health services to a large group of population of Alexandria and nearby areas, so the prevalence detected can reflect a large proportion of the population. This was consistent with Lockwood et al. [7] in his study in England.

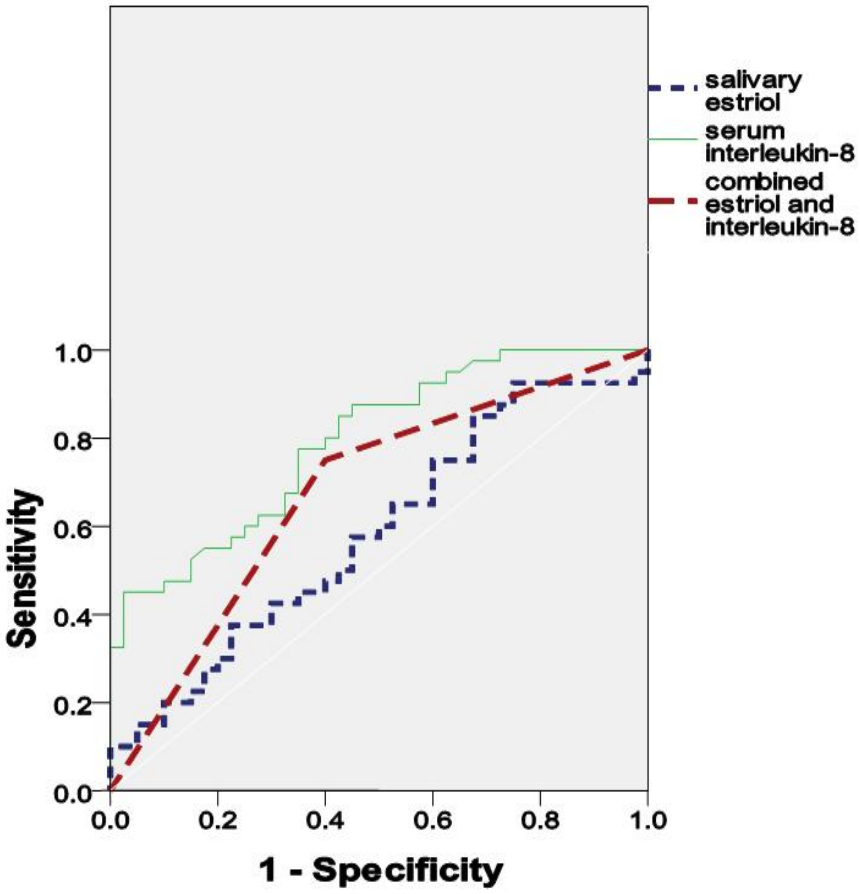

Fig. 2. ROC curve of maternal salivary estriol, serum interleukin- 8 and combined both tests in predicting preterm labor (accuracy 58%, 79% and 68% respectively)

Concerning the assessment of the diagnostic accuracy of the maternal Salivary Estriol/Serum interleukin-8 in prediction of preterm labor, they were used as a screening method for Pregnant women to detect the risk of preterm labor. The highest the maternal salivary estriol and or the highest maternal serum interleukin-8, the increased the risk of preterm labor. Although estriol or interleukin-8 obtains an actual measurement level, test results are typically reported simply as 'positive' or 'negative' depending on whether the level of the predictor is above or below a specified threshold. For diagnostic tests providing a positive or negative result, performance across the study group is usually summarized in terms of sensitivity and specificity. Sensitivity is the probability of testing positive if the disease is truly present. Specificity is the probability of testing negative if the disease is truly absent.

Controversies do exist regarding the cut off point at which the salivary estriol or serum interleukin-8 levels are said to be negative or positive. The present study found that the overall accuracy of maternal salivary estriol to predict preterm labor at cut off point 200 pg/ml was 58%. The sensitivity and specificity were 82.5% and 32.5% respectively. Combinations of maternal salivary estriol and Maternal serum interleukin-8 had overall accuracy, sensitivity and specificity 68%, 75% and 60% respectively. The highest overall accuracy and sensitivity were for the maternal serum interleukin-8 alone 79% and 92.5% respectively. In accordance with the present finding is that of Castracane in Australia 2000 who discovered an increased risk of preterm labor among women who had high salivary estriol level and reported a sensitivity and specificity of 85% and 38% respectively with overall accuracy 57% [16]. Other recent studies [17,18] revealed overall accuracy 60%% with accompanying sensitivity and specificity of 87% and 35% respectively at cut off point 200pg/ml. While Goodwin was in disagreement with this findings as he found that the sensitivity of salivary estriol in prediction of preterm labor was low (56%) at the same cut off point [19].

Concerning the role of maternal serum inreleukin-8 in prediction of preterm labor, many recently published studies were in agreement with the results of our study as they support that the role of interleukin-8 in prediction of preterm labor is superior to the combination of salivary estriol and serum interleukin-8 [20-24]. This is in disagreement with Romero (2003) and Osmers (2005) where they found that the combinations of salivary estriol and interleukin-8 were better than each alone [25,26].

5. CONCLUSION

The overall accuracy of serum interleukin-8 alone in prediction of preterm labor (79%) with 95% CI (69%-89%) was higher than accuracy of salivary estriol alone (58%) or the combination of both (68%).

ETHICAL APPROVAL

Authors have obtained all necessary ethical approval from the ethical committee, Medical Research Institute El-Shatby university hospital of gynecology and obstetrics.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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