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Interleukin-6 bedside test in detecting chorioamnionitis in women with preterm premature rupture of fetal membranes

Tamer E. El-Ghazaly[1], Ibrahim A. Abdelazim[1,2], Amal Elshabrawy[1]

[1]Department of Obstetrics, and Gynaecology, Ain Shams University, Cairo, Egypt
[2]Ahmadi Hospital, Kuwait Oil Company, Ahmadi, Kuwait

ABSTARCT

Objectives: About 30–80% of preterm deliveries following preterm premature rupture of fetal membranes (PPROM) are complicated by histological chorioamnionitis. To evaluate the accuracy of Interleukin-6 (IL-6) bedside test in detecting chorioamnionitis in women with PPROM.

Material and methods: One hundred and ten (110) pregnant women with PPROM > 24 and < 34 weeks' gestation, admitted for conservative management were included in this study. Participants were examined on admission using sterile speculum examination for assessment of IL-6 in the cervico-vaginal secretions using the IL-6 bedside test. The IL-6 bedside test was repeated for all participants once termination of pregnancy (TOP) decided. After TOP, placenta, umbilical cord, and fetal membranes samples were examined for histologic detection of chorioamnionitis (gold standard). The histological results were compared with IL-6 bedside test results to evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis in women with PPROM.

Results: The IL-6 bedside test had 98.6% sensitivity, 94.7% specificity, 97.3% positive predictive value (PPV), 97.3% negative predictive value (NPV) and 97.3% overall accuracy in detecting chorioamnionitis. The sensitivity, specificity, NPV and overall accuracy of IL-6 bedside test (98.6%, 94.7%, 97.3%, and 97.3%; respectively) were significantly higher than the clinical and laboratory parameters of chorioamnionitis (65.3%, 57.9%, 46.8%, and 62.7%; respectively) ($p = 0.04$, 0.02, 0.001 and 0.03; respectively).

Conclusions: The IL-6 bedside test is an accurate, non-invasive bedside test with 98.6% sensitivity, 94.7% specificity, 97.3% PPV, 97.3% NPV, and 97.3% overall accuracy in detecting chorioamnionitis. The IL-6 bedside test had significantly higher sensitivity, specificity, NPV, and overall accuracy than the clinical and laboratory parameters of chorioamnionitis.

Key words: Interleukin-6; bedside test; Chorioquick®; Chorioamnionitis; preterm premature rupture of fetal membranes

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INTRODUCTION

The preterm premature rupture of fetal membranes rupture (PPROM) is one of the common problems in obstetrics [1]. It occurs in approximately 3–5% of all pregnancies [2–4], and accounts for 30–40% of preterm deliveries (PTDs) [5]. About 30–80% of PTDs following PPROM are complicated by histological chorioamnionitis [5].

Management of PPROM should be conservative if PPROM occurs before 34 weeks', while pregnancy should be terminated (labor should be induced) if PPROM occurs ≥ 34 weeks' [1].

PPROM usually associated with prematurity, and infections morbidities, and 5–24% of the neonates delivered after PPROM suffer from neonatal sepsis [6, 7].

Conservative management of PPROM may reduce the risk of prematurity but entails risk of an intrauterine infection (IUI) [2, 3].

Maternal clinical and blood parameters have limited accuracy in detection of an ongoing fetal and/or IUI [8, 9].

Although, the amniotic fluid (AF) IL-6 (interleukin 6) at 745 pg/mL threshold had 93% sensitivity, 91% specificity in

Corresponding author:
Ibrahim A. Abdelazim
Department of Obstetrics, and Gynaecology, Ain Shams University, Cairo, Egypt
e-mail: dr.ibrahimanwar@gmail.com

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detection of AF inflammation [10]. AF sampling is an invasive procedure, and unsuitable for daily routine [11, 12].

Currently, there is no accurate, non-invasive test available for detection of IUI, and Kayem et al. [13] suggested the vaginal IL-6 as non-invasive test for detection of AF and/or IUI. The AF IL-6 is good predictor of fetal inflammatory response, and histologic funisitis [14].

IL-6 bedside test is a new IL-6 based test with the potential to detect IL-6 at three different thresholds for diagnosing chorioamnionitis [5]. Therefore, this study designed to evaluate the accuracy of the IL-6 bedside test in detecting chorioamnionitis in women with PPROM.

Objectives

To evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis in women with PPROM (primary outcome).

To compare the accuracy of IL-6 bedside test in detecting chorioamnionitis to the clinical and laboratory parameters of chorioamnionitis (secondary outcome).

MATERIAL AND METHODS

This prospective comparative double blinded study was conducted from February 2019 till August 2020, after approval by the ethical committee of the Obstetrics and Gynecology department (OB_9012_18), and registration as clinical trial (ACTRN12619000191190).

One hundred and ten (110) women with PPROM > 24 and < 34 weeks gestation, were included in this study after informed consent in accordance with the Declaration of Helsinki to evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis in women with PPROM.

Inclusion criteria include women between 20–40 years old, presented with PPROM > 24 and < 34 weeks, and admitted for conservative management.

Women < 24 or > 34 weeks, not sure of dates, on antibiotic, severe oligohydramnios, fetal anomaly, fetal death, multiple pregnancies, non-reassuring cardiotocography (CTG), PTD, vaginal bleeding, active labor, suspicious of chorioamnionitis (clinical or laboratory), and refused to participate and/or give consent were excluded from this study.

The diagnosis of PPROM was based on patient's history of water gush, confirmed by visualization of amniotic fluid (AF) pooling from the cervical canal during sterile speculum examination, positive nitrazine, AmnioQuick Duo test [1, 15], and amniotic fluid index (AFI) ≤ 5 cm using trans-abdominal ultrasound (TAS) [16].

The gestational age of participants was calculated from the first day of last menstrual period (LMP) and confirmed by early ultrasound scan (≤ 20 weeks gestation) [16].

Participants were subjected to general, and abdominal examinations, abdominal ultrasound, sterile speculum examination for detection of AF pooling, and assessment of IL-6 in the cervico-vaginal secretions (CVS) using the non-invasive IL-6 bedside test (Chorioquick®, Biosynex SA, Strasbourg, France) on admission [5]. During the conservative treatment, studied women received two doses dexamethasone [12 mg intramuscularly 12 hours apart (for induction of fetal lung maturity)], and antibiotics according to ACOG recommendations (intravenous ampicillin 2 g, and erythromycin 250 mg every 6 h for 48 h, followed by oral amoxicillin 250 mg, and erythromycin 333 mg every 8 h for 5 days). One-gram Azithromycin single dose is an alternative to erythromycin if unavailable or poorly tolerated [17].

Participants were also subjected to laboratory tests for detection of chorioamnionitis twice weekly, and fetal well-being assesment using; fetal movements count, non-stress tests daily, and TAS weekly to detect AF volume, fetal growth, and umbilical artery Doppler during the conservative treatment [18].

Short term tocolysis (beta-mimetics or calcium channel blockers) were given for participants who developed uterine contraction before the two dexamethasone doses (after exclusion of chorioamnionitis) [18].

The clinical signs, and laboratory parameters of chorioamnionitis include maternal fever, maternal tackycardia, uterine tenderness, maternal leucocytosis, positive C reactive proteins, and procalcitonin [18].

IL-6 bedside test was performed for all participants on admission and repeated once termination of pregnancy (TOP) or induction of labor decided [16] (Fig. 1).

Management of PPROM should be conservative if PPROM occurs before 34 weeks, while pregnancy should be terminated (labor should be induced) if PPROM occurs ≥ 34 weeks [1].

The conservative treatment was discontinued, and pregnancy was terminated by induction of labor for studied participants before 34 weeks with either development of chorioamnionitis or spontaneous labor pains (Fig. 2).

IL-6 bedside test is a new IL-6 based test to detect chorioamnionitis and has the potential to detect IL-6 in CVS at three different thresholds [IL-6 low (0.1 ng/mL), IL-6 medium (0.25 ng/mL), and IL-6 high (5 ng/mL)] [5].

The IL-6 bedside test was considered positive with the presence of two distinct lines; one at level of C zone (control zone), and another line at level of T zone (test zone), (even of weak intensity) at any of threshold indicators and was considered negative with no visible lines at T zone at any of threshold indicators [5].

The decision of TOP or induction of labor based on the clinical and laboratory parameters of chorioamnionitis was taken by the consultant on-call who was blinded to IL-6 bedside test results. Within 48 hours after delivery, placenta, umbilical cord, and fetal membranes samples were examined for detection of chorioamnionitis (gold standard) by

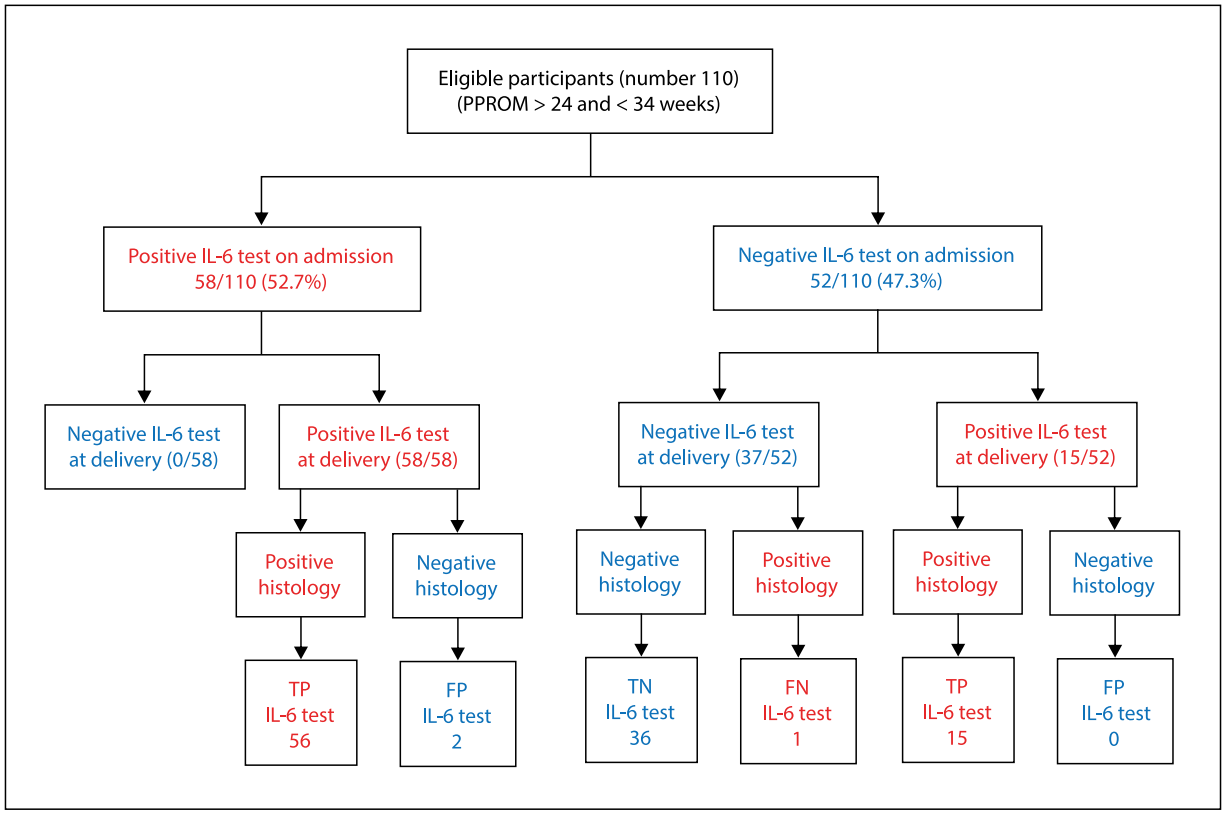

Figure 1. The IL-6 bedside test results in relation to histologic examination of the placenta, umbilical cord, and fetal membranes; FN — False negative; FP — False positive; IL-6 — Interleukin-6; PPROM — Preterm premature ruptured fetal membranes; TN — True negative; TP — True positive

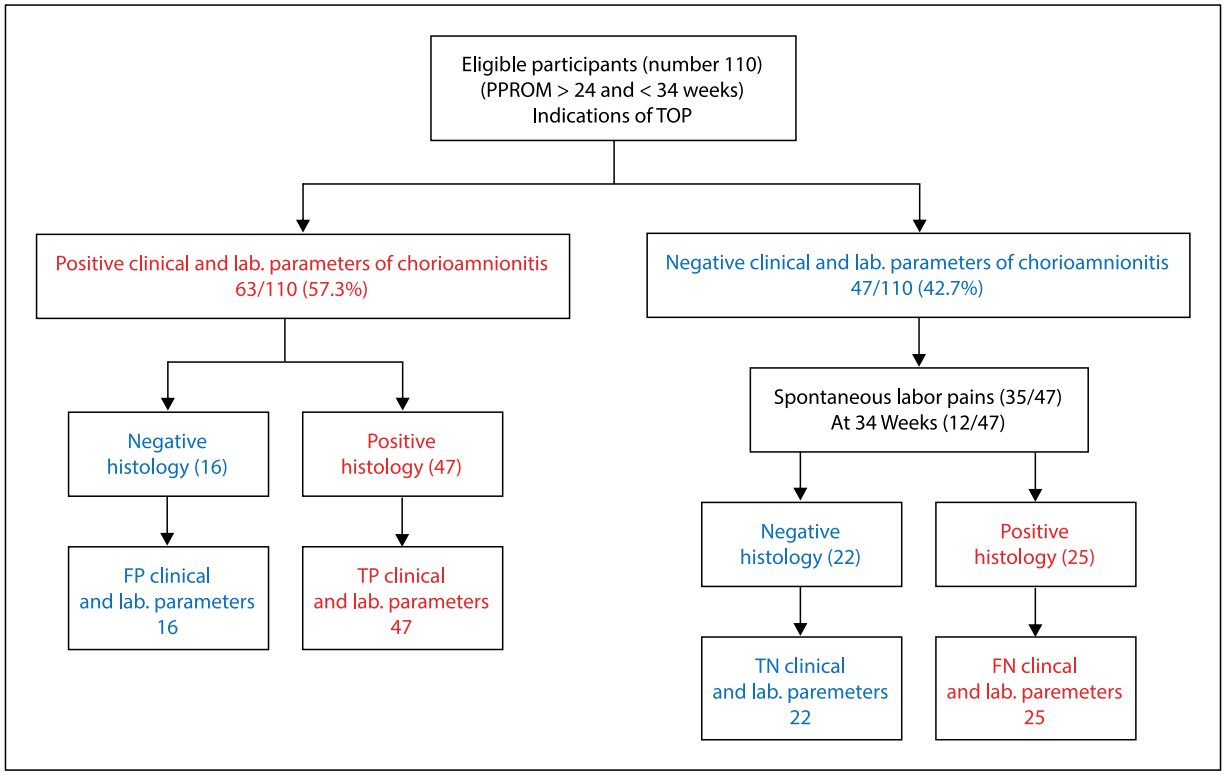

Figure 2. Indications of TOP, and the clinical and lab. parameters of chorioamnionitis in relation to histologic examination of the placenta, umbilical cord, and fetal membranes; FN — False negative; FP — False positive; Lab. — Laboratory; PPROM — Preterm premature ruptured fetal membranes; TN — True negative; TOP — Termination of pregnancy; TP — True positive

histology specialist who was blinded to IL-6 bedside test results (double blinded).

Presence of inflammatory cells in the samples (placenta, umbilical cord, and fetal membranes) in form of multiple (≥ 5) foci of polymorph nuclear leukocytes (PNLs) in the subchorionic fibrin indicates grade 2 inflammation (gold standard for culture-proven AF infection, and chorioamnionitis) [19].

After TOP, the IL-6 bedside test results and the clinical and laboratory parameters of chorioamnionitis were compared to histologic examination of the samples (gold standard) to evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis in women with PPROM (primary outcome) (Fig. 1 and 2).

While the secondary outcome measures the accuracy of IL-6 bedside test in detecting chorioamnionitis compared to the clinical and laboratory parameters of chorioamnionitis.

Sample size justification

The required sample size was calculated from previous studies [14, 20], and using G Power software version 3.17 for sample size calculation, setting α-error probability at 0.05, power (1-β error probability) at 0.95%, and effective sample size (w) at 0.5. An effective sample ≥ 110 women was needed to produce statistically acceptable figure.

Statistical analysis

Collected data were statistically analyzed using Statistical Package for Social Sciences (SPSS): computer software version 20 (Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (± SD), while categorical variables were presented as number (n) and percentage (%). Chi-square test (x^2) was used for analysis of qualitative variables. Sensitivity: proportional detection of individuals with the disease of interest in the population. Specificity: proportional detection of individuals without the disease of interest in the population. Positive predictive value (PPV): proportion of all individuals with positive tests, who have the disease. Negative predictive value (NPV): proportion of all individuals with negative tests, who are non-diseased.

RESULTS

One hundred and ten (110) women with PPROM > 24 and < 34 weeks 'gestation, were included in this study to evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis. The mean maternal age of the participants, parity, body mass index (BMI), gestational age at recruitment, gestational age at TOP, and duration of the conservative treatment were presented in Table 1.

About 25/110 (22.7%) of participants had previous history of miscarriage, 32/110 (29.1%) were smokers, and 17/110 (15.5%) had previous history of PPROM. Regarding the indications of TOP, in 63/110 (57.3%) of participants the pregnancy was terminated due to clinical and laboratory parameters of chorioamnionitis, in 35/110 (31.8%) due to spontaneous labor pains, and in 12/110 (10.9%) at 34 weeks gestation (Tab. 1 and Fig. 2).

After TOP, the IL-6 bedside test results, and the clinical and laboratory parameters of chorioamnionitis were compared to histologic examination of the placenta, umbilical cord, and fetal membranes samples (gold standard).

The clinical and laboratory parameters of chorioamnionitis were TP (true positive) in 47/72 (65.3% = sensitivity), FP (false positive) in 16 cases, while they were TN (true negative) in 22/38 (57.9 = specificity), and FN (false negative) in 25 cases (Fig. 2).

Table 1. Demographic data of the studied women and indications of TOP

Variables	Studied participants (number 110)
Maternal age [years]	29.6 ± 5.2
Parity	3.1 ± 2.4
Previous miscarriage	25/110 (22.7%)
BMI [kg/m^2]	26.7 ± 9.7
Smoking	32/110 (29.1%)
Previous history of PPROM	17/110 (15.5%)
Gestational age at recruitment [weeks]	28.3 ± 2.6
Gestational age at TOP [weeks]	32.5 ± 4.3
Duration of conservative treatment [weeks]	4.2 ± 1.7
Indications of TOP — Clinical and lab. parameters of chorioamnionitis — Spontaneous labor pains — At 34 weeks gestation	 63/110 (57.3%) 35/110 (31.8%) 12/110 (10.9%)

BMI — body mass index; Lab. — Laboratory; PPROM — Preterm premature rupture of fetal membranes; TOP — Termination of pregnancy; Data presented as mean ± SD (standard deviation) and number and percentage (%)

Table 2. Accuracy of the IL-6 bedside test in detecting chorioamnionitis compared to clinical and lab. parameters of chorioamnionitis

Variables	IL-6 bedside test	Clinical and lab. parameters	p-value
Sensitivity (TP ÷ TP + FN) X 100	71 ÷ 71 + 1 = 98.6%	47 ÷ 47 + 25 = 65.3%	0.04*
Specificity (TN ÷ TN – FP) X 100	36 ÷ 36 + 2 = 94.7%	22 ÷ 22 + 16 = 57.9%	0.02*
PPV (TP ÷ TP + FP) X 100	71 ÷ 71 + 2 = 97.3%	47 ÷ 47 + 16 = 74.6%	0.1
NPV (TN ÷ TN + FN) X 100	36 ÷ 36 + 1 = 97.3%	22 ÷ 22 + 25 = 46.8%	0.001*
Accuracy (TP + TN ÷ TP + TN + FP + FN) X 100	71 + 36 ÷ 71 + 36 + 2 + 1 = 97.3%	47 + 22 ÷ 47 + 22 + 16 + 25 = 62.7%	0.03*

*Significant difference. Chi-square test (x^2) was used for statistical analysis. Data presented as number and percentage (%); FN — False negative; FP— False positive; IL-6 — Interleukin-6; Lab. — Laboratory. NPV — Negative predictive value; PPV — Positive predictive value; TN — True negative; TP — True positive

The clinical and laboratory parameters of chorioamnionitis had 65.3% sensitivity, 57.9% specificity, 74.6% PPV, 46.8% NPV and 62.7% overall accuracy in detecting chorioamnionitis (Tab. 2).

The IL-6 bedside test was TP (true positive) in 71/72 (98.6% = sensitivity), FP (false positive) in 2 cases, while it was TN (true negative) in 36/38 (94.7% = specificity), and FN (false negative) in 1 case (Fig. 1).

The IL-6 bedside test had 98.6% sensitivity, 94.7% specificity, 97.3% PPV, 97.3% NPV, and 97.3% overall accuracy in detecting chorioamnionitis (Tab. 2).

The IL-6 bedside test sensitivity, specificity, NPV and overall accuracy (98.6%, 94.7%, 97.3%, and 97.3%; respectively) were significantly higher than the clinical and laboratory parameters of chorioamnionitis (65.3%, 57.9%, 46.8%, and 62.7%; respectively), (p = 0.04, 0.02, 0.001 and 0.03; respectively) (Tab. 2).

DISCUSSION

The PPROM occurs in approximately 3–5% of all pregnancies [2–4], and accounts for 30–40% of PTDs [5]. About 30–80% of PTDs following PPROM are complicated by histologic chorioamnionitis [5]. PPROM usually associated with prematurity, and infections morbidities, and 5–24% of the neonates delivered after PPROM suffer from neonatal sepsis [6, 7]. Currently, there is no accurate, non-invasive test available for detection of IUI [13].

IL-6 bedside test is a new IL-6 based test to detect chorioamnionitis and has the potential to detect IL-6 in CVS at three different thresholds [IL-6 low (0.1 ng/mL), IL-6 medium (0.25 ng/mL), and IL-6 high (5 ng/mL)] [5].

Therefore, one hundred and ten (110) women with PPROM > 24 and < 34 weeks, were included in this study to evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis compared to the gold standard (histologic examination of the placenta, umbilical cord, and fetal membranes) as primary outcome.

While the secondary outcome measures the accuracy of IL-6 bedside test in detecting chorioamnionitis compared to the clinical and laboratory parameters of chorioamnionitis.

The mean maternal age of participants was 29.6 ± 5.2 years, mean gestational age at recruitment was 28.3 ± 2.6 weeks`, mean gestational age at TOP was 32.5 ± 4.3 weeks`, and mean duration of conservative treatment was 4.2 ± 1.7 weeks`. About 25/110 (22.7%) of participants had previous history of miscarriage, 32/110 (29.1%) were smokers, and 17/110 (15.5%) had previous history of PPROM.

Assefa et al. [21] found women with history of abortion had higher risk (3.06 times) to develop PROM (premature rupture of membranes) than those with no history of abortion. Zhou et al. [22] also found an increased risk of PPROM < 28 weeks of pregnancy in those with history of recurrent abortions (OR 2.75).

Assefa et al. [21] found women with history of PROM had higher odds (4–4.5) of developing PROM compared to others with no history of PROM. Similarly, Choudhary et al. and Emechebe et al. [23, 24] found that the previous PROM was significant risk factor for recurrent PROM.

Regarding the indications of TOP, in 63/110 (57.3%) of participants the pregnancy was terminated due to clinical and laboratory parameters of chorioamnionitis, in 35/110 (31.8%) due to spontaneous labor pains, and in 12/110 (10.9%) at 34 weeks.

Navali et al. [25] studied 199 women with PPROM at 29.6 ± 3.4 weeks` gestation, and found the most frequent indications for TOP were reaching 34 weeks, spontaneous labor pains, and chorioamnionitis (most common maternal complication). In addition, Eleje et al. [5] found 30–80% of PTDs following PPROM were complicated by chorioamnionitis.

In this study, the IL-6 bedside test had 98.6% sensitivity, 94.7% specificity, 97.3% PPV, 97.3% NPV and 97.3% overall accuracy in detecting chorioamnionitis in women with PPROM.

In addition, the sensitivity, specificity, NPV, and overall accuracy of the IL-6 bedside test (98.6%, 94.7%, 97.3%, and 97.3%; respectively) were significantly higher than the clinical and laboratory parameters of chorioamnionitis

(65.3%, 57.9%, 46.8%, and 62.7%; respectively) (p = 0.04, 0.02, 0.001 and 0.03; respectively).

Musilova et al. [26] found strong positive correlation between vaginal, and AF IL-6 concentrations, and they found that higher vaginal IL-6 was associated with microbial invasion of AF, and microbial-associated intra-amniotic inflammation.

A vaginal IL-6 of 2500 pg/mL threshold had 53% sensitivity, 89% specificity, 63% PPV, 85% NPV, in detection of AF microbial invasion, while it had 74% sensitivity, 91% specificity, 67% PPV and 94% NPV in detection of intra-amniotic inflammation, and 100% sensitivity, 90% specificity, 57% PPV, and 100% NPV in detection of microbial associated intra-amniotic inflammation [26].

Eleje et al. [5] found the IL-6 bedside test had 97.5% sensitivity, 87.9% specificity, and 93.2% accuracy in diagnosing chorioamnionitis in women with PROM, and it had 100% sensitivity, 91.3% specificity, and 95.8% overall accuracy in diagnosing chorioamnionitis in women with PPROM (< 37 weeks).

Abdelazim et al. [20] found the IL-6 in CVS had 90.7% sensitivity, 91.0% specificity, 87.5% PPV, 93.4% NPV, and 90.9% overall accuracy in detecting chorioamnionitis.

Chaemsaithong et al. [10] found the AF IL-6 at 745 pg/mL threshold had 93% sensitivity, 91% specificity and a positive likelihood ratio of 10 in detecting AF inflammation.

This study concluded that the IL-6 bedside test is an accurate, non-invasive bedside test with 98.6% sensitivity, 94.7% specificity, 97.3% PPV, 97.3% NPV, and 97.3% overall accuracy in detecting chorioamnionitis. The IL-6 bedside test had significantly higher sensitivity, specificity, NPV, and overall accuracy than the clinical and laboratory parameters of chorioamnionitis.

Abdelazim et al. [20] also concluded that the IL-6 in CVS is a sensitive, non-invasive marker in detecting neonatal infection, and chorioamnionitis.

In addition, Musilova et al. [26] concluded that vaginal IL-6 is a rapid, non-invasive, and inexpensive test for detecting intra-amniotic inflammation and/or microbial-associated intra-amniotic inflammation with good specificity, and NPV.

The high accuracy of the IL-6 bedside test in detecting chorioamnionitis in this study can be explained by the ability of IL-6 bedside test to detect IL-6 in CVS at three different thresholds [IL-6 low (0.1 ng/mL), IL-6 medium (0.25 ng/mL), and IL-6 high (5 ng/mL)].

This study was the first prospective comparative double blinded study (consultant decided TOP, and histopathologist) conducted to evaluate the accuracy of IL-6 bedside test in detecting chorioamnionitis in women with PPROM.

Women refused to participate and/or give consent, and shipping of kits from the manufacturer to the study place were the limitations faced during the study.

The accuracy of IL-6 bedside test in diagnosing chorioamnionitis should be confirmed in future studies including the neonatal outcome following chorioamnionitis.

CONCLUSIONS

The IL-6 bedside test is an accurate, non-invasive bedside test with 98.6% sensitivity, 94.7% specificity, 97.3% PPV, 97.3% NPV, and 97.3% overall accuracy in detecting chorioamnionitis. The IL-6 bedside test had significantly higher sensitivity, specificity, NPV, and overall accuracy than the clinical and laboratory parameters of chorioamnionitis.

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Conflict of interest

Authors declare no conflict of interests in relation to this study.

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