The Role of Il6 in Spontaneous Preterm Labour

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Abstract

Objective: Preterm birth (PTB) and Preterm labour (PTL) (PTL is defined as 'regular uterine contractions, which result in cervical changes before 37 Week of pregnancy. The main cause of neonatal morbidity and mortality with 5-18% of pregnancies was the preterm labour. Interleukin-6 (IL-6) amniotic fluid is an important cytokine used to identify intra-amniotic inflammation and those at risk to imminent premature delivery in patients with elevated AF IL-6. However, results of the traditional measurement method (ELISA) are generally unavailable in time in order to inform care. The aim of this study was to establish if intra-amniotic inflammation and/or infectious patients and those intended to spontaneous pre-term delivery among women with preterm labour and intact membranes can be identified through a point of care (POC) test or lateral-flowimmunoassay for AF IL-6 concentration measurement.

Methods: In this study, one hundred and thirty-six singleton pregnant women who had symptoms of premature labor and amniocentesis were included. At the time of diagnosis, amniocentesis was carried out. In this study, the determination of AF (white blood cells, gram stain) was happened. By the results of AF culture, microbial invasion of the amniotic cavity (MIAC) was defined. Enzyme Linked Immunosorbent Assay (ELISA) and the lateral flow based immunoassay used to determineAF IL-6 concentrations. Define AF ELISA IL-6 as ≥ 2600 pg/ml as the primary result for intra- amniotic inflammation

Results: (1) The concentrations of AF IL-6 has been determined by a POC test with a specificity (91%), sensitivity (93%) and a positive likelihood ratio (10) where Intraamniotic inflammation identified with the threshold of 740 pg/ml; (2) The POC test and IL-6's ELISA are also used to identify patients at risk of acute placenta inflammation, MIAC and impending spontaneous preterm delivery.

Conclusion: Intra-amniotic inflammation in women who present subsequently with spontaneous delivery before 34 week of gestation or those who will present with preterm and intact membranes can be identified by POC AF IL-6 test. It can be achieved within 20 minutes – this has important clinicalimplications and opens up opportunities for early diagnosis and treatment of intra-amniotic infection / inflammation.

Keywords*: Interleukin-6, Preterm birth, Preterm labor, Neonatal mortality, Inflammation.*

Introduction

The leading cause of neonatal morbidity and mortality [2] can be considered preterm birth which affects on 5 – 18 % of pregnancies [1]. In the women who deliver preterm, one in four of them infected with an intraamniotic infection that is largely subclinical [3,4]. Inflammatory processes (that mediated Microbial associated preterm labour) involving production of cytokines such as interleukin IL-6 [5,6], IL-1 [7], IL-10 [8], matrix degrading enzymes [9], chemokines [6], tumor necrosis factor-alpha (TNF-α) [6,10] and other inflammatory-related proteins activate common parturition pathway [1]. Multiple studies showed that IL-6 amniotic fluid (AF) is superior to AF (glucose, Gram stain, white blood cell (WBC) counts) , or equal to proteomic markers for identification of the amniotic cavity intraamniotic and amniotic microbial invasions

(MIAC) [11]. In addition, the elevated concentrations of AF IL-6 , even if the amniotic cavity absence the demonstrable microorganisms, is associated with an increase risk of neonatal outcomes and adverse pregnancy in the context of preterm prelabor rupture of the membranes (preterm PROM) [12], preterm labor [13] and a short cervix [14]. The concentrations of AF IL-6 thereforehave both diagnostic and prognostic value.

The determination of AF IL-6 concentrations takes usually hours and results often cannot be made available on time in order to inform clinical decisions. In adult and neonatal sepsis [15] aswell as in other inflammation-related conditions [16] , there was widely used a POC (lateral flow- based immunoassay) test. Recently, these tests were applied in obstetrical applications. In the pilot study our group has found that AF IL-6 levels determined through POC tests correlated strongly with those measured through conventional immunosorbent (ELISA) (Spearman's $\rho = 0.92$) [17]. In addition, our group has shown strong correlations. In addition, the POC IL-6 test results may identify preterm PROM patients intended for preterm delivery and/or acute histological chorioamnionitis [18].

In the present study determined by a POC test, we investigate whether AF IL-6 concentrations are able to identify patients (with intact membranes and preterm labour) who deliver spontaneously before term and/ or have intraamniotic infection and or inflammations, relative to the concentrations performance determined by conventional ELISA.

Materials and Methods

Study populations

A retrospective cohort study used to identify patients with intact membranes with a diagnosis of spontaneous preterm labor. If the following criteria were met, the patients could be included: (1) microbiological studies conducted for 20 to 35 weeks of transabdominal amniocentesis (2); available AF for microbiological research performance (3) singleton gestation; and (4) neonatal results known. Patients who had a fetus with structural or chromosomal abnormality or they had placenta previa, were excluded. Patients diagnosed with preterm labor associated with intact membranes, were told by their treating doctors about the potential value of microorganisms for AF identification. For research reasons outside of the clinical studies, women who agreed to undergo an amniocentesis were asked to donate AF. The doctor in charge of the furthertreatment of these patients. All patients received informed consent in writing and the use of clinical data and biological specimens were approved.

Samples and biological analyzes

To the clinical laboratory for genital mycoplasma and (anaerobic, aerobic bacteria) and in a syringe with a capped sterile, AF was transported. The centrifuge of AF, that is not required for clinical assessment, was for 15 min at 4 °C and stored at −75 °C until analysis. The assessment was also carried out soon after gram stain, glucose, WBC count and AF were collected. To know if there is intraamniotic inflammations and /or infection, the concentrations of AF IL-6 needed and by ELISA was determined.

Clinical definitions

Preterm labor was diagnosed in patients with cervical changes involving at least two regular uterine contractions every 10 minutes, related to gestational age from 20 to 36 6/7 weeks. Acute histologic chorioamnionitis was diagnosed with the above criteria [19]. Funisitis was diagnosed by the use of previously reported criterion for infiltration by neutrophils in walls of the umbilicus or Wharton jelly [20]. When the AF IL-6 concentration was ≥2600 pg/ml (≥2.6 ng/ml), that determine by ELISA, Intra-amniotic inflammation has been diagnosed [21]. Based on the results of AF culture, MIAC was defined. The combination of intra-amniotic inflammation and MIAC was defined as intra-amniotic infection.

IL-6 concentrations and analyzing it by AF samples

In the case of AF IL-6 concentrations (pg/ml), the Enzyme Linked Immunosorbent Assay and lateral immuno-assay POC tests were both determined. The immunoassays from R&D Systems for ELISA

have been used to determine AF IL-6 concentrations (Minneapolis, MN). A lateral flow-based immunoassay test POC was used to determine AF IL-6 concentrations (pg/ml). ELISA [6,11]and POC immunoassay details and performance have been described previously [17]. For IL-6 POC tests, the intra-assay variation coefficients and inter are 12.1% and 15.5% respectively.

Study outcomes

The main results of this study are intra-amniotic inflammation and positive AF culture. While Spontaneous preterm (24 hour, 48 hour and 7days admission), acute inflammatory placental lesions (acute histologic chorioamnionitis and / or acute funisitis) with spontaneous preterm delivery (<28 week and <34 week of gestation) are considered the secondary results. The relation between acute chorioamnionitis histologically and amniotic fluid IL-6 concentrations were examined in 60 patients administered three days after amniocentesis. In this interval, a significant temporal relation between placental pathology and the amniocentesis results has been maintained.

Statistical Analysis

In order to evaluate normality in arithmetic data distributions, the Kolmogorov–Smirnov test used. Kruskal–Wallis and Mann–Whitney U tests were performed to compare the groups of arithmetic variables. Chi-square or Fisher's exact test was used for comparisons of the categorical variable. SPSS 19 (IBM Corp., Armonk, NY) and SAS 9.4 were used for statistical analysis (Cary, NC). Statistically significant was a p value <0.05.

Results

Characteristics of study populations

In this study, 136 women have been included with preterm labour with intact membranes. In Table 1, The clinical features are listed. The prevalence was nearly 16% (23/136) for MIAC and nearly 44% (60/136) for intra-amniotic inflammation. Spontaneous preterm deliveries were reported in most participants, nearly 22.7% (31/136) for < 28 weeks, 54.1% (74/136) for < 34 weeks and 64.2% (87/136) for < 37 weeks. In 24 hr, 48 hr, and 7 days, spontaneous delivery ratesranged between 33.7% (46/136), 43.5% (59/136) and 47.7% (65/136) respectively. In amniocentesis, the median gestational age was 30.8 weeks (27–32.4). 57.2% (31/54) of the 54 women with an acute histological chorioamnionitis and a large number of funisitis were diagnosed within 3 days after amniocentesis and placenta pathology reports [67.8% (21/31)].

Table 1. ' Study populations' clinical features or characteristics

Table 1. Clinical characteristics of the study population.

Characteristic	Median (interquartile range) or percent ($n = 136$)
Maternal age (years)	24 (20–29)
Nulliparity	33.8% (46/136)
Prior preterm delivery	37.5% (51/136)
Gestational age at amniocentesis (weeks)	30.9 (27–32.4)
Amniotic fluid glucose (mg/dl)	24 (17–30.8)
Amniotic fluid white blood cell (cell/m^3)	1.5 (0–13)
Microbial invasion of the amniotic cavity (%)	16.2% (22/136)
Intra-amniotic inflammation (ELISA IL-6 $\geq$ 2600 pg/ml) (%)	44.1% (60/136)
Gestational age at delivery (weeks)	33.3 (28.2–36.9)
Interval from amniocentesis to delivery (d)	8 (1–36.8)
Spontaneous deliver within one day after amniocentesis (%)	33.8% (46/136)
Spontaneous deliver within two days after amniocentesis (%)	43.4% (59/136)
Spontaneous deliver within seven days after amniocentesis (%)	47.8% (65/136)
Spontaneous delivery at <28 weeks of gestation (%)	22.8% (31/136)
Spontaneous delivery at <34 weeks of gestation (%)	54.4% (74/136)
Spontaneous delivery at <37 weeks of gestation (%)	64% (87/136)
Acute histologic chorioamnionitis (%)*	57.4% (31/54)
Acute funisitis (%)*	38.9% (21/54)
Acute inflammatory lesions of placenta (%)*	57.4% (31/54)

The data presented as % (*n*) or median. Inflammatory lesions of placenta acutely include acute chorioamnionitis histologically and acute funisitis which included only patients who had intervalfrom amniocentesis to delivery < 4 d (n= 58).

In Table 2, the microorganisms identified by culture AF, gestational aging at delivery, IL-6 levels (by ELISA and POC), inflammatory AF and placental lesion type or absence of acute inflammation in MIAC women are listed. Ureaplasma urealyticum, which was found in 18 percent (4/22) of these women, was the most often identified microorganism.

Table 2. Inpatients with microbe invasion of the cavity using cultivation techniques, clinical characteristics, inflammatory amniotic fluid response, and acute placental inflammatory lesions.

Table 2. Clinical characteristics, amniotic fluid inflammatory response and acute inflammatory placental lesions in patients with microbial invasion of the amniotic cavity using cultivation techniques.

No.	Organisms	GA at delivery (weeks)	AF glucose (mg/dl)	AF WBC (cell/mm^3)	ELISA IL-6 (pg/ml)	Point of care IL-6 (pg/ml)	Acute histological chorioamnionitis	Acute funisitis
1.	*Prevotella* spp., *Enterococcus faecalis*	25^{+1}	10	1	52 637	3208	No	No
2.	*Mycoplasma hominis*	33	1	420	172 301	4613	N/A	N/A
3.	*Ureaplasma urealyticum*	28^{+6}	13	180	9433	10 000	Acute chorioamnionitis	No
4.	*Candida albicans*	26^{+3}	10	2160	201 261	4448	Necrotizing chorioamnionitis	No
5.	*Streptococcus agalactiae*	25	10	4	93 638	3575	Necrotizing chorioamnionitis	No
6.	*Candida albicans, Lactobacillus* spp.	33^{+1}	10	43	200 626	3554	Acute subchorionitis	No
7.	*Haemophilus influenza*	30^{+6}	10	40	92 063	6467	Necrotizing chorioamnionitis	Necrotizing funisitis
8.	*Fusobacterium* spp., Gram-negative bacilli	21^{+6}	19	1564	317 655	6228	Subchorionic microabscesses	Necrotizing funisitis
9.	Gram-negative bacilli	21^{+1}	20	66	242 699	5934	Subacute chorioamnionitis	Umbilical arteritis
10.	*Streptococcus agalactiae*	25^{+2}	19	5	248 889	8208	Acute chorioamnionitis	Umbilical arteritis
11.	Gram-positive cocci	22^{+5}	10	125	470 626	5540	Necrotizing chorioamnionitis	Umbilical arteritis
12.	*Fusobacterium* spp., Gram-negative bacilli	28^{+1}	1	22	301 426	3996	Acute chorioamnionitis	Umbilical arteritis
13.	*Ureaplasma urealyticum*	33	10	500	85 962	4628	Acute chorioamnionitis	Umbilical phlebitis/chorionic vasculitis
14.	*Streptococcus anginosus, Streptococcus mitis*	22^{+6}	10	10	73 254	7246	Acute chorioamnionitis	Umbilical phlebitis/chorionic vasculitis
15.	*Bacteroides* spp., *Mobiluncus* spp., *Clostridium sporogenes*	22^{+4}	10	295	517 846	4748	Necrotizing chorioamnionitis	Umbilical phlebitis/chorionic vasculitis
16.	*Ureaplasma urealyticum*	39^{+2}	19	2	1274	155	No	No
17.	Gram-negative bacilli	26^{+5}	N/A	610	1779	10 000	N/A	N/A
18.	*Streptococcus* spp., *Gemella morbillorum*	31^{+6}	10	1920	741	6796	Necrotizing chorioamnionitis	Umbilical arteritis
19.	*Candida albicans*	32^{+4}	10	1292	96 334	4252	Acute chorioamnionitis	Necrotizing funisitis
20.	*Staphylococcus capitis*	28^{+6}	20	24	360 503	4374	Subacute chorioamnionitis	Umbilical arteritis
21.	*Mobiluncus* spp.	32	10	570	76 888	8144	Acute chorioamnionitis	Umbilical phlebitis/chorionic vasculitis
22.	*Ureaplasma urealyticum*	34^{+3}	24	0	244	60	Acute subchorionitis	No

N/A: results were not available: WBC, white blood cell count; AF, amniotic fluid: acute subchorionitis/chorionitis = acute histologic chorioamnionitis stage 1; acute chorioamnionitis = acute histologic chorioamnionitis stage 2; necrotizing chorioamnionitis and subacute chorioamnionitis = acute histologic chorioamnionitis stage 3: subchorionic microabscesses = severe acute histologic chorioamnionitis; umbilical phlebitis/chorionic vasculitis = acute funisitisstage 1; umbilical arteritis = acute funisitis stage two; necrotizing funisitis = stage three acute funisitis.

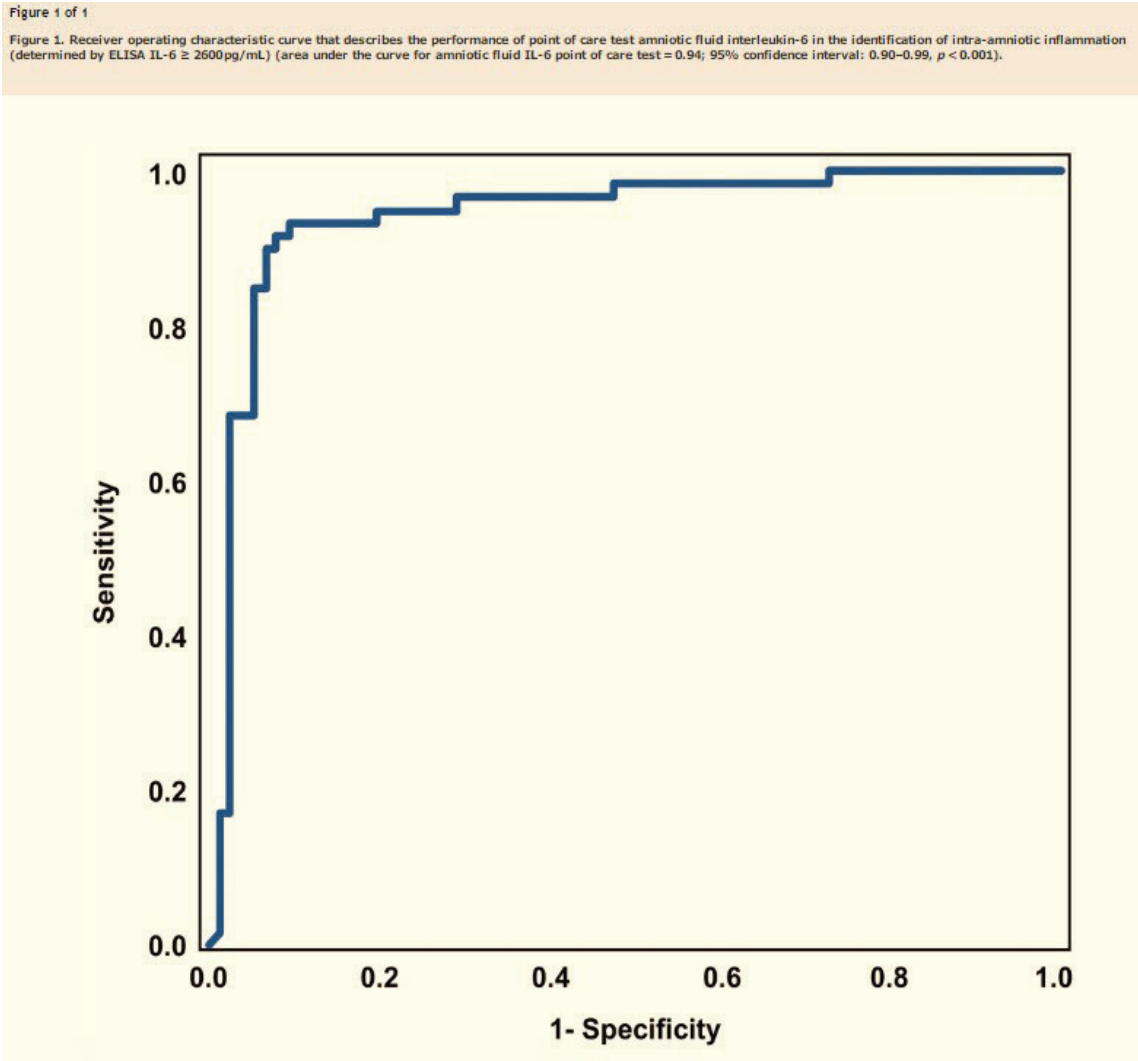

Figure 1. Characteristic curve of the operating receiver describes the performance of an amnioticFluid Interleukin-6 test in intra-amniotic inflammation identification (the area under curve for amniotic fluid IL-6 point =0.93; 96% confidence interval: 0.91–0.98, P<0.002).

The diagnosis of an AF IL-6 POC test to identify the inflammation of the intraamniotic A threshold of = 745 pg/ml was selected for the POC test after inspecting a recipient operationalcharacteristic curve to identify an intraamniotic inflammation [zone of curve = 0.94 (0.90–0.99)].(Figure 1). The POC test was given a sensitivity of 93% and a specialty of 91% in Table 3 lists.

The diagnostic performance of an AF IL-6 POC test for the identification of MIAC and acute inflammatory lesions of placenta

Table 3 shows that the POC test performance was equivalent to conventional ELISA when identifying MIAC and placental lesion patients in line with acute inflammation. 18.2% (4/22) of MIAC patients showed negative results for ELISA IL-6 (Table 2). In two of these four patients, however, the POC AF IL-6 was raised. One of those patients with acute histological chorioamnionitis and funisitis implies a real intraamniotic infection. A placental pathology reportwas not provided to the other patient. Note, the potential for a contamination is suggested by one of two patients who had AF IL-6 negatives in both trials (POC and ELISA) delivered at the term of the trial and had not placental lesions consistent with acute inflammation.

The identification of preterm delivery The AF IL-6 POC test

In **Table 3**, the tests for women spontaneously deliveries are presented with Point of care test and Enzyme Linked Immunosorbent Assay AF IL-6. Table 2. Both tests had positive probability equivalents in identifying patients who had spontaneous preterm delivery within one of the days of amniocentesis or patients who spontaneously delivered after a gestation of less than 28 weeks. Each one had marginally a greater sensitivity and specificity than ELISA for the POC test in determining women who would spontaneously deliver within two or seven days of amniocentesis. In comparison with ELISA's results the sensitivity for spontaneous preterm delivery was slightly higher at less than 34 weeks of gestation, while the specificity was slightly less. However, confidence intervals in the assessment of the diagnostic performance of the POC test have overlapped the ELISA test, statistic equivalent performance in the assessment of the risk of spontaneous premature delivery.

Discussion

The main findings from the study: (1) The POC-determined AF-IL-6 concentrations are highly sensitive (93%) and are specific (91%) to identify intra-amniotic inflammation with a 745 pg/mL threshold and (2) IL-6 determination by POC test and ELISA was performed similarly in patients identifications with acute inflammatory lesions of placenta, MIAC and the patient with intact membrane and preterm labour at risk of spontaneous preterm delivery.

AF IL-6 POC test for intra-amniotic inflammation identification and imminent preterm delivery Preterm labor and other adverse effects are at greater risk of intraamniotic inflammation, as demonstrated by compelling evidence without identifiable microorganisms [13]. In patients with preterm labor and intact membranes, sterile intra-amniotic inflammation, an inflammatory process in which neither culture nor molecular methodology can be observed, has previously been demonstrated to be more prevalent than intra-amniotic, microbial inflammation. [22], preterm PROM and asymptomatic sonographic short cervix [14]. We have also shown that sterile inflammation intraamniotic is connected to unhealthy pregnancy; hence intraamniotic inflammation is important [22, 14].

In this study, we have shown that the point of care AF IL-6 test is highly sensitive and specific to identify spontaneous premature delivery and intraamniotic inflammations. The results of the POC test are compared with AF IL-6 concentrations determined by ELISA in the identification of infection-inflammation-related obstetric outcomes, but they could be determined within 20 minutes. Therefore, contrary to conventional ELISA, the POC AF IL-6 results can be available on time for clinical decisions, similarly to an MMP 8 rapid matrix test which has demonstrated that patients with preterm labor and intact membranes with >80 percent susceptibility and >90 percent specificity have an intraamniotic infection or inflammation [23]. In addition, the MMP-8 test has been shown to be useful in identifying intra-amniotic inflammation in preterm PROM, MIAC in preterm delivery risk patients, and funisitis in preterm delivery patients.

Interestingly, six out of seven patients with POC and ELISA negative results had spontaneous early (<34 weeks) preterm delivery within a period of two days after amniocentesis. This suggests that the POC test provides additional risk information beyond the standard ELISA tests. It should also be noted that two out of four POC negative and ELISA positive which at term delivered, one of whom did not have acute inflammation with placental lesions and the result was positive (2609 pg/ml). In the previous study, we showed that the concentrations of AF IL-6 that determined by POC test were 30 percent less on average than those established by conventional ELISA. Therefore, it is no surprise that the POC selected the lower AF IL-6 cut-off for intra amniotic

inflammation (THI) patients (THI 745 pg/ml) in this study). Kacerovsky and others suggested a higher reduction (1000 pg/ml) to detect MIAC in a study that used the same test for AF IL 6 levels among preterm MIAC women or the combination of MIAC with acute histological chorioamnionitis. Other POC test researchers reported a high negativity of IL-6 detection predictive value in vaginal fluid in women with preterm PROM, comparable to that found in ourstudy (97.6 percent versus

94.4 percent) [23]. However, our study showed more positive predictive value than the concentration of IL-6 vaginal fluid POC test (88.9 percent versus 50 percent). Using POC IL-6 in vaginal fluid for pregnancy results has been reported by Vousden et al. in asymptomatic high risk patients with preterm birth [18]. A cut off of 56 pg/ml had 81 percent sensitivity and 65 percent specificity for the vaginal fluid IL-6 concentration for identifying people who were given under 28 weeks of gestation [18]. The diagnostic performances in this study are somewhat lower than POC AF IL-6. In line with the risk/benefit ratios for specific actions, the optimal cutoff value is to be determined.

Strengths and Limitations

The study strengths include: - (1) Test POC for the purpose of informing treatment was not used and (2) including a group of patients with preterm labour with intact membrane instead of patient with preterm prelabour rupture of membranes who have high prevalence of infection and/or inflammation. One constraint is the use of cultivation techniques to identify amniotic cavity microorganisms, therefore, it may not be possible to detect non-cultural bacteria that could have been identified using molecular microbiological techniques.

Conclusions

Intra-amniotic inflammation can be identified by a POC AF IL-6 test as determined by ELISA in women with premature labour and intact membranes and also by equivalently identifying thosewho deliver spontaneously before the term subsequent to this test. Further studies are necessary to determine whether the results of POC AF IL-6 inform sufficient therapeutic decisions to improve pregnancy results in patients of this type.

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Ethical Clearance: This study is ethically approved by the Institutional ethical Committee.

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