JEMTAC
Journal of Emergency Medicine Trauma & Acute Care
A PEER REVIEWED JOURNAL

OPEN ACCESS

Conference paper

The measurement of hypoxia-inducible factor-1α and interleukin-6 levels in pregnancies with threatened preterm labor

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https://doi.org/10.5339/jemtac.2024.cism.6

Submitted: 25 October 2023
Accepted: 10 December 2023
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ABSTRACT

Background: Preterm birth has a significant impact on neonatal health and the healthcare system as it increases neonatal morbidities and mortality rates. Interleukin-6 is one of the pro-inflammatory cytokines that can trigger the production of chemokines and uterine activation proteins, consequently causing uterine contraction and subsequent cervical change. Hypoxia-inducible factor-1α plays a pivotal role in the hypoxic adaptive response of tissues. It has been suggested that hypoxia has a vital role in the initiating and/or strengthening of uterine contractions, proposing that hypoxia-inducible factor-1α could be involved in this process.

Aim: Investigate whether serum concentrations of interleukin-6 and hypoxia-inducible factor-1α would differ between women with threatened preterm labor who deliver prematurely and those who continue their pregnancy till term.

Patients and Methods: The case-control study was extended over 12 months, including women in their 28th to 35th weeks of gestation and with a single viable fetus. The women were divided into three groups: women with threatened preterm labor who delivered prematurely (27 women), women with threatened preterm labor who continued their pregnancy till term (23 women), and women with matching gestational age and uncomplicated pregnancies (the controls = 40 women). The serum levels of interleukin-6 and hypoxia-inducible factor-1α were measured by Enzyme-linked immunosorbent assay.

Results: The mean values of interleukin-6 and hypoxia-inducible factor-1α were significantly different between the study groups (p-value <0.001 by one-way ANOVA), where women with threatened preterm labor who delivered prematurely had higher serum values of interleukin-6 and hypoxia-inducible factor-1α (124.5 and 102.4, respectively) than the women with threatened preterm labor who continued their pregnancy till term (71.0 and 55.2, respectively), and than the women in the control group (55.3 and 50.0, respectively). There was a significant negative statistical correlation between the values of interleukin-6 and hypoxia-inducible factor-1α and the timing of delivery (R = -0.786 and -0.644, respectively, p-value < 0.001).

Cite this article as Al-mashhadani SAM, Aljanabi HH, Hassan IF, Mahdi RD. The measurement of hypoxia-inducible factor-1α and interleukin-6 levels in pregnancies with threatened preterm labor. *Journal of Emergency Medicine, Trauma & Acute Care*. 2024(1):6 https://doi.org/10.5339/jemtac.2024.cism.6

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Conclusions: Both interleukin-6 and hypoxia-inducible factor-1α serum concentrations can help differentiate pregnant women who are genuinely in preterm labor from those who have preterm contractions but are not at risk of imminent delivery.

Keywords: preterm labor, interleukin-6, hypoxia-inducible factor-1α

INTRODUCTION

Preterm delivery is defined as the delivery of a baby before 37 completed weeks of pregnancy.[1] Clinical criteria such as regular uterine contractions followed by a change in cervical dilatation, effacement, or both characterize preterm labor.[2] PTL can be classified into three categories: extremely early preterm (before 32 weeks), early preterm (32 0/7 to 33 6/7 weeks), and late preterm (34 0/7 to 36 6/7 weeks).[3]

The worldwide rate of PTL was estimated to be 10.6%, with 80% of all cases occurring in South Asia and sub-Saharan Africa.[4,5] Preterm birth remains a serious public health problem. Babies born before 37 weeks of gestation are at an increased risk for neonatal morbidity and mortality; preterm birth is the direct cause of 35% of all neonatal deaths worldwide.[6] Survivors remain at high risk for complications in early childhood,[7,8] adolescence,[9,10] and adulthood,[11,12,13] where many of them face a lifetime of disabilities, among other issues.[14]

In general, approximately 50% of preterm births are caused by spontaneous preterm labor, about 25% are caused by preterm pre-labor rupture of membranes (PPROM), and the remaining 25% of preterm births are intentional (iatrogenic), medically indicated by maternal or fetal complications.[15]

Spontaneous PTL is not a single disease entity but is a syndrome that can be induced by various factors, such as intrauterine infection, cervical pathology, multiple pregnancies, hydramnios, uterine fundal abnormalities, progesterone deficiency, vascular alterations (uteroplacental ischemia, decidual hemorrhage), maternal and fetal stress, allergic phenomena, and probably other several unknown factors.[16-20] All the etiologies mentioned above can lead to the pathological activation of decidua/fetal membranes, causing uterine contractility, cervical ripening, and rupture of membranes. These events represent labor's "common pathway" and could be initiated days or weeks before labor onset.[20]

Interestingly, inflammation was a key trigger of these events, whether in term or preterm labor. Thus, the onset of inflammation seems to be a common denominator initiating term and preterm labor.[21] The current understanding of this process is that the switch of the myometrium from a quiescent to a contractile state is accompanied by a shift in signaling between anti-inflammatory and pro-inflammatory pathways, including chemokines (interleukin-8), cytokines (interleukin-1 and -6), and contraction-associated proteins (oxytocin receptor, connexin 43, prostaglandin receptors).[22] Progesterone maintains uterine quiescence by repressing the expression of these genes.[22]

Biomarkers are substances that are measured in a biological sample. For predicting PTL, different markers are tested in various biological fluids, such as cervicovaginal fluid (CVF), amniotic fluid, urine, blood serum, and saliva.[23] It has been shown that different pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) are involved in both term and preterm labor. The mentioned cytokines trigger the production of uterine activation proteins and chemokines, causing uterine contractility and subsequent cervical change. Hence, these markers warrant investigation as potential screening tools for PTL.[24-27]

Interleukins (IL) are a type of cytokines. Cytokines are small (15–20 kDa) and short-lived proteins essential in autocrine, paracrine, and endocrine signaling.[28] The IL-6 cytokine family consists of IL-6, IL-11, IL-27, and leukemia inhibitory factor. IL-6, the most important pro-inflammatory cytokine in this family, plays a critical role in the inflammation cascade.[19] IL-6 is a multifunctional, pleiotropic cytokine that regulates immune responses, acute-phase responses, hematopoiesis, and inflammation. It is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to different stimuli (IL-1, IL-17, and TNF-α) during systemic inflammation. IL-6 promotes T-cell proliferation, B-cell differentiation and survival, and plasma-cell production of IgG, IgA, and IgM.[20]

The levels of IL-6 in the blood of healthy individuals are in the range of 1–5 pg/mL. IL-6 levels increase several thousand-fold during inflammatory states and can even reach levels of several μg/mL under lethal septic conditions.[29]

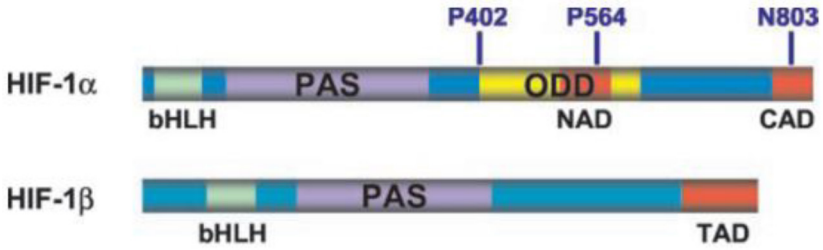

Figure 1. Schematic representations of HIF-1α and HIF-1β.

Hypoxia-inducible factor-1 (HIF-1) is a heterodimer composed of a 120-kDa HIF-1α subunit and a 91–94-kDa β subunit, both of which are members of the basic helix-loop-helix (bHLH)-PAS family. PAS is an acronym for the three members first recognized (Per, ARNT, and Sim).[24,30]

Figure 1 depicts the different schematic representations of HIF-1. HIF-1α is required for heart development, chondrogenesis, and bone formation.[25] The HIFs are produced throughout all aspects of normal placental differentiation, growth, and function during the first trimester at the physiologically low oxygen level and mid and late gestation when adequate maternal blood supply and placental oxygenation occur.[25] Placentation develops in a low-oxygen environment during early pregnancy before ten weeks of gestation when there is limited blood flow into the intervillous space.[26]

HIF-1α can be upregulated in pathological pregnancies under placental hypoxia/ischemia or inflammation oxidative dependent pathways, as shown in eclampsia.[27,31] Previous studies found that pregnant women with pre-eclampsia had high blood levels of HIF-1α compared to normal healthy controls.[26,32] Clinical studies have also shown the upregulation of HIF-1α in trophoblasts of patients with missed abortions.[33,34]

Aim

This study aimed to investigate whether serum concentrations of interleukin-6 and hypoxia-inducible factor-1α would differ between women with threatened preterm labor who will deliver prematurely and those who will continue their pregnancy till term.

PATIENTS AND METHODS

The case-control study lasted 12 months, from March 1, 2021, to February 28, 2022. Women were recruited from the obstetrical department of Al-Yarmmok Teaching Hospital, Al-Yarmouk Community Health Care Center, and Al-Dakhiliya Health Care Center. A total of 90 women were included: 50 women with threatened PTL and 40 women with healthy, normal pregnancies. They were divided into three groups:

- **Preterm delivery (PD):** Included 27 women with threatened PTL who did not continue to term and delivered before 37 weeks of gestation. All women in the PD group had delivered within 72 hours after admission.
- **Term delivery (TD):** Included 23 women with threatened PTL who continued their pregnancy and delivered after 37 weeks of gestation.
- **Control group:** Included 40 women with healthy, normal pregnancies.

The following flow chart (Figure 2) displays the classification of the study population.

During their antenatal visits, the women in the control group were recruited from two healthcare centers, namely Al-Yarmouk Community Healthcare Center and Al-Dakhiliya Healthcare Center. Women from the PD and TD groups were recruited from the obstetrical department of Al-Yarmmok Teaching Hospital with the diagnosis of threatened preterm labor, which was defined by the following criteria:

1. Four or more regular uterine contractions in 20 minutes, or six or more are present in one hour, with each contraction lasting more than thirty seconds.
2. Less than 2 cm of cervical dilatation.
3. Less than 80% of cervical effacement.

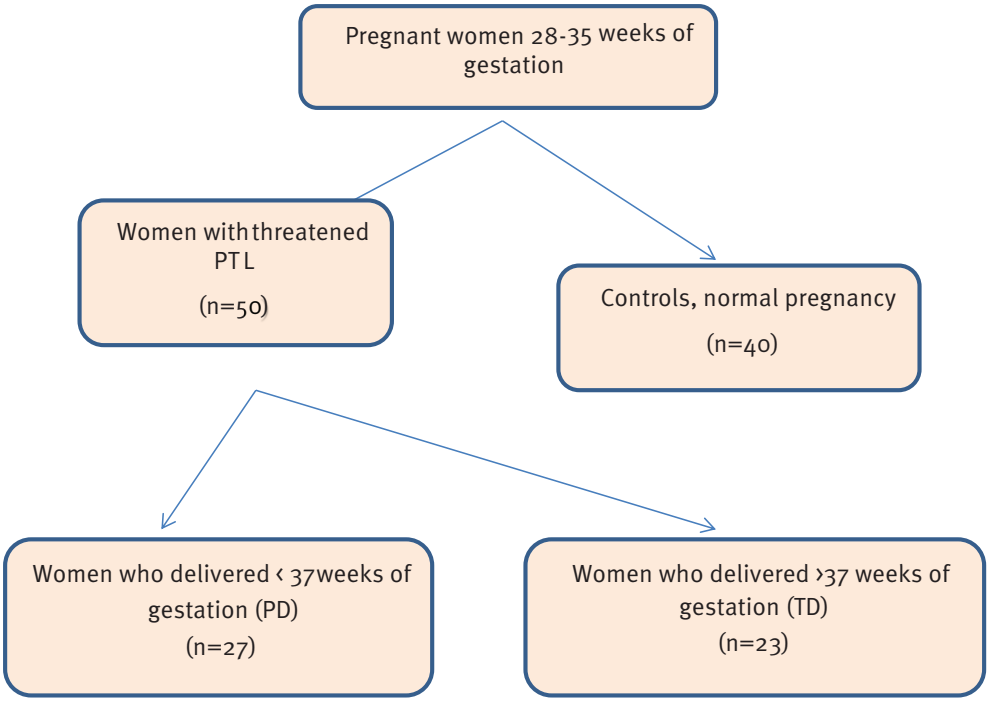

Figure 2. Flowchart for the study population.

The inclusion and exclusion criteria were set as follows:

Inclusion Criteria

- Women aged between 18 and 40 years old.
- In their 28th to 35th weeks of gestation, carrying single-viable fetuses.

Exclusion Criteria

1. Pregnant women with chronic systemic diseases (diabetes mellitus, gestational diabetes, hypertension, pre-eclampsia, cardiac diseases),
2. Inflammatory diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel diseases…etc),
3. Evidence of infection,
4. Rh iso-immunization,
5. Anemia (hemoglobin <10 g/L),
6. Placental abruption,
7. Premature rupture of membrane,
8. Polyhydraminous,
9. Uterine anomalies,
10. Fetal anomalies,
11. Intrauterine growth restriction (IUGR),
12. Using anti-inflammatory medication such as aspirin and steroids.

History

Women's age, parity, history of abortion, LMP, past obstetrical, past medical, past surgical, and drug histories were recorded. GA was estimated depending on the LMP in women with regular menstruation and/or first-trimester ultrasound scans.

Physical Examination

Blood pressure measurement, pulse rate, temperature, height, and weight were recorded. BMI was calculated using the following equation: BMI = weight/square height in meters. Abdominal examination: for assessing fundal height, fetal lie and presentation, and the presence of uterine

contractions. Pelvic examination: for the cervical dilatation and effacement, presentation, and station of the fetus was done for the women in the case group.

Diagnostic Procedures

- Ultrasounds were performed to confirm fetal viability, GA, and absence of fetal anomalies and to assess fetal lie and weight, amniotic fluid, placenta, and cervical length measurement.
- An electronic cardiotocogram (CTG) was used to detect the number and duration of uterine contractions, fetal basal heart rate, acceleration, and deceleration, confirming the diagnosis of threatened PTL.
- Urine samples were taken for urine analysis.
- Blood samples were collected to assess the blood group and Rh, complete blood count, biochemical analysis, and measurement of HIF-1α and IL-6.

Measurement of HIF-1α and IL-6

Blood samples were withdrawn from the women at admission before interference. Five cc of blood was collected in plain tubes and placed in a centrifuge after 30 minutes of collection to allow clots formation. It was then centrifuged at 4000 rounds per minute for 10 minutes to separate the serum. After separation, serum was stored at -80°C until the time of the analysis.

The serum levels were determined by the Enzyme-linked Immune Sorbent Assay (ELISA) procedure, following the manufacturer's instructions (Sunred Biotechnology Co., Aviscera Bioscience Inc., Shanghai, China; catalog no.: 201-12-0091 for IL-6 and 201-12-0423 for HIF-1α). Measurement of the absorbance was performed in a microplate reader at 450 nm. A standard curve was plotted from known concentrations vs. measured absorbances, and the HIF-1α and IL-6 levels were expressed as pg/mL.

Ethical Consideration

The Arab Board of Health Specializations' Supervising Committee approved the study idea. This study has also received approval from the health authorities at Al-Yarmouk Teaching Hospital, Al-Yarmouk Community Health Care Center, and Al-Dakhiliya Health Care. The purpose and scope of the study were explained to the participants, and they gave their verbal consent.

Statistical Analysis

The Statistical Package for Social Science Version 24 (SPSS 24) was used for data collection and statistical analysis. The normal distribution of the data was assessed using the Kolmogorov-Smirnov test. Data following normal distribution were presented as means and standard deviations (SD), and independent sample T-tests and one-way ANOVA were employed to test their statistical differences. For the correlation analysis, Pearson correlation was used. In cases where the data did not follow a normal distribution, the Kruskal-Wallis Test was applied to test the statistical differences. For the correlation analysis, the Spearman correlation was used. The Receiver Operating Characteristic (ROC) curve was used to calculate the cutoff value for the predicting PTL. The significance level (p-value) was set to be less than 0.05.

RESULTS

The study sample was divided into three groups: women with threatened preterm labor who delivered before 37 weeks of gestation (PD group), women with threatened preterm labor who delivered at term (TD), and women in the control group. All women in the PD group had delivered within 72 hours after admission.

There were no significant statistical differences in the mean maternal age, BMI, and GA at assessment between the three groups in the study, where the p-value was more than 0.05. GA at delivery had the only significant statistical difference between the study groups (p-value < 0.001). Regarding the obstetrical history, the number of gravidity and parity showed no significant statistical association with the delivery timing, with a p-value greater than 0.05. These findings are shown in Table 1.

The mean values of IL-6 and HIF-1α were significantly different between the study groups, with higher values observed in the preterm delivery group (124.5 and 102.4, respectively) and lower values found in the control group (55.3 and 50.0, respectively)—Tables 2 and 3 present these results.

Table 1. Comparison in demographic characteristics between the study groups.

Variable	PD (n=27)	TD (n=23)	Control (n=40)	P value
Age (years)	25.7 ± 5.2	26.5 ± 5.6	27.4 ± 5.3	0.45*
BMI (Kg/m2)	26.6 ± 3.1	27.5 ± 3.0	27.4 ± 2.9	0.50*
GA at assessment (weeks)	32.0 ± 2.1	32.2 ± 2.0	32.0 ± 2.0	0.93*
GA at delivery (weeks)	32.5 ± 2.2	37.6 ± 0.7	37.8 ± 0.7	< 0.001**
Primigravida	7 (25.9%)	4 (17.4%)	12 (30.0%)	0.54***
Multigravida	20 (74.1%)	19 (82.6%)	28 (70.0%)	
Nullipara	15 (55.6%)	11 (47.8%)	16 (40.0%)	0.45***
Multipara	12 (44.4%)	12 (52.2%)	24 (60.0%)	

*Significance was determined using one-way ANOVA.
**Significance was determined using the Kruskal-Wallis Test.
***Significance was determined using Pearson Chi-square.

Table 2. Comparison in IL-6 levels between study groups.

	IL-6 values (pg/ml)				
Group	Mean	SD	Min	Max	P value*
Preterm delivery (n=27)	124.5	28.2	67.5	183.5	< 0.001
Term delivery (n=23)	71.0	21.7	34.8	105.6	
Control (n=40)	55.3	21.5	20.4	97.8	

*Significance was determined using one-way ANOVA.

Table 3. Comparison in HIF-1α levels between study groups.

	HIF-1α values (pg/ml)				
Group	Mean	SD	Min	Max	P value*
Preterm delivery (n=27)	102.4	23.3	62.5	163.2	< 0.001
Term delivery (n=23)	55.2	13.7	35.6	89.2	
Control (n=40)	50.0	15.4	24.8	85.0	

*Significance was determined using one-way ANOVA.

Correlation Analysis

There was a significant negative statistical correlation between the values of IL-6 and HIF-1α and the timing of delivery (correlation coefficient R = -0.786 and -0.644, respectively, p-value < 0.001), indicating that lower values of IL-6 and HIF-1α were found in women who delivered at higher gestational age (GA). However, there were no significant correlations between IL-6 and HIF-1α levels and maternal age, BMI, parity, gravidity, and the GA at assessment in the three study groups, as shown in Table 4.

The distribution of IL-6 and HIF-1α values in the study groups according to GA at assessment is shown in Tables 5 and 6, and the distribution of IL-6 and HIF-1α values in the study groups according to GA at delivery is presented in Tables 7 and 8.

Table 4. Correlation analysis.

		IL-6	HIF1
Age	R	- 0.108	- 0.089
	P value	0.310	0.406
BMI	R	- 0.051	- 0.112
	P value	0.633	0.295
Parity	R	- 0.063	- 0.016
	P value	0.555	0.882
Gravidity	R	- 0.023	- 0.012
	P value	0.829	0.908
GA at assessment	R	- 0.257	- 0.138
	P value	0.075	0.196
GA at delivery	R	**- 0.786**	**- 0.644**
	P value	**< 0.001**	**< 0.001**

Table 5. Distribution of IL-6 values of the study groups according to GA at assessment.

		Mean IL-6 values (pg/ml)			
GA at assessment	**No. of women**	**Preterm delivery**	**Term delivery**	**Control**	**Total sample**
28	3	183.5	-	79.4	114.1
29	9	144.0	90.1	75.6	103.2
30	9	138.9	65.9	58.1	86.8
31	14	113.2	66.7	41.0	70.5
32	15	144.8	81.50	57.7	88.9
33	15	124.3	74.8	63.5	79.2
34	12	106.1	65.30	41.0	61.3
35	13	98.72	59.2	56.9	73.7

Table 6. Distribution of HIF-1α values of the study groups according to GA at assessment.

		Mean HIF-1α values			
GA at assessment	**No. of women**	**Preterm delivery**	**Term delivery**	**Control**	**Total sample**
28	3	118.3	-	46.9	70.7
29	9	106.0	53.2	61.5	73.6
30	9	123.9	47.1	49.9	73.9
31	14	107.3	60.9	47.0	70.5
32	15	104.2	51.9	49.4	64.8
33	15	104.8	62.8	48.1	64.3
34	12	93.3	57.9	53.6	64.2
35	13	81.9	51.1	46.1	61.4

DISCUSSION

Preterm birth represents a significant public health challenge, exposing neonates to an elevated risk of morbidity, mortality, and long-term disabilities.[6,14] Consequently, efforts have been focused on the screening and prediction of preterm labor (PTL) to enable early interventions for primary prevention through procedures such as cervical cerclage or progesterone administration. Secondary prevention

Table 7. Distribution of IL-6 values of the study groups according to GA at delivery.

		Mean IL-6 values (pg/ml)			
GA at delivery	No. of women	Preterm delivery	Term delivery	Control	Total sample
29	3	157.0	-	-	157.0
30	2	149.6	-	-	149.6
31	3	129.2	-	-	129.2
32	6	121.9	-	-	121.9
33	5	132.2	-	-	132.2
35	5	92.3	-	-	92.3
36	3	116.8	-	-	116.8
37	25	-	80.9	66.3	72.7
38	26	-	69.9	56.0	60.8
39	12	-	55.1	36.8	41.4

Table 8. Distribution of HIF-1α values of the study groups according to GA at delivery.

		Mean HIF-1α values			
GA at delivery	No. of women	Preterm delivery	Term delivery	Control	Total sample
29	3	117.6	-	-	117.6
30	2	123.3	-	-	123.3
31	3	100.7	-	-	100.7
32	6	111.8	-	-	111.8
33	5	100.6	-	-	100.6
35	5	88.3	-	-	88.3
36	3	82.8	-	-	82.8
37	25	-	55.8	50.0	52.5
38	26	-	51.2	50.3	50.6
39	12	-	64.9	49.4	53.3

strategies involve addressing the impact on newborns through corticosteroid administration for lung maturity and magnesium sulfate for neuroprotection.[35]

Prediction of PTL can be approached in two primary contexts: the first involves predicting PTL at a distant time from the onset of labor, aiming for prophylactic therapy (primary prevention). The second aims to predict preterm delivery in symptomatic women, distinguishing those genuinely in PTL from those with preterm contractions not at imminent risk (threatened PTL).[1]

In this study, the focus was on the second scenario for predicting PTL. The aim was to investigate whether interleukin-6 (IL-6) and hypoxia-inducible factor-1α (HIF-1α) could differentiate and potentially predict women with threatened PTL who would deliver prematurely from those delivering at term.

Comparing IL-6 and HIF-1α values between study groups revealed significant statistical differences. The preterm delivery group exhibited higher serum values of IL-6 and HIF-1α compared to the term delivery and control groups. IL-6 and HIF-1α levels negatively correlated with the delivery timing, decreasing with an increase in gestational age. Serum values above 92.9 pg/ml for IL-6 and 68.2 pg/ml for HIF-1α were identified as predictors of preterm delivery within 72 hours in women with threatened PTL. The sensitivity and specificity were greater than 88% for IL-6 and 92.6% and 88.9% for HIF-1α, respectively.

A study by Akkaya Firat et al. also explored the association between preterm delivery and serum IL-6 and HIF-1α levels in women diagnosed with threatened PTL. Their findings align with the current study, suggesting that elevated concentrations of IL-6 and HIF-1α may serve as biomarkers for

identifying true PTL in women with threatened premature labor. Cutoff points in their study were set at 49.2 pg/ml for both IL-6 and HIF-1α, with sensitivity and specificity values of 80.2%, 72.3%, 75.1%, and 75.5%, respectively, slightly lower than the cutoff points reported in the present study.[36]

Another study by Herrera-Muñoz et al. concluded that threatened PTL and preterm birth were associated with inflammatory changes on the maternal side. The study reported that serum IL-6 concentrations were higher in women with threatened PTL (the cases) than those with matched GA but not in labor (the controls) and those in the prodromal labor phase at term. The study also found a negative correlation between IL-6 concentrations and GA at birth, aligning with the results of the current study.[37]

Other studies examining the IL-6 levels in the amniotic fluid of women with spontaneous PTL concluded that elevated levels of IL-6 in the amniotic fluid could be a biomarker for predicting women at high risk for preterm birth.[38,39]

In the current study, IL-6 levels were observed to be positively correlated with levels of HIF-1α, consistent with the findings of the paper by Akkaya Firat et al.[36]

It has been hypothesized that PTL is strongly mediated by an inflammatory response.[21] IL-6, a pro-inflammatory cytokine, is implicated in both preterm and term labor, triggering the production of chemokines and uterine activation proteins, leading to uterine contraction and subsequent cervical changes. Moreover, IL-6 has been shown to induce oxytocin secretion in human uterine smooth muscle cells and increase prostaglandin E2 production from human amnion and decidual cells.[22]

Data have highlighted that HIF-1α is essential in the hypoxic adaptive response of tissues. Additionally, there is evidence suggesting that hypoxia plays a crucial role in the initiating and/or strengthening of uterine contractions, proposing the involvement of HIF-1α in this process. It has been suggested that contractions, through repeated metabolic and transcriptomic changes, can episodically reduce blood flow, resulting in recurrent hypoxic stress and triggering uterine contractions. Importantly, this mechanism is independent of the oxytocin.[40]

CONCLUSIONS

The results of the current study lead to the conclusion that both IL-6 and HIF-1α serum concentrations can aid in differentiating pregnant women who are genuinely in PTL from those who have preterm contractions but are not at risk of imminent delivery. This distinction would enable the obstetrician to take appropriate action, such as transferring patients to tertiary centers with intensive neonatal care units and administering corticosteroids for fetal lung maturity and magnesium sulfate for neuroprotection.

Recommendation

The present study recommends routinely measuring IL-6 and HIF-1α serum concentrations in women with threatened PTL at GA between 28 and 35 weeks as potential biomarkers for predicting preterm delivery. Further studies are essential to expand our understanding of the possible mechanisms underlying PTL and investigate additional possible biomarkers for its prediction.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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