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Evaluation of immunological cytokines among preterm and normal labor at AL-Najaf province

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Abstracts.

Human labour at term is a physiological event that involves a coordinated set of changes in the uterine tissues (the myometrium, decidua, and uterine cervix) over the course of a few days or weeks. The physiologic-inflammatory process of labour is influenced by a combination of endocrine and mechanical factors, and it is pathologically initiated by uterine stretch and bleeding, which causes a fetus to be expelled from the uterus. During the study period from April 2024 to December 2024, a total of 60 clinical samples were obtained from patients who attended Al-Zahraa and Al-Hakiem hospitals in Al-Najaf province. The specimens, 30 serum samples, were collected from patients with preterm labor, in addition to 30 serum samples obtained from normal labor. Human Enzyme-Linked Immuno-sorbent Assay (ELISA) Kits were used to measure the levels of progesterone, IL-1α, IL-1β, and MCP-1 in serum. Findings indicate that there are no significant differences (p-<0.05) in progesterone levels between preterm labour women and normal pregnant women, but there are significant differences (p-<0.05) in IL-α and IL-β levels between preterm labour women and normal pregnant women, as well as significant differences (p-<0.05) in MCP-1 levels (p-<0.05).

Key words: preterm labor, cytokines, hormones.

Introduction:

Labor is the physiologic-inflammatory process influenced by interaction between both endocrine and mechanical factors, and pathologically started with uterine stretch and bleeding by which a fetus is expelled from the uterus **(1)**. Labor at term may best be regarded physiologically as a release from the inhibitory effects of pregnancy on the myometrium rather than as an active process mediated by uterine stimulants. During pregnancy, the uterus is maintained in a state of functional quiescence (phase 0) through the action of various putative inhibitors, including progesterone, prostacyclin, relaxin, nitric oxide, parathyroid hormone–related peptide, corticotropin-releasing hormone, human placental lactogen, calcitonin gene–related peptide, adrenomedullin, and vasoactive intestinal peptide **(2)**.

Preterm labor (PTL), labor starting before 37 weeks of gestation, continues to be one of the most important causes of neonatal morbidity and mortality worldwide. With the perinatal care progressing, the natural growth rate has significantly declined, but preterm birth is still responsible for ~11% of global live births and is linked with severe long-lasting sequelae, including neurodevelopmental disabilities, development of respiratory distress syndrome, and a higher risk of death in infancy **(3)**. Various treatments have been

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studied to prevent preterm delivery, and one of the most promising is progesterone (3).

Progesterone is an important hormone for pregnancy to continue through promoting uterine quiescence, inhibiting cervical ripening, and suppressing myometrial contractions. The utility of vaginal and intramuscular progesterone has been explored as a technique to decrease the unacceptably high rate of preterm labor, particularly among patients with a history of spontaneous preterm birth or those with ultrasound–confirmed signs of arrested preterm labor. The results of randomised control trials show that progesterone replacement leads to a dramatic reduction in PTB risk, particularly in high-risk pregnancies (4).

Progesterone's immune-modulatory effect, in addition to its effects on T cells and T Helper cells have also been studied in recent research, particularly progesterone's effect on regulatory T cells (Tregs), which can potentially be responsible for preventing PTL (5). Even with these advancements, the precise manner through which progesterone exerts its preventive effects on preterm birth, particularly among women who previously had a preterm birth after arrest of labor, is an active area of research (6).

Although progesterone has been extensively investigated for treatment to prevent PTL, the involvement of other hormones, like Relaxin, is not clear. Relaxin is a peptide hormone mainly secreted from the corpus luteum during pregnancy. It plays a crucial role in the initiation processes that prepare the body for childbirth: softening of cervical tissue, connective tissue remodeling, and relaxation of pelvic ligaments (7). Whilst Relaxin, which is essential for myometrial quiescence in normal term labour, has a role in preterm labour, its function in this context is less certain. A few investigations indicate that Relaxin levels' dysregulation causes early cervical alteration, which results in preterm labor. Furthermore, the involvement of Relaxin in mediating uterine function and the promotion of pregnancy maintenance has started to attract much attention among investigators as a novel therapeutic target for the amelioration of preterm labour. Recent studies also investigate how the hormone's role in the breakdown of collagen and the remodeling of the connective tissue could affect the risk for preterm labor onset.

An inflammatory state in the maternal-fetal compartment, either caused by intrauterine infection or sterile inflammation, is a characteristic of preterm birth. Initiation of this process is believed to be mediated by pro-inflammatory cytokines, such as interleukin-1α (IL-1α), interleukin-1β (IL-1β), and interleukin-8 (IL-8), which contribute to uterine contractions, cervical ripening, and the rupture of fetal membranes (8). Increased concentrations of these cytokines have been found in amniotic fluid, fetal membranes, and maternal blood in preterm labor, especially in the setting of intra-amniotic infection (9). IL-1β and IL-8 have been observed to recruit neutrophils and other immune cells to the infection site, thus amplifying the inflammatory response and leading to preterm labor.

Materials and methods:

- **Sample Collection**

Blood samples: from pregnant women at different gestational ages, especially from suspected cases of preterm deliveries or in control groups for comparison. This study continued from April 2024 to December 2024, and 60 clinical samples were collected from the attending patients at Al-Zahraa and Al-Hakiem hospitals in Al-Najaf province. A sample of 30 serum were collected from cases of preterm labor, and 30 samples of serum were collected from normal labor.

- **Cytokines estimation:**

The concentration of IL-1 α, IL-1β, and MCP-1 in serum, and also Progesterone and Relaxin, was detected by using human Enzyme-Linked

Immunosorbent Assay (ELISA) Kits (AccuBind, USA).

Results and discussion:

The levels of several biomarkers, including progesterone, IL8, MCP1, IL1β, IL1α, and IL8, are contrasted in Figure 1 between preterm labour and regular labour. The results are discussed as follows: Preterm labour had greater IL8 levels (31.24) than regular labour (26.7). Given that IL8 is a chemokine involved in inflammation and neutrophil recruitment, this points to an elevated inflammatory response in preterm labour. The highest of all the markers is MCP1, which is somewhat higher in preterm labour (77.38) than in regular labour (74.41). Our data's findings were consistent with those of another study by Yousuf *et al. (*2023), which found that preterm women had non-significantly higher mean MCP-1 levels. Another study that addressed the connection between cytokines and preterm birth focused on the effect of MCP-1, noting that levels rose over time **(10,11)**.

The little variation suggests that although MCP1 contributes to both preterm and normal labour, its impact in preterm labour may be slightly stronger. Compared to normal labour (25.39), preterm labour had considerably higher levels of IL-1β (31.93). This result is consistent with IL-1β's established function as a pro-inflammatory cytokine that promotes uterine contractions and cervical ripening, two processes that are exacerbated in premature labour. Both groups had comparatively modest levels of IL1α, while preterm labour had somewhat higher levels (6.44) than regular labour (5.66). This suggests that although IL1α may have a role in inflammation, it does so to a lesser extent than other markers such as IL8 or IL1β. Compared to regular labour (21.32), preterm labour (23.48) had greater progesterone levels. This is a little surprising because progesterone usually prevents labour; it may be related to preterm labour because of functional withdrawal or receptor sensitivity.

MCP1, IL8, IL1β, IL1α, relaxin, and progesterone are the six variables whose Pearson correlation coefficients (r values) are displayed in Table 1. The range of correlation coefficients is -1 to 1: The intricate relationships between inflammatory and hormonal variables during labour are highlighted by this correlation table. Progesterone seems to have anti-inflammatory properties, especially through its interactions with relaxin and IL8. In inflammation, MCP1 and IL8 play different but complementary roles. A greater understanding of these relationships may help control preterm labour and the hazards that come with it.

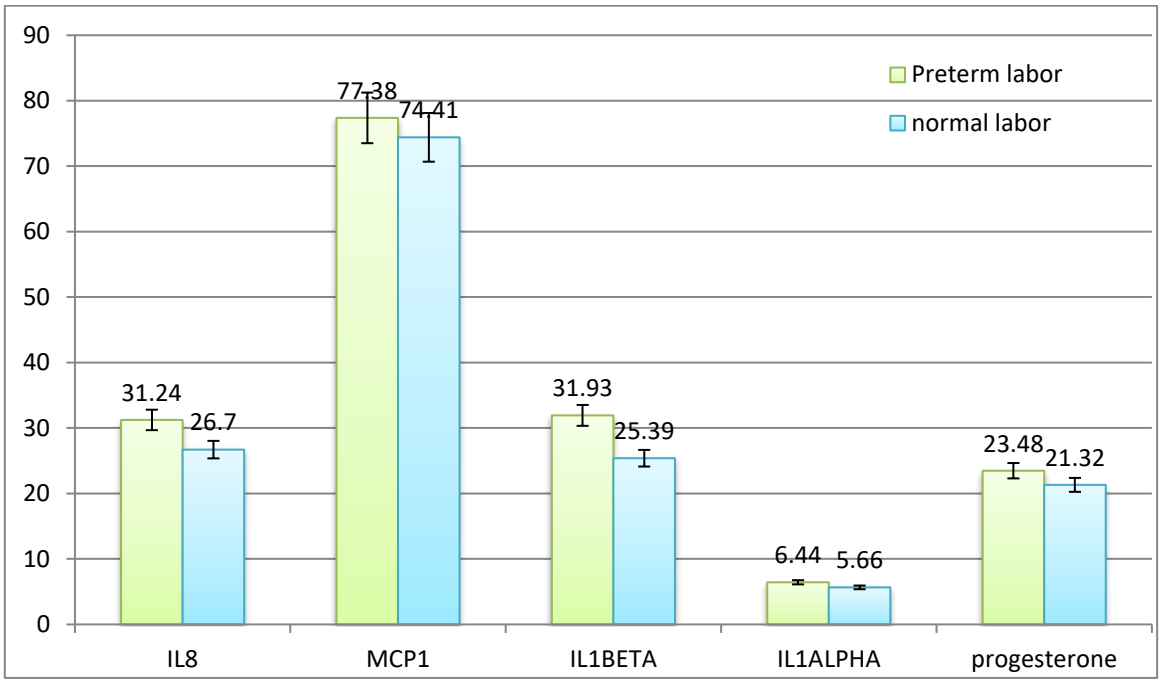

Figure 1: The mean and SE of variables among preterm and normal labor.

Table (1): Pearson Correlations among variables.

Correlations							
Variables		MCP1	IL8	IL1β	IL1αA	Relaxin	progesterone
MCP1	Pearson Correlation	1	-.467-*	.091	-.100-	-.397-*	-.109-
	Sig. (2-tailed)	0	.019	.664	.635	.049	.603
IL8	Pearson Correlation	-.467-*	1	-.095-	-.186-	.029	.449*
	Sig. (2-tailed)	.019	0	.652	.375	.892	.024
IL1β	Pearson Correlation	.091	-.095-	1	-.041-	.144	.095
	Sig. (2-tailed)	.664	.652	0	.847	.493	.652
IL1α	Pearson Correlation	-.100-	-.186-	-.041-	1	-.055-	-.265-
	Sig. (2-tailed)	.635	.375	.847	0	.795	.201
Relaxin	Pearson Correlation	-.397-*	.029	.144	-.055-	1	-.434-*
	Sig. (2-tailed)	.049	.892	.493	.795	0	.030
progesterone	Pearson Correlation	-.109-	.449*	.095	-.265-	-.434-*	1
	p-value	.603	.024	.652	.201	.030	0

*. Correlation is significant at the 0.05 level (2-tailed).

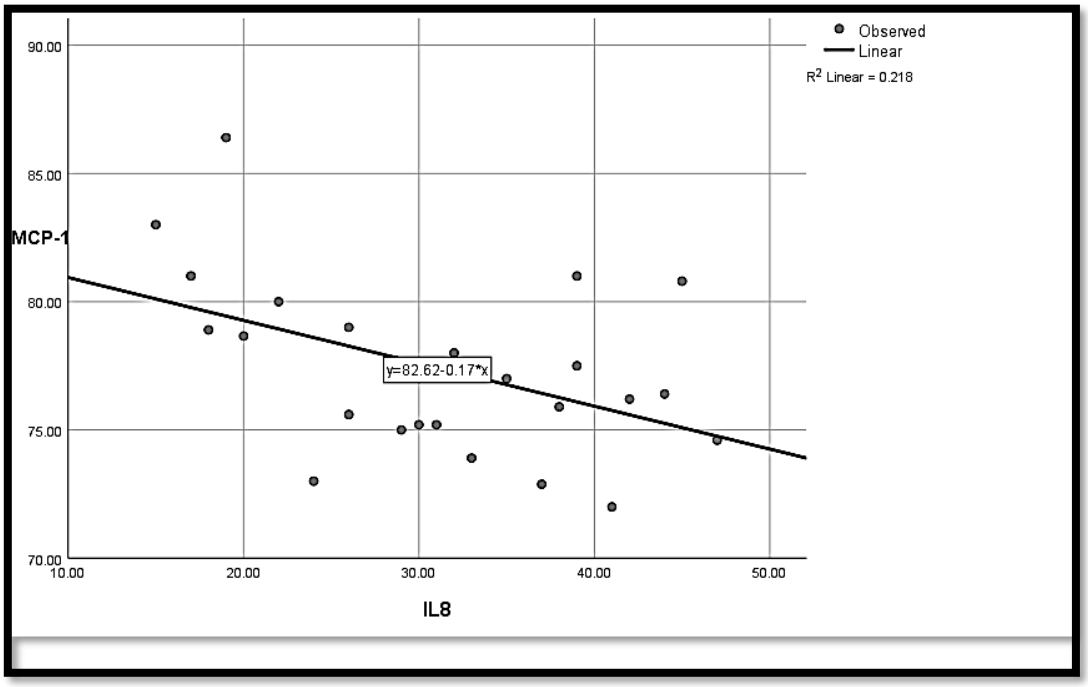

Figure 2: Correlation between MCP1 and IL8 in preterm labor.

where MCP1 and IL8 have an inverse relationship, meaning that IL8 tends to decline as MCP1 rises. This could suggest a unique control or function in the inflammatory processes of labour. MCP1 levels had a negative connection with relaxin ($r = 0.397$, $p = 0.049$), suggesting that relaxin and MCP1 may play opposing functions in labour control. The scatter figure supports the hypothesis that MCP-1 and IL-8 have an inverse relationship, with IL-8 explaining a moderate part of MCP-1 variability. This relationship indicates their possible involvement in controlling inflammation during labor, while further work is needed to account for additional relevant factors.

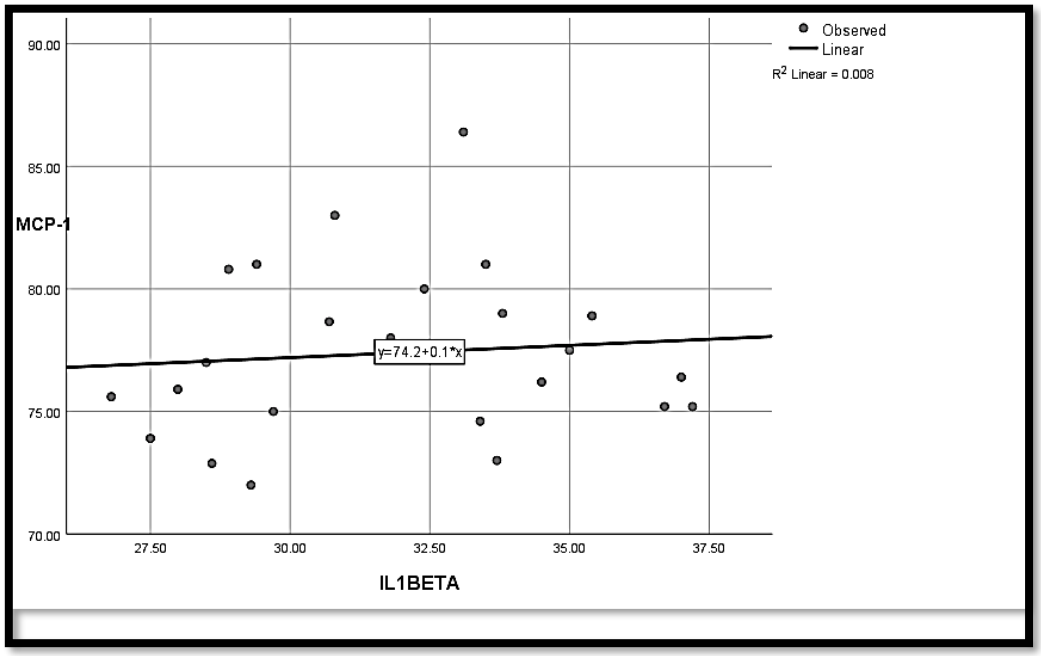

Figure 3: Correlation between MCP1 and IL1 β in preterm labor.

There is no discernible relationship between IL1β and any other variable. This could imply that its interactions are mediated through other channels or that its impacts on labour processes are unrelated to the variables studied here.

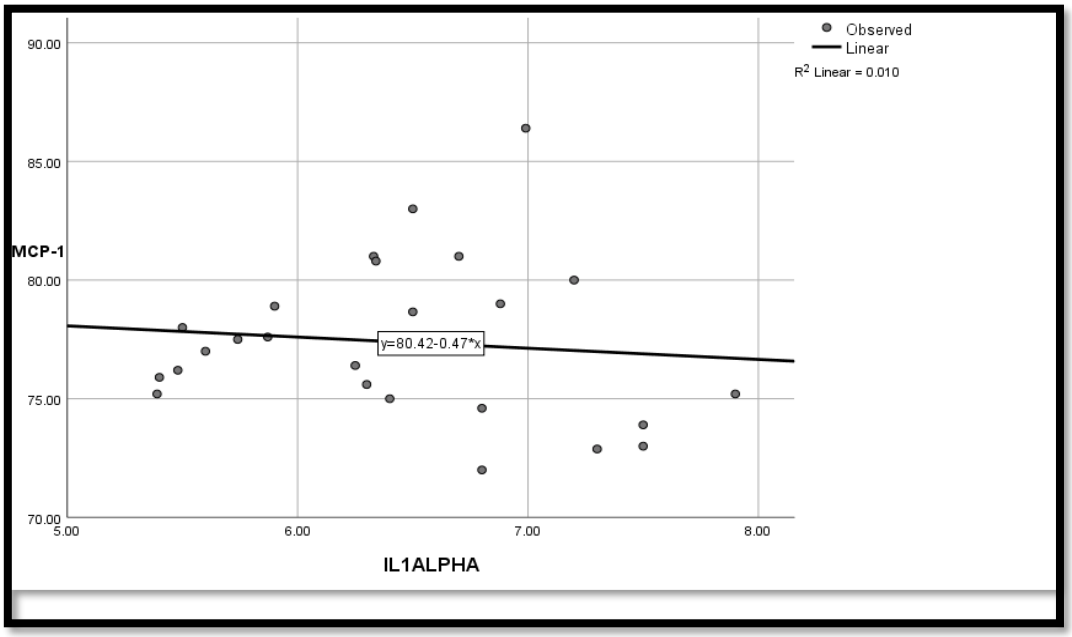

Figure 4: Correlation between MCP1 and IL1 α among preterm labor.

IL1α shows weak, non-significant associations with all variables, just like IL1β. It might have a more nuanced role in labour or involve other mediators that cannot be assessed.

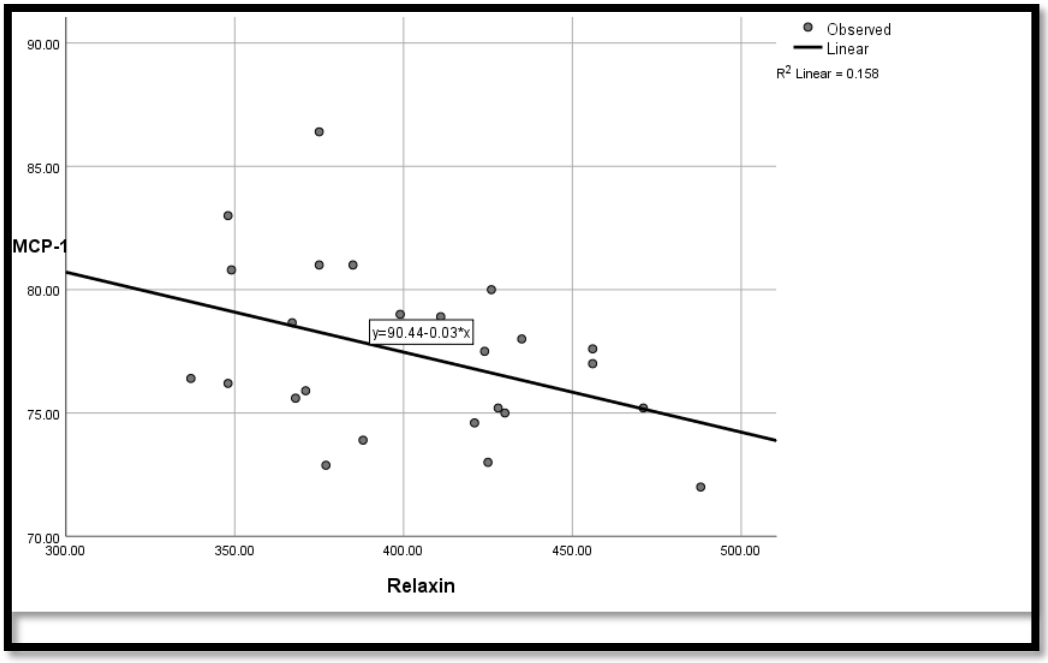

Figure 5: Correlation between MCP1 and Relaxin in preterm labor.

Non-significant Correlations between MCP1 and Relaxin, weak correlations with MCP1, IL-8, IL1β, and IL-1α, although the MCP1 relationship approaches significance.

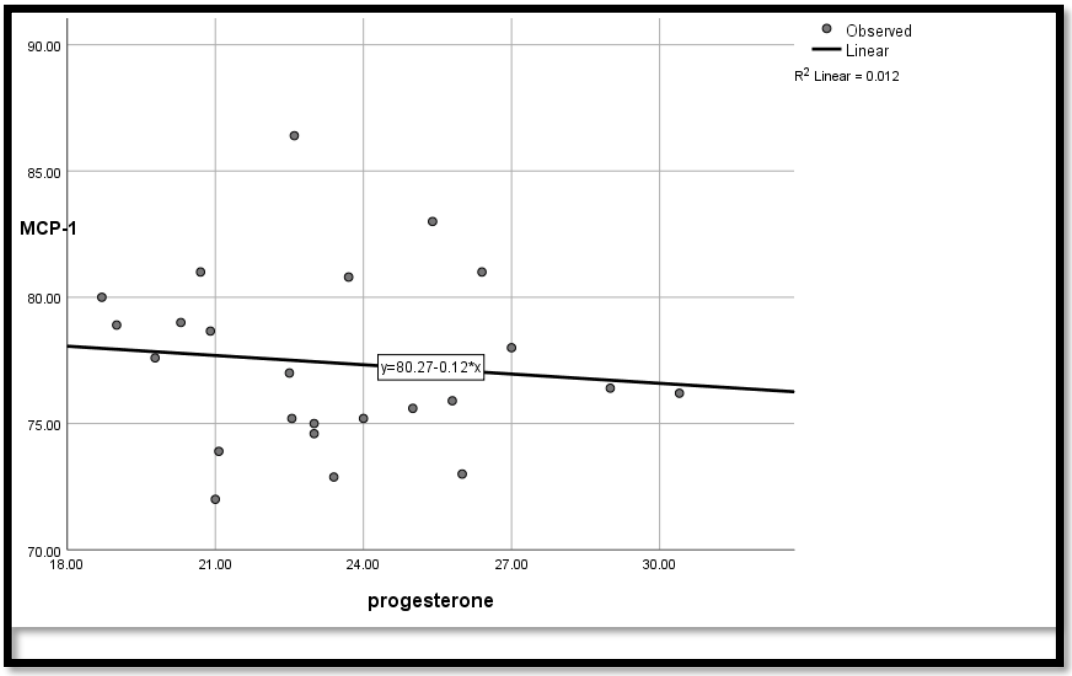

Figure 6: Correlation between MCP1 and progesterone in preterm labor.
Weak, non-significant relationships with MCP1, IL1β, and IL1α.

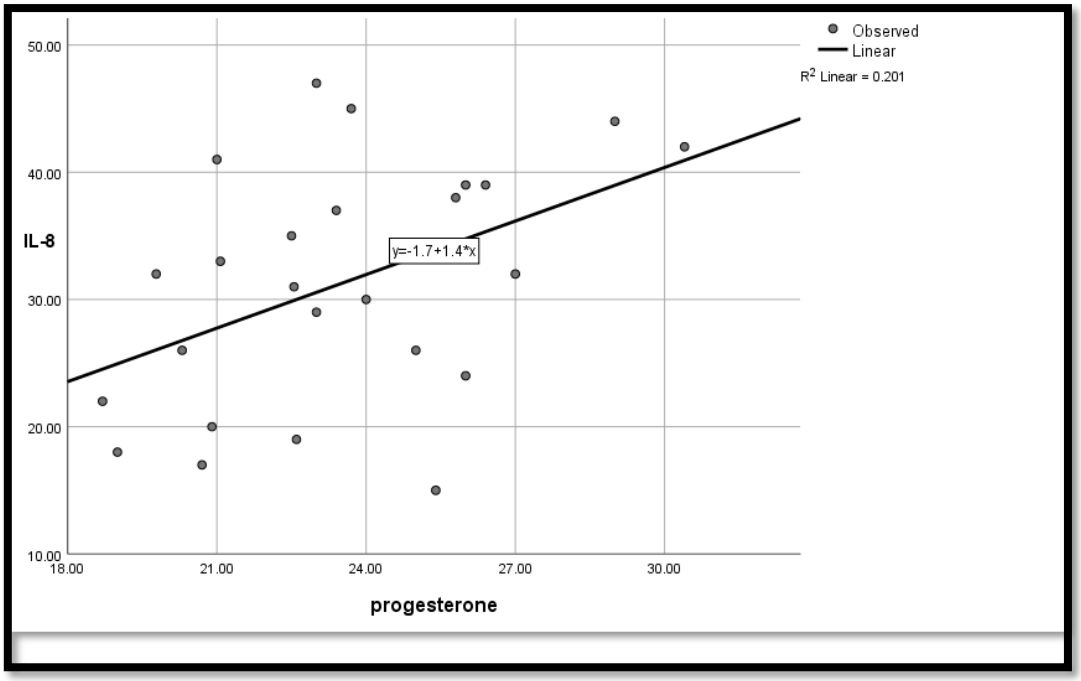

Figure 7: Correlation between IL-8 and progesterone in preterm labor.
Progesterone's anti-inflammatory properties are evident, as higher progesterone levels are associated with lower IL8.

Conclusion:

The study demonstrates that important inflammatory markers (IL-1α, IL-1β, and MCP-1) are markedly increased in preterm labour, although progesterone levels do not differ significantly between preterm and regular labour. These results imply that preterm labour is mostly caused by inflammatory pathways rather than hormonal imbalance.

Conflict of interest: NIL

Funding: NIL

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