Original Research Paper

Volume - 13 | Issue - 03 | March - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

A STUDY TO EVALUATE THE ASSOCIATION OF MATERNAL INFLAMMATORY BIOMARKERS WITH SPONTANEOUS PRETERM DELIVERY

Dr. Somya Mittal* Third year postgraduate student, Department of Obstetrics and gynaecology, Sawai man Singh medical College, Jaipur, Rajasthan *Corresponding Author

Dr. Jyotsna Vyas Senior Professor, Department of Obstetrics and gynaecology, Sawai man Singh medical College, Jaipur, Rajasthan

ABSTRACT **Background:** Preterm delivery, defined as delivery before 37 weeks of gestation, is a major challenge in obstetrics and children's healthcare. It has been estimated that 5 to 18% of all pregnancies end up in preterm delivery which poses an extensive healthcare burden mainly due to neonatal morbidity and mortality.1,2 Spontaneous preterm birth has multifactorial etiologies, including premature activation of the foetal endocrine system, pathological distension, and inflammation/infection.3 In this study, we aimed to evaluate the association of maternal inflammatory biomarkers with spontaneous preterm delivery which could supplement the existing tests to identify women at high risk of preterm birth. **Methods:** An observational cross sectional study was undertaken in 92 pregnant females presenting with gestational age between 28 to 40 weeks with labour pains in department of Obstetrics and Gynaecology, SMS Medical College, Jaipur. Patients were divided into 2 groups based on gestational age, preterm (before 37 weeks) and term (at or after 37 weeks). Written and informed consent was taken. After thorough history and examination, blood samples were taken for evaluating CBC and hs CRP. Ultrasonography was performed for gestational age and fetal well- being and the progress of labour was monitored. **Results:** The mean age for preterm group was 25.43 years and for term group was 25.4 years. The mean period of gestation for preterm group was 34.04 weeks and for term group was 38.2 weeks. Values of CBC parameters like WBC, NLR, PLR, MPV and RDW and hs CRP were significantly higher in preterm group as compared to term group. Mean WBC, NLR, PLR, MPV and RDW were significantly higher in group with neonates requiring NICU admission as compared to those who did not require NICU admission. ROC curve analysis showed that highest area under curve was of NLR. **Conclusion:** The evaluated inflammatory biomarkers were significantly associated with preterm labour and thus the measurement of hs-CRP, PLR, NLR, MPV and RDW could be considered as promising markers and in future could be used as potential predictors of preterm labour.

KEYWORDS : Preterm delivery, Inflammation, Biomarkers

INTRODUCTION

Preterm delivery, defined as delivery before 37 weeks of gestation, is a major challenge in obstetrics and children's healthcare. It has been estimated that 5 to 18% of all pregnancies end up in preterm delivery which poses an extensive healthcare burden mainly due to neonatal morbidity and mortality.[1,2] In addition to the increased risk of mortality, it has been shown that children born preterm suffer from various short and long-term morbidities and adverse outcomes such as neurological deficits, learning disabilities, and respiratory problems.[3] Spontaneous preterm birth has multifactorial etiologies, including premature activation of the foetal endocrine system, pathological distension, and inflammation/infection.[3]

Determining the association between inflammatory biomarkers and preterm labour which, in future, could be used for prediction of spontaneous preterm birth is important because it could allow for the identification of women at high risk of preterm birth, in whom a specific intervention could be tested. Many markers have been used to predict preterm labour. These include the patient's history, evaluation of maternal signs and symptoms, clinical examination, biochemical markers and cervical length.

Inflammatory responses drive the pathogenesis of infection-induced preterm labor. Lipopolysaccharide (LPS) or other toxins elaborated by bacteria are recognized by pattern-recognition receptors such as toll like receptors. These receptors are present on mononuclear phagocytes, decidual cells, cervical epithelia, and trophoblasts. Activation of toll-like receptors induces a signaling cascade that activates production of chemokines such as interleukin 8 (IL-8) and cytokines such as IL-1β. Activation also recruits immune cells into the reproductive tract. Cytokines are produced by immune cells and by cells within the cervix, decidua, membranes, or fetus itself.

IL 1β promotes prostaglandin formation that induces cervical ripening and loss of myometrial quiescence. Proteases such as matrix metalloproteinases (MMPs) are also induced by IL-1β and function to break down extracellular matrix components such as collagen or elastic fibers. This disrupts the structural integrity of foetal membranes and cervix.

A Complete Blood Count (CBC) and hs CRP is simple and inexpensive. As inflammation is one of the main components in initiation of preterm labour, through this study, we aim to identify, if any, association exists between preterm labour and inflammation with the help of changes in maternal serum inflammatory biomarkers.

METHODS

This observational cross sectional study was conducted in the Department of Obstetrics and Gynaecology in SMS Medical College, Jaipur between April 2021 to April 2022.

The study was carried out on 92 patients presenting with labour pains and fulfilling inclusion and exclusion criteria. Inclusion criteria were women >18 and < 35 years of age and with singleton viable pregnancies between 28 to 40 weeks of gestation, preterm(28 to <37 weeks) and term (≥37 to 40 weeks) presenting with labour pains. Women presenting with regular uterine contractions 4 times in every 20 minutes or cervical dilatation >3cm were selected for the study. Exclusion criteria were pregnant women with premature rupture of membranes (PROM) and with significant obstetrical and medical complications.

All patients with symptoms of preterm labour between 28 and 37 weeks of gestation and term labour between 37 to 40 weeks were hospitalized for surveillance after diagnosis of labour. After proper counselling regarding the purpose of the study, a written informed consent from all the women and attendants was taken and were recruited for the study. A detailed history with proper general, systemic, per abdominal and per vaginal examination was performed. Blood samples were taken at the time of admission and Complete Blood Count (CBC) and hs CRP levels were obtained. The biomarkers evaluated from CBC are- WBC count, NLR, PLR, MPV and RDW. Ultrasonography was performed for gestational age and fetal well-being and the progress of labour was monitored.

Outcome will be evaluated as follows:

Patients with labour were divided into two groups based on gestational age. Patients in group A delivered before 37 weeks (preterm delivery group), whereas those in group B delivered at or after 37 weeks (term delivery group). The two groups were compared in terms of levels of serum markers which were obtained at admission and statistical evaluation was done.

Statistical analysis

To determine which serum markers predict the preterm delivery, univariate analysis and subsequently multivariate regression analysis was performed. A receiver operating characteristic (ROC) curve was

used to evaluate sensitivity, specificity and optimal cut off values of each marker in predicting preterm delivery. p-value <0.5 was considered to be statistically significant for all analyses. The confidence interval was considered equal to 95% in all the statistical analysis.

RESULTS

Table 1: Demographic factors in preterm and term group

		Preterm group (n=46)	Term group (n=46)	p value
Mean age (in years)		25.43	25.4	0.97
Residence	Rural	19	16	0.51
	Urban	27	30	0.51
Socioeconomic status	Lower	26	18	0.9
	Middle	19	27	0.09
	Upper	1	1	1
Religion	Hindu	37	36	0.7
	Muslim	9	10	0.8
Literacy status	Literate	33	29	0.37

92 pregnant women between 28 to 40 weeks of gestation were recruited in this study. The mean age of 46 women in each group, i.e., preterm and term was 25.43 and 25.4 years respectively. There were more patients from urban areas as compared to rural areas, 57.6% women in pre-term group and 65.2% women in term group belonged to urban areas. 80.4% women in pre-term group and 78.2% women in term group belonged to Hindu religion. 56.5% women in pre-term group and 39.13% women in term group were belonging to lower class.

Table 2: Comparison of various CBC parameters in preterm and term group

	Preterm group		Term group		p value
	Mean	SD	Mean	SD	
WBC count(x103)	11.6	1.95	8.04	1.11	<0.0001
Neutrophil to Lymphocyte Ratio (NLR)	7.2	3.07	2.7	0.64	<0.0001
Platelet to Lymphocyte Ratio (PLR)	155.5	38.28	104.9	18.91	<0.0001
Red cell Distribution Width (RDW)	16.53	1.97	11.99	1.96	<0.0001
Mean Platelet Volume (MPV)	10.4	0.92	8.8	0.62	<0.0001

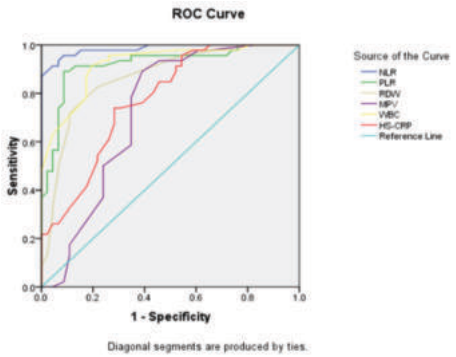

Table No 3: ROC Analysis

	AUC	P	95	CUT	SEN	SP	PPV	NPV	Accuracy
NLR	0.98	<0.0001	0.965-1.004	3.25	97.8	84.8	86.54	97.5	91.3
PLR	0.921	<0.0001	0.863-0.980	111.5	93.5	69.6	75.44	91.33	81.52
RDW	0.81	<0.0001	0.917-0.990	13.5	95.7	73.9	63.77	91.3	70.65
MPV	0.791	<0.0001	0.927-0.996	9.15	97.8	69.6	60	94.12	66.3
WBC	0.7	<0.0001	0.931-1.002	8.95	95.7	47.8	65.22	95.65	72.83
CRP	0.775	<0.0001	0.681-0.868	6	80.4	56.5	64.91	74.29	63.48

The mean values of various CBC parameters like WBC count (11.6*1000 versus 8.04*1000), NLR(7.2 versus 2.7), PLR(155.5 versus 104.9), MPV(16.53 versus 11.99), RDW (10.4 versus 8.8) and hs CRP (6.93 versus 5.1) were significantly higher in preterm group as compared to the term group. The ROC curve analysis showed that area under the curve for NLR, PLR, RDW, MPV, WBC and CRP was 0.98, 0.92, 0.81, 0.79, 0.7 and 0.77 respectively.

DISCUSSION

Preterm delivery (PTD), as defined by the World Health Organization (WHO), refers to all births occurring before 37 completed weeks (up to 36 weeks + 6 days) of gestation since the first day of the last menstrual period. Infection/ inflammation is a frequent and important mechanism of disease in premature labour and delivery. CBC parameters like NLR, PLR, RDW and MPV and serum hs CRP levels can be useful supplements to predict preterm births and are emerging as novel biomarkers.

In our study, maximum patients were in the age group of 21-26 years in both term and pre term. The above table shows that mean age for pre-term group was 25.43 years and for term group mean age was 25.4 years. There was no significant statistical difference in age group in both the groups. These results were almost similar to study done by **Tolunay H et al[4](2020)** in which no significant difference was found between age distribution of term and preterm groups.

In our study, we found that majority 80.4% women in pre-term group and 78.2% women in term group were Hindus, thus showing demography of the area being studied. The study showed that more women i.e., 57.6% women in pre-term group and 65.2% women in term group were living in urban areas. The less percentage of rural patients may be due to difference in catchment area or due to lack of awareness.

According to Kuppuswamy's socio economic classification, 56.5% women in pre-term group were belonging to lower socioeconomic status and 58.6% women in term group were belonging to middle socioeconomic status. Ours is a government hospital so more number of cases were from lower and middle socioeconomic status. Majority 71.3% women in pre-term group and 63.04% women in term group were literate.

We compared WBC, NLR, PLR, RDW and MPV in between two groups. The mean values of WBC count (11.6*1000 versus 8.04*1000), NLR (7.2 versus 2.7), PLR(155.5 versus 104.9), MPV(16.53 versus 11.99) and RDW (10.4 versus 8.8) were significantly higher in preterm group as compared to term group with p value <0.05. **Gezer et al[6]** investigated the diagnostic ability of leukocyte subtypes, platelet, CRP, NLR and PLR at admission for predicting delivery time in women with spontaneous, late and preterm labour. The mean values of leukocyte ($p < .001$), neutrophil ($p < .001$), CRP ($p ¼ .001$), NLR ($p < .001$) and PLR ($p ¼ .003$) were significantly higher, whereas lymphocytes ($p ¼ .012$) were significantly lower in preterm delivery group compared to term delivery group. In study conducted by **Farzaneh et al[5]** , the values of WBC, hemoglobin, relative neutrophil count (%), NLR, platelet count, platelet count, PLR, ESR and hs-CRP were significantly higher in preterm group (P<0.05).

On ROC curve analysis, we found that area under the curve for NLR, PLR, RDW, MPV, WBC and CRP was 0.98, 0.92, 0.81, 0.79, 0.7 and 0.77 respectively. The study shows that highest area under curve is of NLR with a cut off value of 3.25 and PPV and NPV value of 86.5 and 97.5 respectively and accuracy of 91.3. These results were almost similar to study done by **Farzaneh et al[5]** where at the respective cut off values of ≤22% and >3.21, lymphocyte % and NLR represented high sensitivities with respectively lower specificities and NPVs for predicting preterm labor.

The limitation of NLR as a marker is that neutrophilia and lymphocytopenia are general innate immune responses to a wide range of stressful events in pregnancy. These factors such as acute infective or inflammatory processes caused by other organs, malnutrition and drug treatments should be assessed as confounding variables and excluded before using NLR as a diagnostic tool for the prediction of preterm birth.

CONCLUSION

The measurement of inflammatory biomarkers by simple routine inexpensive tests will help us to identify women who are at high risk of

preterm delivery and thus can be offered prophylactic intervention to reduce this risk and the huge personal, economic and health impacts associated with it. The evaluated inflammatory biomarkers were significantly associated with preterm labour and thus the measurement of hs-CRP, PLR, NLR, MPV and RDW could be considered as promising markers and in future could be used as potential predictors of preterm labour.

Funding: *No funding sources*

Conflict of interest: *None declared*

Ethical approval: *The study was approved by the Institutinal Ethics Committee*

REFERENCES

1. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012 Jun 9;379(9832):2162-72. doi: 10.1016/S0140-6736(12)60820-4.
2. Cynthia Bannerman, Stephanie E Purisch. "Epidemiology of preterm birth," Seminars in perinatology, vol. 417, 2017, pp. 387-391, 10.1053/j.semperi.2017.07.009.
3. Baker AM, Haeri S, Camargo CA Jr, Espinola JA, Stuebe AM. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. J Clin Endocrinol Metab. 2010 Nov;95(11):5105-9. doi: 10.1210/jc.2010-0996.
4. Tolunay HE, Elci E. Importance of haemogram parameters for prediction of the time of birth in women diagnosed with threatened preterm labour. J Int Med Res. 2020 Apr;48(4):300060520918432. doi: 10.1177/0300060520918432.
5. Farzaneh, Farah, Shamin Ghobadi and Abdorrahim Absalan. "The accuracy of selected hematology and inflammatory indices for predicting preterm labor; a cross-sectional study." *Immunopathologia Persa* (2019): n. pag.
6. Gezer C, Ekin A, Solmaz U, Sahingoz Yildirim AG, Dogan A, Ozeren M. Identification of preterm birth in women with threatened preterm labour between 34 and 37 weeks of gestation. J Obstet Gynaecol. 2018 Jul;38(5):652-657. doi: 10.1080/01443615. 2017. 1399990.