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ORIGINAL ARTICLE

Maternal Plasma Cytokines and the Subsequent Risk of Uterine Atony and Postpartum Haemorrhage

Uma Pandey[1], Neeraj Agarwal[2], Surendra Pratap Mishra[3], Snehal Agarwal[4]

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ABSTRACT

Background: Postpartum hemorrhage (PPH) remains a leading cause of maternal morbidity and mortality, particularly in low-resource settings. Uterine atony is the most common etiology, marked by inadequate uterine contraction following delivery. Emerging evidence suggests a role for inflammatory cytokines, including interleukin-6 (IL-6) and interleukin-1 beta (IL-1β), in regulating uterine contractility and vascular remodelling.

Aim: This study aimed to evaluate maternal plasma levels of IL-6 and IL-1β in women with PPH due to uterine atony compared to controls, to assess their potential as predictive biomarkers and explore their clinical utility in risk stratification.

Materials and Methods: A case-control study was conducted involving 88 pregnant women—44 with PPH secondary to uterine atony and 44 matched controls without PPH. Blood samples were collected antepartum and within 24 hours postpartum, and cytokine levels were measured using enzyme-linked immunosorbent assay (ELISA). Demographic, obstetric, hematologic, and clinical management data were recorded. Statistical analyses included t-tests, chi-square tests, and receiver operating characteristic (ROC) curve analysis.

Results: IL-6 levels were significantly higher in cases than controls (45.58 ± 29.83 vs. 13.83 ± 5.86 pg/mL; $p < 0.0001$), as were IL-1β levels (25.01 ± 15.44 vs. 8.39 ± 4.02 pg/mL; $p = 0.01$). IL-6 showed superior diagnostic accuracy (AUC = 0.812), with 100% sensitivity and 70% specificity for severe PPH. Elevated cytokines were associated with greater blood loss, increased transfusion needs, adverse maternal outcomes, longer hospital stays, and higher rates of surgical intervention.

Conclusion: IL-6 is a promising biomarker for predicting PPH severity and identifying high-risk patients early. Its incorporation into postpartum risk assessment protocols could enhance maternal care. Further multicenter studies are warranted to validate these findings and explore targeted anti-inflammatory therapies.

AUTHOR'S AFFILIATION:

[1] Professor, Department of Obstetrics & Gynecology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

[2] Department of Endocrinology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

[3] Department of Biochemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

[4] Department of Obstetrics & Gynecology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

CORRESPONDING AUTHOR:

Uma Pandey, Professor, Department of Obstetrics & Gynecology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

E-mail: uma.pandey2006@yahoo.com

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• Postpartum Hemorrhage (PPH) • Uterine Atony • Interleukin-6 (IL-6) • Interleukin-1 Beta (IL-1β) • Cytokines • Biomarkers • Obstetric Risk Factors • Predictive Diagnostics

INTRODUCTION

Postpartum hemorrhage (PPH) is a major obstetric emergency and a significant cause of maternal morbidity and mortality, particularly in low-resource settings. It is clinically defined as blood loss of more than 500 mL following vaginal delivery or more than 1,000 mL following caesarean section.[1] PPH is further categorized into primary PPH, which occurs within the first 24 hours post-delivery, and secondary PPH, which occurs from 24 hours to six weeks postpartum.[1] Globally, PPH accounts for nearly one-quarter of all maternal deaths, with the highest burden in developing countries where access to timely medical care is limited.[2]

The most common etiology of PPH is uterine atony, a condition in which the uterus fails to contract effectively after childbirth. Normally, following placental separation, the uterus contracts to compress the spiral arteries and prevent excessive blood loss.[3] In cases of uterine atony, this physiological contraction is impaired or absent, resulting in ongoing bleeding from the placental bed.[4] Without rapid intervention, this can escalate to life-threatening hypovolemic shock, organ failure, and death.[5]

While PPH poses an immediate threat to maternal survival, it can also lead to long-term health consequences, including chronic anemia, psychological trauma, and infertility, especially when surgical interventions like hysterectomy are required.[9] Therefore, preventive strategies and early identification of women at risk are critical to improving maternal outcomes.

However, dysregulation of cytokine production can disrupt this balance, potentially impairing uterine myometrial function and vascular remodeling. Elevated levels of pro-inflammatory cytokines like IL-6 and IL-1β have been associated with decreased contractility of uterine smooth muscle cells, resulting in insufficient uterine contraction and prolonged bleeding.[11]

Obstetric risk assessments could allow clinicians to anticipate which patients are most likely to develop PPH, Cytokine profiling has emerged as a promising approach for identifying biomarkers that predict the risk of uterine atony and PPH. Studies suggest that elevated maternal plasma levels of specific cytokines during labor or early postpartum may indicate a predisposition to inadequate uterine contractility.[13] Additionally, an imbalance between pro-inflammatory and anti-inflammatory cytokines (e.g., low IL-10 in the presence of high IL-6 or TNF-α) may heighten the risk of hemorrhagic complications.[14]

The implications of these findings are far-reaching. Incorporating cytokine biomarkers into enabling earlier intervention and more tailored treatment plans. Future therapeutic approaches may also focus on modulating cytokine signaling pathways to restore effective uterine contractility and prevent excessive postpartum bleeding.[15]

AIMS AND OBJECTIVES

This study aims to compare the levels of interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) in cases of uterine atony and postpartum hemorrhage (PPH), with the goal of evaluating their potential as biomarkers for identifying women at risk of PPH. Additionally, these cytokine pathways may serve as promising therapeutic targets for the prevention and management of PPH.

MATERIALS AND METHODS

This study utilized a combination of retrospective and prospective methodologies to assess the relationship between maternal plasma cytokines specifically IL-6 and IL-1β and the occurrence of uterine atony leading to postpartum hemorrhage (PPH). Conducted at a tertiary care hospital's Obstetrics and Gynecology Department, the study involved 88 pregnant women, split evenly between those who developed PPH due to uterine atony and those who experienced normal deliveries

without excessive bleeding. After obtaining informed consent, participants were selected based on defined inclusion and exclusion criteria to minimize confounding factors. Blood samples were collected at two points—prior to delivery and within 24 hours after birth—and cytokine concentrations were measured using enzyme-linked immunosorbent assay (ELISA) techniques. Clinical information, including delivery method, estimated blood loss, and the interventions used to manage PPH, was documented. Data were analyzed using a range of statistical tools, including logistic regression to control for potential confounders. Ethical clearance was obtained, and patient confidentiality was strictly maintained. Despite limitations such as a moderate sample size and potential external influences on cytokine levels, this study provides important initial data that could support the development of predictive markers and therapeutic strategies for PPH.

RESULT

Women with PPH due to uterine atony were significantly older than controls (29.66 vs. 26.86 years, p = 0.002), with more cases in the 31–35 age group (p = 0.037). Gestational age and multigravidity were slightly higher in cases but not statistically significant. Caesarean deliveries were more common in cases (65. 91%) than controls (52.27%), while vaginal births were more frequent in controls. Preterm vaginal deliveries occurred only in the case group. Overall, maternal age appears to be a significant risk factor, while other variables warrant further study.

The distribution of pre-existing obstetric risk factors among women with uterine atony and postpartum hemorrhage (cases) and those without (controls). Twin pregnancies were reported exclusively in the case group (13.6%), whereas macrosomia, preterm labor, and post-dated pregnancies were found only in the control group. The prevalence of multigravida was equal in both groups (11.36%). A higher proportion of women in the control group (68.18%) had no identifiable risk factors compared to the case group (43.18%). The difference in distribution was statistically significant (χ^2 = 15.37, p = 0.0089), suggesting that specific antenatal risk factors—particularly twin pregnancy—may contribute to uterine atony and PPH (Figure 1).

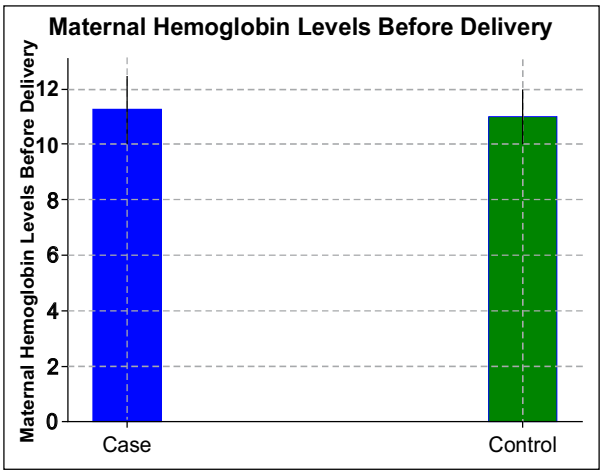

Figure 1: The frequency of each pre-existing risk factor in case vs. control groups

The mean maternal hemoglobin levels prior to delivery were comparable between groups (cases: 11.26 ± 1.21 g/dL; controls: 11.01 ± 0.93 g/dL). The difference was not statistically significant (t = 1.073, p = 0.287), and quartile distributions were nearly identical. These results suggest that antepartum anemia did not significantly contribute to the risk of uterine atony or PPH (Figure 2).

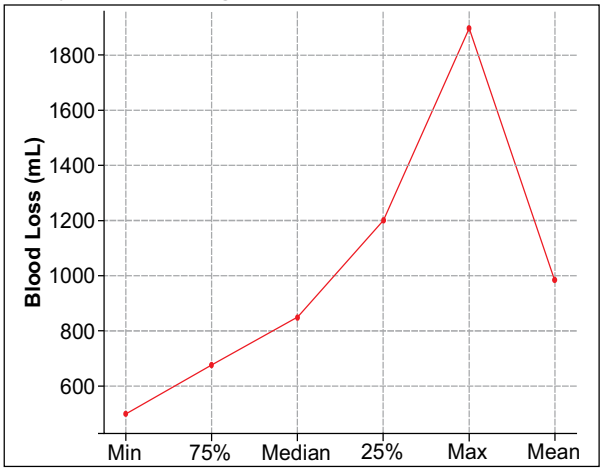

Figure 2: Mean hemoglobin levels with error bars (±SD) for both groups

There was no statistically significant difference in platelet counts between the case and control groups (mean: 1.812 vs 1.686 lakh/mm³, *p* = 0.30). Similarly, white blood cell (WBC) counts did not differ significantly (mean: 8772.72 vs 9171.41 cells/mm³, *p* = 0.537). These findings suggest that neither platelet count nor WBC count alone serves as a distinguishing hematologic parameter between women with uterine atony & PPH and those without (Table 1).

Table 1: Comparison of Platelet and White Blood Cell (WBC) Counts Between Case and Control Groups

Parameter	Group	Count	Mean	Std Dev	Max	t- statistic	p- value
Platelet (lakh/m m³)	Case	44	1.812	0.689	3.6	1.044	0.3
Platelet (lakh/m m³)	Control	44	1.686	0.4	3.1		
WBC (cells/m m³)	Case	44	8772.72	3021.1	14200	-0.6205	0.537
WBC (cells/m m³)	Control	44	9171.41	3005.78	16100		

IL-6 levels were significantly elevated in the case group (45.58 ± 29.83 pg/mL) compared to controls (13.83 ± 5.86 pg/mL), with strong statistical significance ($t = 6.720$, $p < 0.0001$). This indicates a potential inflammatory component in the pathophysiology of uterine atony and PPH. Similarly, IL-1β levels were also significantly higher in cases (25.01 ± 15.44 pg/mL) than in controls (8.39 ± 4.02 pg/mL), with statistical significance ($t = 6.905$, $p = 0.01$). However, IL-1β showed lower diagnostic accuracy than IL-6 in ROC analysis (data not shown here) (Table 2).

Table 2: Comparison of Interleukin-6 (IL-6) and Interleukin-1 Beta (IL-1β) Levels in Case and Control Groups

Statistic	IL-6 Case	IL-6 Control	IL-1β Case	IL-1β Control
Count	44	44	44	44
Mean	45.58	13.83	25.01	8.39
Std Dev	29.83	5.86	15.44	4.02
t-statistic	6.72	–	6.905	–
p-value	<0.0001	–	0.01	–

The distribution of estimated blood loss among the case group. The mean blood loss was 981.82 mL, ranging from 500 to 1900 mL (SD: 432.55 mL). This wide variability underscores the substantial hemorrhagic burden associated with uterine atony (Figure 3).

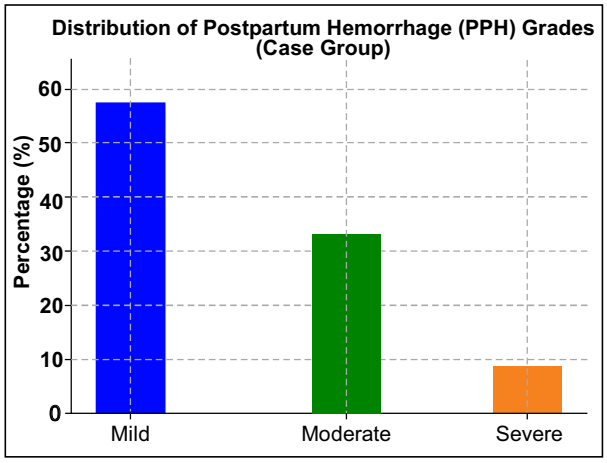

Figure 3: Estimated Blood Loss in Case Group Only

The distribution of PPH severity among cases. Mild PPH was most prevalent (59.09%), followed by moderate (31.81%) and severe (9.09%) cases. The observed distribution was statistically significant ($\chi^2 = 16.54$, $p = 0.00025$), highlighting that while most cases were mild, a meaningful proportion experienced clinically significant bleeding (Figure 4).

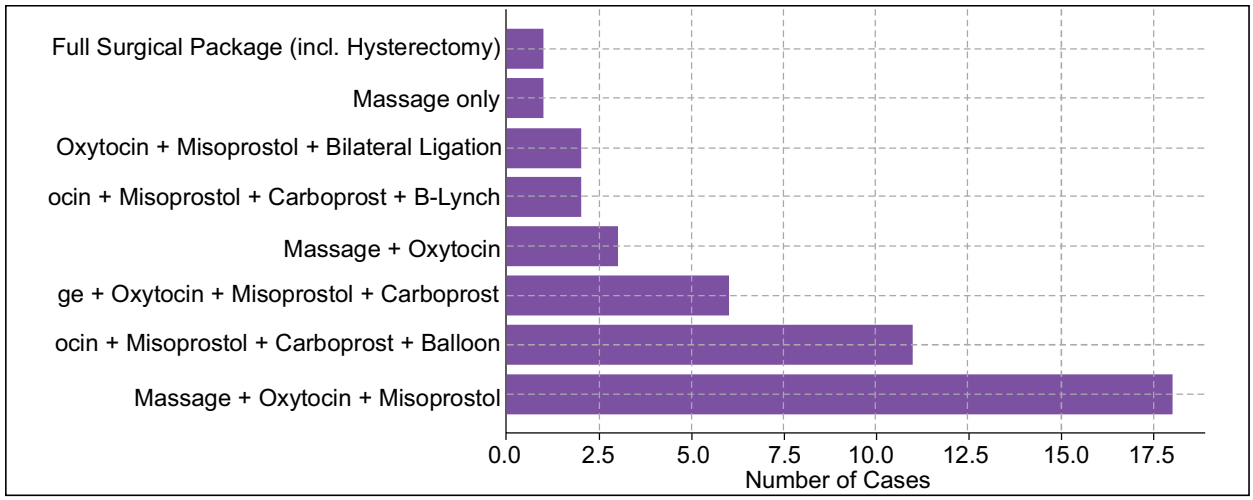

Figure 4: Frequencies of mild, moderate, and severe PPH

The most common management strategy involved uterine massage with oxytocin and misoprostol (administered to 40.91%). More severe cases required escalation to carboprost, balloon tamponade, B-Lynch sutures, or caesarean hysterectomy. No interventions were necessary in the control group, underscoring the clinical burden in patients with uterine atony.

The range and frequency of interventions employed to manage postpartum hemorrhage (PPH) among women with uterine atony. The most utilized method was a combination of uterine massage with oxytocin and misoprostol (40.91%). In more severe cases, escalation to second-line interventions such as carboprost, balloon tamponade, B-Lynch sutures, and ultimately caesarean hysterectomy was observed. Notably, none of the control group required any PPH interventions, reflecting the significant difference in clinical management requirements between groups (Figure 5).

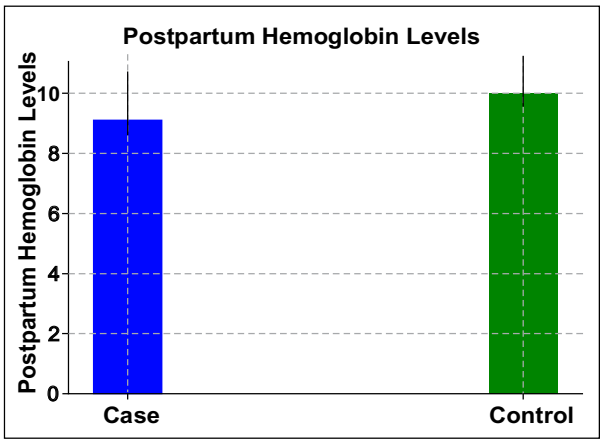

Figure 5: Horizontal bar chart of PPH interventions in case vs. control groups

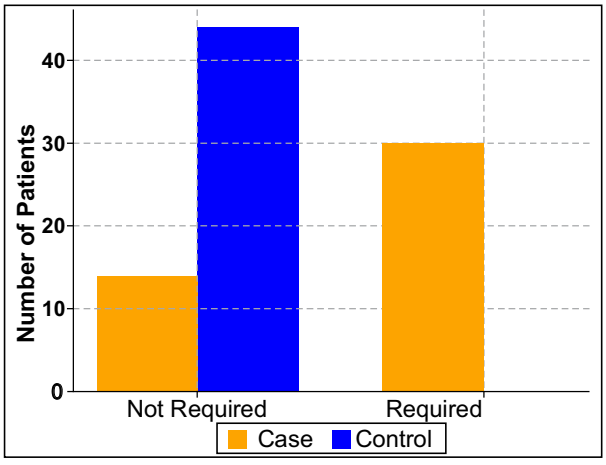

Figure 6: Bar chart comparing mean postpartum hemoglobin levels between groups

Postpartum hemoglobin (Hb) levels were significantly lower in the case group (9.17 ± 1.36 g/dL) than in the control group (10.34 ± 0.94 g/dL). The difference was highly statistically significant ($t = 9.7175$, $p < 0.0001$). This substantial decline in hemoglobin among cases reflects the extent of blood loss experienced during or after delivery, reinforcing the clinical burden of uterine atony and PPH (Figure 6).

While none of the women in the control group required any blood products, 68.18% of the case group required transfusions, with combinations of packed red blood cells (PRBC), fresh frozen plasma (FFP), and random donor platelets (RDP) administered based on severity. Only 14 women (31.82%) in the case group avoided transfusion. The association between PPH and transfusion need was statistically significant ($p < 0.0001$, Fisher's Exact Test), underscoring the hemodynamic impact of atony-related hemorrhage (Figure 7).

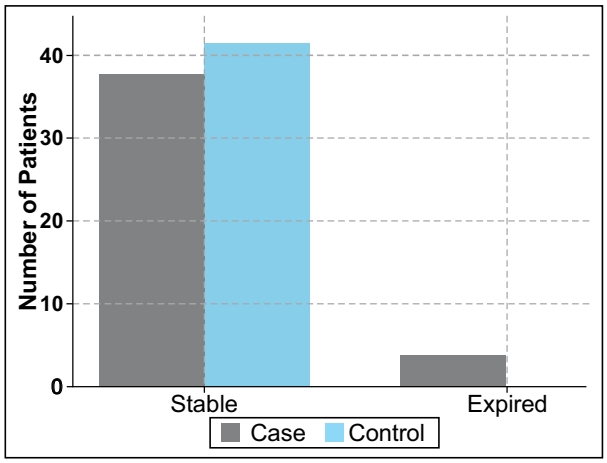

Figure 7: Grouped bar chart of transfusion frequencies by blood product and group

While all women in the control group remained stable postpartum, there were 4 maternal deaths (9.09%) in the case group. Although this difference did not reach statistical significance ($p = 0.115$, Fisher's Exact Test), the mortality observed in the case group highlights the potentially life-threatening nature of untreated or refractory uterine atony and PPH (Figure 8).

The results of the ROC analysis evaluating IL-6 and IL-1β as biomarkers for PPH severity. IL-6 demonstrated excellent diagnostic accuracy in identifying severe PPH (AUC = 0.812), with 100% (Figure 9).

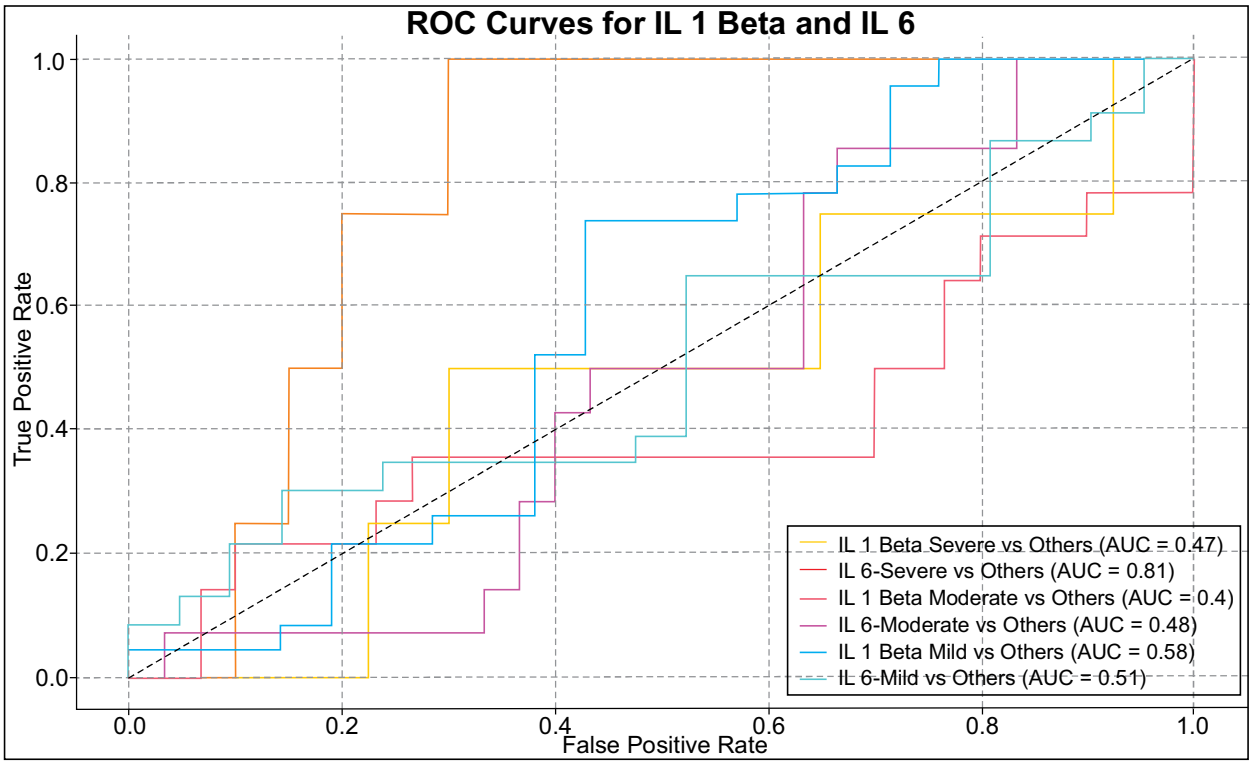

Figure 9: ROC curves comparing IL 1 Beta and IL 6 against each severity grade of postpartum hemorrhage (PPH)

DISCUSSION

This study highlights the link between elevated maternal plasma cytokines—especially IL-6 and IL-1β—and the risk of uterine atony and postpartum hemorrhage (PPH). Women with severe PPH exhibited significantly higher levels of these pro-inflammatory cytokines, supporting their role in impaired uterine contractility and excessive bleeding.

Elevated IL-6 and IL-1β levels are consistent with previous findings that associate them with uterine dysfunction. Additionally, markers like WBC count and platelet dysfunction, influenced by cytokines, may further contribute to bleeding risk.

Pre-existing risk factors such as twin pregnancies, preterm labor, and advanced maternal age may exacerbate cytokine imbalance and increase PPH susceptibility. Older age, in particular, was linked to altered immune responses and a greater likelihood of hemorrhage.

The mode of delivery also influenced inflammatory profiles, with higher cytokine levels observed in cesarean deliveries, further associating them with increased PPH risk.

Overall, the study emphasizes the potential of cytokines as biomarkers and therapeutic targets in predicting and managing PPH, especially in high-risk pregnancies.

CONCLUSION

This study underscores IL-6 as a more effective biomarker than IL-1β in predicting postpartum hemorrhage (PPH) severity, demonstrating 100% sensitivity and 70% specificity. Incorporating IL-6 into postpartum monitoring may facilitate early identification of high-risk patients, allowing timely interventions to reduce maternal morbidity. Limitations include moderate sample size, assay variability, and single-center design. Future research should focus on larger, multicenter, prospective studies and refined cytokine assays. Exploring inflammatory pathway modulation could offer novel therapeutic options. Overall, IL-6 shows promise for clinical use in early PPH risk assessment, with implications for improving maternal outcomes, especially in resource-limited setting

Authors Contribution:

UP: conceptualisation, thesis checking and thesis writing, plan for testing

NA: concept of laboratory testing
SA: thesis writing under supervision
SM: laboratory testing

REFERENCES

1. Belardelli FI. Role of interferons and other cytokines in the regulation of the immune response. Apmis. 1995 Jan;103(1-6):161-79.
2. Mousa A, Bakhiet M. Role of cytokine signaling during nervous system development. International journal of molecular sciences. 2013 Jul 4;14(7):13931-57.
3. Mousa A, Bakhiet M. Role of cytokine signaling during nervous system development. International journal of molecular sciences. 2013 Jul 4;14(7):13931-57.
4. Orsi NM, Tribe RM. Cytokine networks and the regulation of uterine function in pregnancy and parturition. Journal of neuroendocrinology. 2008 Apr;20(4):462-9.
5. Shynlova O, Lee YH, Srikhajon K, Lye SJ. Physiologic uterine inflammation and labor onset: integration of endocrine and mechanical signals. Reproductive sciences. 2013 Feb;20(2):154-67.
6. Gomez-Lopez N, StLouis D, Lehr MA, Sanchez-Rodriguez EN, Arenas-Hernandez M. Immune cells in term and preterm labor. Cellular & molecular immunology. 2014 Nov;11(6): 571-81.
7. Christiaens I, Zaragoza DB, Guilbert L, Robertson SA, Mitchell BF, Olson DM. Inflammatory processes in preterm and term parturition. Journal of reproductive immunology. 2008 Oct 1;79(1):50-7.
8. Vidaeff AC, Ramin SM. Potential biochemical events associated with initiation of labor. Current medicinal chemistry. 2008 Mar 1;15(6):614-9.
9. Kelly RW. Pregnancy maintenance and parturition: the role of prostaglandin in manipulating the immune and inflammatory response. Endocrine reviews. 1994 Oct 1;15(5):684-706.
10. Moncrieff G. Postpartum haemorrhage: Aetiology and intervention. British Journal of Midwifery. 2018 Apr 2;26(4):224-31.
11. Gallo DM, Romero R, Bosco M, Chaiworapongsa T, Gomez-Lopez N, Arenas-Hernandez M, Jung E, Suksai M, Gotsch F, Erez O, Tarca AL. Maternal plasma cytokines and the subsequent risk of uterine atony and postpartum hemorrhage. Journal of perinatal medicine. 2023 Feb 23;51(2):219-32.
12. Qu J, Jiang H, Shi H, Huang N, Su J, Zhang Y, Chen L, Zhao Y. Novel predictive biomarkers for atonic postpartum hemorrhage as explored by proteomics and metabolomics. BMC Pregnancy and Childbirth. 2025 Jan 30;25(1):96.
13. Sebghati M, Chandraharan E. An update on the risk factors for and management of obstetric haemorrhage. Women's Health. 2017 Aug;13(2):34-40.
14. Festic E, Johnson MM, Moraghan TJ. Postpartum Uterine Atony and Diabetes Insipidus; A Case Report: 626. Critical Care Medicine. 2004 Dec 1;32(12):A176.
15. Annecke T, Geisenberger T, Kürzl R, Penning R, Heindl B. Algorithm-based coagulation management of catastrophic amniotic fluid embolism. Blood coagulation & fibrinolysis. 2010 Jan 1;21(1):95-100.
16. Shen Y, Oda T, Tamura N, Kohmura-Kobayashi Y, Furuta-Isomura N, Yaguchi C, Uchida T, Suzuki K, Itoh H, Kanayama N. Elevated bradykinin receptor type 1 expression in postpartum acute myometritis: Possible involvement in augmented interstitial edema of the atonic gravid uterus. Journal of Obstetrics and Gynaecology Research. 2019 Aug;45(8):1553-61.
17. Jiang H, Shi H, Chen L, Yang J, Yuan P, Wang W, Pang Y, Wei Y, Zhao Y. Is there a relationship between plasma, cytokine concentrations, and the subsequent risk of postpartum hemorrhage?. American journal of obstetrics and gynecology. 2022 Jun 1;226(6):835-e1.
18. Zhang P, Jia Y, Song H, Fan Y, Lv Y, Geng H, Zhao Y, Cui H, Chen X. Novel biomarkers for prediction of atonic postpartum hemorrhage among 'low-risk'women in labor. Frontiers in Immunology. 2024 Jul 11;15:1416990.
19. Baird EJ. Identification and management of obstetric hemorrhage. Anesthesiology clinics. 2017 Mar 1;35(1):15-34.
20. Carter SW, Neubronner S, Su LL, Dashraath P, Mattar C, Illanes SE, Choolani MA, Kemp MW. Chorioamnionitis: an update on diagnostic evaluation. Biomedicines. 2023 Oct 28;11(11):2922.
21. Santoso JT, Saunders BA, Grosshart K. Massive blood loss and transfusion in obstetrics and gynecology. Obstetrical & gynecological survey. 2005 Dec 1;60(12):827-37.

22. Shynlova O, Lee YH, Srikhajon K, Lye SJ. Physiologic uterine inflammation and labor onset: integration of endocrine and mechanical signals. Reproductive sciences. 2013 Feb;20(2):154-67.

23. Beagley JC, Whitman KJ, Baptiste KE, Scherzer J. Physiology and treatment of retained fetal membranes in cattle. Journal of veterinary internal medicine. 2010 Mar;24(2):261-8.

24. O'brien D, Babiker E, O'Sullivan O, Conroy R, McAuliffe F, Geary M, Byrne B. Prediction of peripartum hysterectomy and end organ dysfunction in major obstetric haemorrhage. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2010 Dec 1;153(2):165-9.

25. Martínez-Martínez C, Adaya-Leythe EA, Ángeles-Vázquez MD, Jiménez-De Luna AJ, Cepeda-Nieto AC. Transfusion-related acute lung injury in obstetric hemorrhage: prevalence and risk factors. Ginecología y obstetricia de México. 2021;89(4):318-24.

26. Rivers JM. Transfusión. Trali and taco OB. Revista Mexicana de Anestesiología. 2011;34(S1):322-33.

27. Mordak R, Stewart PA. Periparturient stress and immune suppression as a potential cause of retained placenta in highly productive dairy cows: examples of prevention. Acta Veterinaria Scandinavica. 2015 Dec 2;57(1):84.

28. Mahendra V, Clark SL, Suresh MS. Neuropathophysiology of preeclampsia and eclampsia: A review of cerebral hemodynamic principles in hypertensive disorders of pregnancy. Pregnancy Hypertension. 2021 Mar 1;23:104-11.