Amina Berour - Written evidence (PRT0046)

My name is **Amina Berour**, and I am an **intern doctor** and early career researcher with an interest in women's health research, specifically in maternity care. By submitting this evidence, I aim to shed light on the prognosis and monitoring of premature ruptured membranes (PPROM), and their effects pregnancy and birth. By joining this discussion, I hope to dig deeper into the topic of preterm birth and find ways to apply research findings in real-world healthcare settings. My passion for women's health research drives me to share what I know and have meaningful conversations that can make a difference in the care of pregnant individuals and their little ones.

Title: Inflammation and Premature rupture of membranes (PROM):

Is This Predictive Puzzle Worth Solving?

1. **What is The Problem?**

Pregnancy has a complex physiology that shifts the maternal immune system. As part of continual adaptations required to accommodate the growing fetus.[1] A major concern during pregnancy is the risk of premature rupture of membranes (PROM), characterized by the amniotic membranes surrounding the fetus rupturing before 37 weeks of gestation. PROM is a serious complication that can lead to adverse outcomes for both the mother and the baby. This condition affects around 2-4% of pregnancies and it is commonly linked with infection and inflammation.[2] Inflammation; the natural response of the immune system to injury or infection. In the context of pregnancy, inflammation plays a significant role in multiple physiological processes, with both positive and negative effects. It acts as a protective mechanism by aiding tissue repair and

combating pathogens, ensuring the health of both mother and fetus. However, excessive or dysregulated inflammation can lead to adverse outcomes, such as premature rupture of membranes. Fetal membranes are essential in protecting the fetus by providing mechanical and immune protection against microbial invasion. However when this barrier becomes compromised, it will generate microbial invasion, inflammation, and membrane weakening, ultimately resulting in preterm premature rupture of membranes. PROM is a condition affecting the fetal membranes, where the inflammation-oxidative stress axis significantly contributes to pathways leading to membrane weakening through various processes.[3] In recent years, there has been growing interest in understanding inflammation in the context of PROM pathogenesis, because **if we can monitor inflammation effectively, we might be able to predict PROM and its serious complications**. This makes it a valuable area of research, as it could lead to improved outcomes for pregnant individuals and their babies, **making it a predictive puzzle worth solving.**

2. What are The Tools?

In the context of monitoring inflammation related to PROM, biomarkers can be categorized into three main groups:

a) Serum Biomarkers:

Serum biomarkers are substances found in the bloodstream that can indicate the presence of inflammation or other physiological processes. In the context of PROM, cytokines or interleukins such as IL-6, IL-8, procalcitonin, and C-reactive protein (CRP) can indicate systemic inflammatory responses associated with PROM.

b) Cervical or Vaginal Biomarkers:

Biomarkers found in the cervical or vaginal compartments, such as cervical IL-6, high concentrations of CRP, metalloproteinase-8 (MMP-8),

and other interleukins, offer localized indicators of inflammation and tissue damage in the reproductive tract.

a) Amniotic Fluid Biomarkers:

Amniotic fluid biomarkers provide a direct reflection of the inflammatory environment within the amniotic sac, where the fetus resides., including amniotic fluid interleukin (IL)-6, selected proteomic biomarkers like calgranulins A and C, and neutrophil defensins 1 and 2.These biomarkers help clinicians assess the intrauterine environment.

3. What is The Evidence of The Clinical utility?

Although there is no consensus on the role of inflammatory markers in the diagnosis of chorioamnionitis in premature rupture of the membrane (PPROM)[4]. The NICE guidelines acknowledge its common practice in clinical settings.[5] This recognition is especially crucial considering that timely diagnosis and effective treatment of infection is particularly important, given that sepsis is a common direct cause of maternal death. Despite the lack of consensus, studies have reported potential uses of these markers to aid clinical decision-making. Here are key points summarizing their clinical utility and implications:

- Placental inflammation resulting from histological chorioamnionitis, predicted by Neutrophil-to-Lymphocyte Ratio (NLR), aids in managing pregnancies complicated by PPROM, with high NLR values significantly associated with adverse perinatal outcomes. Studies have also shown that subclinical infection is often detected in PPROM and preterm labor.[6]
- Biomarkers in amniotic fluid demonstrate superior predictive value compared to blood samples, with C-reactive protein (CRP) and interleukin-6 (IL-6) showing promise for identifying intrauterine infection.[7]

- According to guidelines, prophylaxis should be administered after PPROM. however, there is no consensus on specific antibiotics or timing of antibiotics in case of failure. Monitoring of biomarkers can help determine the duration of antibiotic treatment. Nevertheless, further studies should be conducted to examine the relationship between biomarker levels and antibiotic levels over the duration of antibiotic therapy if delivery not occur.[7]
- Maternal serum CRP and NLR are biomarkers of histological chorioamnionitis (HCA) in women with PPROM. Although procalcitonin (PCT) requires further investigation, the addition of serum markers to gestational age in PPROM provides a noninvasive method for predicting adverse outcome.[8]
- The proposed clinical role of tests in PPROM is to guide interventions such as delivery or expectant by accurately identifying pregnancies with chorioamnionitis.[4]
- The correlation between maternal blood cell counts and inflammatory responses has been extensively studied. Examining the dynamic changes in leukocyte populations and their activation status during pregnancy has provided insights into systemic immune responses that could contribute to susceptibility to premature rupture of membranes.[6]
- Inflammatory biomarkers found in vaginal fluid upon admission for PPROM have the potential to predict adverse perinatal outcomes.[9]

4. What are The Main Limitations?

A systematic review looked into using maternal serum markers like C-reactive protein (CRP), procalcitonin (PCT), or interleukin-6 (IL6) to detect infections like chorioamnionitis (HCA) and funisitis in cases of preterm premature rupture of membranes (PPROM). However, the review found that these tests often give incorrect results. They can wrongly

suggest there's an infection when there isn't (false positive), or miss an infection when it's actually there (false negative). Even though it's easy to take a blood sample for these tests, relying on them alone for deciding when to deliver a baby can sometimes cause problems, it can lead to unnecessary preterm labor, impacting neonatal outcomes and survival, particularly in earlier pregnancies. Therefore, caution is advised when interpreting the results of these tests in the context of managing PPROM.[4]

5. What is The Next Step Towards Better Care for PROM?

The next step in optimizing PROM management is to identify biomarkers that are highly specific for amniotic fluid and easily detectable in the cervicovaginal fluid, especially at low levels in cases of PPROM. The challenge is to differentiate those that do not deliver within 48 hours, before subclinical infections, which are associated with poor neonatal outcomes. Relevant biomarkers with good sensitivity and specificity to facilitate specific management strategies aim to improve maternal and neonatal outcomes in PPROM, and they should be easy to collect and to interpret.

Furthermore, incorporating clinical variables into these biomarkers may facilitate the development of high-value predictive models based on artificial intelligence, if such models can be incorporated into daily clinical practice no compromises to provide optimal treatment to patients with PPROM.[7] Furthermore, further studies are needed to measure specific biomarkers that can be routinely used clinically to predict timing of delivery, potentially prolonging gestation, and enhancing neonatal outcomes.

6. Bibliography:

1. Talbot L, Maclennan K. Physiology of pregnancy. *Anaesthesia & Intensive Care Medicine*. 2016;17(7):341-345. doi:10.1016/j.mpaic.2016.04.010

2. Ryu HK, Moon JH, Heo HJ, Kim JW, Kim YH. Maternal c-reactive protein and oxidative stress markers as predictors of delivery latency in patients experiencing preterm premature rupture of membranes. *International Journal of Gynecology & Obstetrics*. 2017;136(2):145-150. doi:10.1002/ijgo.12024

3. Menon R, Richardson LS. Preterm prelabor rupture of the membranes: A disease of the fetal membranes. *Semin Perinatol*. 2017;41(7):409-419. doi:10.1053/j.semperi.2017.07.012

4. Etyang AK, Omuse G, Mukaindo AM, Temmerman M. Maternal inflammatory markers for chorioamnionitis in preterm prelabour rupture of membranes: a systematic review and meta-analysis of diagnostic test accuracy studies. *Syst Rev*. 2020;9(1):141. doi:10.1186/s13643-020-01389-4

5. Overview | Preterm labour and birth | Guidance | NICE. Published November 20, 2015. Accessed March 27, 2024. https://www.nice.org.uk/guidance/ng25

6. Esercan A, Demir I. Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratio in Preterm Premature Rupture of Membranes. *Cureus*. 2023;15(5):e38664. doi:10.7759/cureus.38664

7. Feduniw S, Pruc M, Ciebiera M, et al. Biomarkers for Pregnancy Latency Prediction after Preterm Premature Rupture of Membranes-A Systematic Review. *Int J Mol Sci*. 2023;24(9):8027. doi:10.3390/ijms24098027

8. Shi H, Sun L, Wang Z, et al. Non-invasive prediction of histologic chorioamnionitis using maternal serum markers in women with preterm prelabour rupture of membranes. *Am J Reprod Immunol*. 2022;88(3):e13594. doi:10.1111/aji.13594

9. Dorfeuille N, Morin V, Tétu A, et al. Vaginal Fluid Inflammatory Biomarkers and the Risk of Adverse Neonatal Outcomes in Women with PPROM. *Am J Perinatol*. 2016;33(10):1003-1007. doi:10.1055/s-0036-1582130

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