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Increased Risk of Neonatal Pneumonia in Pregnant Women with Atypical Pre-Labor Rupture of Membrane Assessed at Pregnancy Week 39

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Abstract

Purpose: Neonatal pneumonia is a major newborn disease with a high morbidity rate. We aimed to evaluate whether atypical prelabor rupture of membranes (PROM) is a high-risk factor for causing neonatal pneumonia in a prospective real-world study. **Patients and Methods:** A total of 250 pregnant women at pregnancy week 39 were non-selectively recruited. All were examined by PROM and neonatal pneumonia related clinical, bedside and lab tests, including body temperature, blood pressure, increased vagina discharge, posterior vault pooling, abdominal tenderness, WBC count, nitrazine test, amniotic fluid index, Leakection (a sICAM-1 based lateral flow immunoassay) and vagina streptococcus examinations. Increased vagina discharge with a Leakection positivity was adopted as a working criterium for identifying atypical PROM. Neonatal pneumonia was diagnosed based on the clinical presentation and lab tests. **Results:** Twenty cases of neonatal pneumonia (8.0%) were diagnosed after the deliveries of the 250 pregnant women. In these neonatal pneumonia cases, 12 (16.7%) occurred in 72 deliveries with atypical PROM, 2 (16.7%) in 12 deliveries with typical PROM, and 6 (3.6%) in 166 deliveries with non-PROM. **Conclusion:** In this real-world study, we find that a systematic screening at pregnancy week 39 was very meaningful in revealing atypical PROM. Moreover, atypical PROM is a major risk factor for neonatal pneumonia. Therefore, an early diagnosis and intervention on atypical PROM could potentially reduce the occurrence of neonatal pneumonia.

Keywords

Atypical Prelabor Rupture of Membranes, Neonatal Pneumonia, Soluble Intercellular Adhesion Molecule-1

1. Introduction

Neonatal pneumonia accounts for 46% of all neonatal diseases [1]. Moreover, the morbidity rate of neonatal pneumonia is 3.5% to 25% due to various complications, especially septicemia and respiratory distress syndrome [2]. Consequently, neonatal pneumonia is one of the main reasons leading to perinatal death. Early onset neonatal pneumonia is usually caused by pathogens aspirated by the neonates in the intrauterine environment, or in the birth canal during vaginal delivery [3]. The risk of developing neonatal pneumonia is particularly high if the mother has chorioamnionitis, an infection of the intrauterine tissues, and PROM is the main cause leading to chorioamnionitis [4].

PROM is the rupture of the fetal membranes before the onset of labor, and reportedly occurs in 6% - 19% of term pregnancies [5]. Optimal approaches to assessment and treatment of women with term and preterm PROM remains challenging. A typical PROM can be diagnosed by the presence of vaginal pooling of amniotic fluid or vernix or meconium observed at speculum examination [6]. However, in pregnant women who feel wet at the opening of the vagina but without obvious pooling of fluid, the diagnosis of PROM needs to use bedside and lab tests for confirmation or exclusion [7]. The so-called atypical PROM was previously assessed by using a bedside rapid test, Leakection, a soluble intercellular adhesion molecule-1 (sICAM-1) based lateral flow immunoassay. The sensitivity and specificity of Leakection were previously shown to be 97.0% and 91.1% respectively for the diagnosis of atypical PROM in a real-world assessment [8]. In the current prospective real-world study, we aimed at the identification of atypical PROM at pregnancy week 39 using Leakection test in conjunction with other clinical and lab examinations in the hope of evaluating whether atypical PROM is a risk factor for neonatal pneumonia.

2. Materials and Methods

2.1. Subjects

The research protocol was approved by the Institutional Review Board of Pengzhou People's Hospital, and all patients provided informed consent. All participants were Chinese of Han race. A total of 250 pregnant women aged between 21 and 41 years at pregnancy week 39 were non-selectively recruited. These women were in a regular social and economic status in the local city. The sample size was determined and considered to be large enough so that the study results could be meaningfully statistically evaluated and reflect a real-world situation. All women were examined by PROM and neonatal pneumonia related

clinical and bedside and lab tests, including body temperature, blood pressure, increased vagina discharge, posterior vault pooling, abdominal tenderness, WBC count, nitrazine test, amniotic fluid index, Leakection and vagina streptococcus exam. Neonatal pneumonia was diagnosed based on respiratory symptoms, physical examination, and increased WBC and neutrophil count.

Typical PROM was diagnosed when vaginal pooling of amniotic fluid or vernix or meconium was observed at speculum examination with a positive Leakection test. Increased vagina discharge with a Leakection positivity was adopted as a working criterium for identifying atypical PROM.

2.2. Nitrazine Test

A nitrazine test paper was placed at the posterior vault for approximately 5 seconds on a pregnant woman at speculum examination. The test paper change into blue color was considered as a positive result.

2.3. Leakection Test

Posterior vault samples were collected by avoiding visible blood contamination from each patient. Each sample was collected underneath the posterior cervical lip. For the collection a sterile cotton-tipped swab was placed at the designated position and rotated 5 times for approximately 10 - 15 seconds. The swab was then dipped into a test tube containing 0.8 ml of sterile phosphate-buffered saline, and rotated 5 times during approximately 10 seconds. Following the collection, the sample was added into the sample well of the Leakection test card (Origissay Diagnostic, Ltd., Chengdu, Sichuan, China). One or two lines could be seen in the control and test window within 3 - 5 minutes. The presence of both the orange-purple test line and control line was determined as positive. The absence of the test line and the presence of the control line was determined as negative [9] [10].

2.4. Statistical Analyses

Chi square test was used for the statistical analyses to compare variable parameters between women with PROM and women with no PROM, and $P \leq 0.05$ was considered significant.

3. Results

A total of 250 pregnant women, aged between 21 and 41 years, at pregnancy week 39 were non-selectively recruited for PROM screening using clinical examinations and bedside and lab tests. In the study, we used increased vagina discharge with a Leakection positivity as a working criterium for identifying atypical PROM. As depicted in **Figure 1**, in the 84 cases with vagina discharge (33.6% of the 250 cases), 12 were found to have typical PROM (14.3%) and 72 (85.7%) were identified as atypical PROM. The occurrence of atypical PROM was significantly higher ($P \leq 0.01$) than that of typical PROM. Eighty-four of the

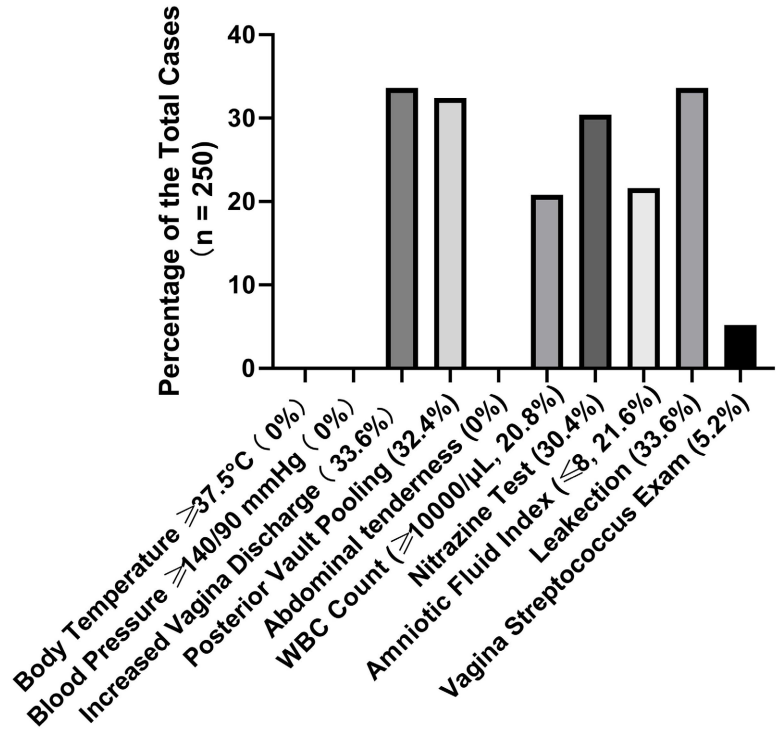

Figure 1. Results of PROM and neonatal pneumonia related clinical and lab examinations in all the recruited women at pregnancy week 39.

250 cases were found positive by Leakection test (33.6%), 81 with posterior vault pooling (32.4%), 76 positive by nitrazine test (30.4%), 54 with decreased amniotic fluid index (21.6%), 52 with increased WBC count (20.8%), and 13 with positive vagina streptococcus exam (5.2%). None of them presented with abdominal tenderness, increased body temperature, or increased blood pressure (**Figure 1**).

In the 250 deliveries, a total of 20 newborn children developed neonatal pneumonia (8.0%). Fourteen neonatal pneumonia children (16.7% of the 84 cases, **Figure 2**) were delivered by pregnant women with PROM. Out of the 14 cases, only 2 (12.5%) were found from pregnant women with typical PROM, and the remaining 12 (87.5%) occurred in the pregnant women with atypical PROM. Six neonatal pneumonia cases were found in pregnancies of non-PROM women (3.6% of 166 cases), much less than the cases occurred in the deliveries with PROM ($P \leq 0.01$). In the 20 neonatal pneumonia cases, 70% were delivered by pregnant women with PROM (**Figure 3**), and only 6 were found with increased WBC count, and 5 with positive vagina streptococcus results. None of them had a fever or increased blood pressure.

4. Discussion

This was a prospective and non-controlled real-world study. Because of the non-controlled characteristics, though the data presented were very interesting and meaningful, they should be interpreted and accepted as preliminary, and a

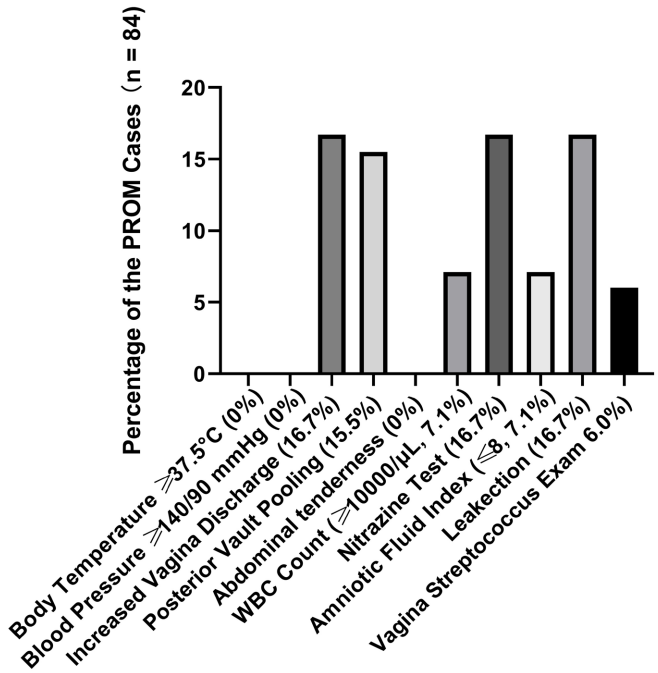

Figure 2. Results of PROM and neonatal pneumonia related clinical and lab examinations of the 14 women that delivered neonatal pneumonia children in proportion of all the 84 pregnant women with PROM. It indicated that in the pregnant women with increased vagina discharge and positive Leakection test 16.7% of the newborn children developed pneumonia.

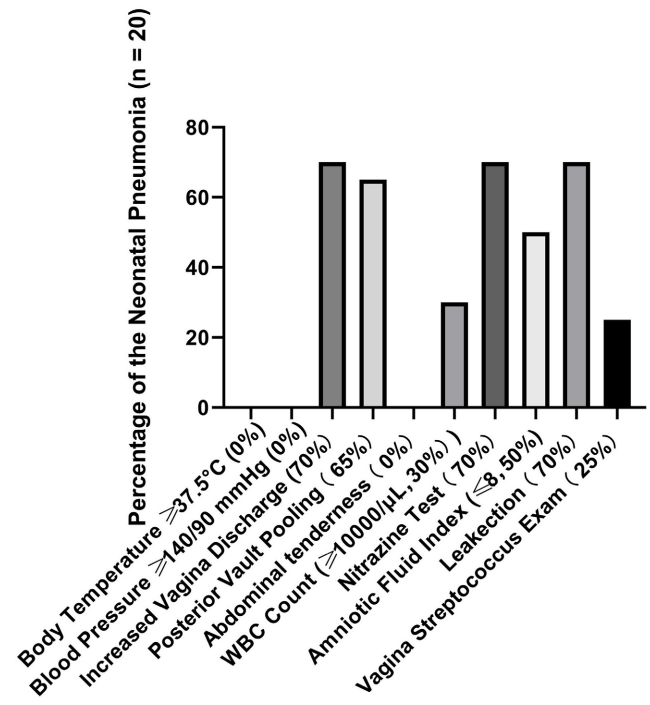

Figure 3. Results of PROM and neonatal pneumonia related clinical and lab examinations of the 20 women that delivered neonatal pneumonia children. It revealed that increased vagina discharge and positive Leakection and nitrazine tests were major risk factors for neonatal pneumonia.

controlled confirmative study is warranted. In the current study, 250 pregnant women were non-selectively recruited at pregnancy week 39 for the assessment of atypical PROM. As high as 33.6% of these women were found positive for increased vagina discharge, and all of these women were tested positive by Leakection. Meanwhile, other classic examinations detecting PROM were positive at a lower positive rate. The prevalence of atypical PROM (72/250, 28.8%) detected by increased vagina discharge and Leakection was surprisingly high, and it suggests that atypical PROM was likely under estimated in the previous and current clinical practice. This under-estimation was also observed in a previous study [8].

A total of 20 neonatal pneumonia cases (8.0%) were diagnosed and treated from the 250 deliveries. Further classification indicated that 70% of the pneumonia neonates (14 cases) were delivered by pregnant women with Leakection identified typical or atypical PROM. Importantly, the majority (12/14) of these neonatal pneumonia cases were delivered by pregnant women with atypical PROM, indicating that atypical PROM is a high-risk factor for the neonatal pneumonia. Therefore, atypical PROM as a main cause for neonatal pneumonia was probably previously under-estimated. The remaining 30% of neonatal pneumonia cases (6/20 cases) occurred in the women with no PROM. The prevalence of neonatal pneumonia was much higher in the deliveries with PROM (16.7%) than in those in the absence of PROM (3.6%). The striking difference indicates that the Leakection examination is very useful for identifying typical and atypical PROM, and is an excellent test for warning the potential occurrence of neonatal pneumonia. Furthermore, screening atypical PROM in pregnant women in the near-labor period seems to be essential in an attempt to reduce the occurrence of neonatal pneumonia, as an early identification will give the clinicians a signal for managing the atypical PROM that is proposed in the current study as the main risk factor for neonatal pneumonia.

5. Conclusion

In this prospective real-world study we find that a systematic screening at pregnancy week 39 is meaningful in revealing both typical and atypical PROM. As atypical PROM is a major risk factor for neonatal pneumonia, an early intervention is thought to be able to reduce the occurrence of neonatal pneumonia. A controlled study is warranted to confirm this assumption, and to verify whether an early intervention could reduce the occurrence of neonatal pneumonia in deliveries with atypical PROM.

Conflicts of Interest

Huaizhong Hu is a shareholder of Origissay Diagnostics Ltd. The remaining authors state no conflicts of interest.

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