Risks for preterm premature labor: Many of them are preventable

Jun-Hung Lin[a,b], Yueh-Han Hsu[a,b], Peng-Hui Wang[a,c,d,e,*]

[a]Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Department of Obstetrics and Gynecology, National Yang-Ming University, Taipei, Taiwan, ROC; [c]Female Cancer Foundation, Taipei, Taiwan, ROC; [d]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [e]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, ROC

Preterm premature rupture of membranes (PPROM) and PPROM associated with preterm birth, defined as the delivery before 37 full gestational weeks,[1,2] is still a biggest challenge in modern obstetrics, contributing to a significantly increasing maternal or neonatal morbidity and/or mortality, and a subsequently heavy socioeconomic burden if the sequelae occurs, including limitation to the newborns, such as cerebral palsy, neurodevelopment impairment, retinopathy, and bronchopulmonary dysplasia, or to the mothers, including postpartum hemorrhage, sepsis, and many.[3–5] There are many precipitating factors associated with the occurrence of PPROM and/or preterm premature labor, including maternal (medical illness, such as pregnancy-induced hypertension, preeclampsia, shortening of cervix, and autoimmune disease), neonatal (congenital anomaly as an example), and environmental factors (exposure of heavy metal intoxication, deficiency of essential micronutrients, stress, etc).[6–10]

In the March issue of the *Journal of the Chinese Medical Association*, one study from the Egypt focusing on the identification of risk factors associated with PPROM and severe preterm labor[11] attracts us, partly because both situations are associated with maternal and neonatal morbidity and mortality and partly because both of them may be preventable. The authors found that history of abortion and heavy vaginal bleeding as well as elevated vaginal pH were significantly associated with an increased risk of PPROM and moreover, adolescent (<20 years of age), history of abortion, heavy growth of vaginal organisms, and growth of Gram-negative bacilli were statistically risky for intact membrane-type preterm birth.[12] Summary of data showed adolescent, abortion history, elevated vaginal pH, and heavy growth of vaginal organisms were an independent risk factor for PPROM and severe preterm labor.[11] Since these factors are often related to infectious status, therefore, the authors recommended the importance for infection control in pregnant women. We congratulate authors' successful publication and we are also happy to learn much more efforts of the studies focusing on this topic, contributing to the urgent needs to discuss this more.

Extremely age pregnant women, either by too young (≤20 years) or by too elder (elder mother ≥35 or 40 years), are always highly risky for worse pregnancy outcomes, which occurs not only for fetus but also for mother.[1] Furthermore, this population is also highly risky for malnutrition, contributing to the statistically increased risk of preterm labor or abortion.[1] Therefore, it is surprising to find out that the adolescent pregnancy is at the high risk of preterm labor and PPROM, as shown by authors. In terms of minimizing the occurrence of preterm premature labor and PPROM, education and knowledge of contraception and safe sexual activity is very important for junior and senior high school students or adolescents, because they may have a high risk of unprotected sexual activity, with subsequent occurrence of unwanted and accidental pregnancy.

Abortion is defined as loss of pregnancy before vital fetus birth.[10] Although two definitions are often used, <6 months of gestational weeks and <500 g of birth weight, evidence is strong enough to show the strong association between abortion history and subsequent pregnancy loss.[10] A certain part of population with abortion can be identified by causes. For example, submucosal myoma and shortening of the cervix (cervical incompetence) can be surgically corrected before attempting next conception.[10] An emerged knowledge-related new insights into mechanisms behind miscarriage provide the prospect of novel effective interventions to prevent its occurrence.[13]

Elevated vaginal pH and heavy growth of vaginal microorganisms, especially for those Gram-negative bacilli overgrowth, are associated with increased preterm premature labor and PPROM.[11] The authors found this clinical situation is of most critique in the occurrence of preterm premature and PPROM and suggested that genitourinary tract infection should be managed and prevented adequately in pregnant women.[11] However, the needs of screening and treatment for bacterial vaginosis (BV) are still highly controversial, and furthermore, how to identify those pregnant women who will be beneficial in the prevention and/or treatment for BV is also a challenge. The PREMEVA (Early Clindamycin for Bacterial Vaginosis in Pregnancy) separated 3105 pregnant women into three groups (single-course clindamycin, triple-course clindamycin, and placebo) to investigate whether therapy of BV decreases late miscarriage or spontaneous very preterm birth.[14] The results showed that there is no difference of late miscarriage or spontaneous very preterm delivery among three groups or between treatment and placebo groups with relative risk (RR) of 1.10 and 95% CI of 0.53 to 2.32, and in addition, the fetal and neonatal outcomes are also similar among three groups or between two groups, such as fetal death >22 weeks (RR = 0.75, 95% CI = 0.27-2.11), neonatal pulmonary disease (RR = 0.78, 95% CI = 0.43-1.42), neonatal

*Address Correspondence. Dr. Peng-Hui Wang, Department of Obstetrics and Gynecology, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: phwang@vghtpe.gov.tw; pongpongwang@gmail.com (P.-H. Wang).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2020) 83: 421-422.

Received February 29, 2020; accepted February 29, 2020.

doi: 10.1097/JCMA.0000000000000296.

sepsis (RR = 0.77, 95% CI = 0.49-1.22), and neonatal death (RR = 0.75, 95% CI = 0.10-6.44), suggesting that asymptomatic women without a history of previous early delivery should not be screened or treated for BV.[14] Since active treatment using prophylactic antibiotics might not be beneficial for pregnant women with BV, the other strategy might be considered. For example, lactobacillus supplementation might be a better choice, since *Lactobacillus* species are a critical and dominant component in the healthy vagina to produce a substantial amount of lactic acid and hydrogen peroxide (both are a potent and broad-spectrum bactericide and virucide) to maintain an acidic vaginal environment (pH 3.5-4.5) as well as to continue inhibiting overgrowth of harmful microorganisms, such as Group B *Streptococci*, *Escherichia coli*, *Staphylococcus aureus*, *Gardnerella vaginalis*, Gram-negative bacillus, or other fastidious or uncultivated anaerobes or virus.[15]

The cause of preterm premature labor and PPROM is multifactorial and some of them are preventable. We should revisit these relatively troublesome complications occurring in pregnant women and enrich our understanding and knowledge for these to provide a better prenatal and perinatal care. A further and hopefully definite trial for early intervention or prevention by means of various tools to minimize the rate of preterm premature labor and PPROM is urgently needed.

ACKNOWLEDGMENTS

This article was supported by grants from the Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 106-2314-B-075-061-MY3) and Taipei Veterans General Hospital (V108C-085 and V109C-108). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

REFERENCES

1. Yeh CC, Chen CY, Wang PH. Infection and preterm birth. *J Chin Med Assoc* 2017;**80**:530–1.
2. Liu CH, Wang TS, Wang PH, Yen MS. Necrotizing fasciitis following a preterm caesarean delivery. *Taiwan J Obstet Gynecol* 2019;**58**:577–8.
3. Lee FK, Lin YL, Wang PH. Mesenchymal stem cells and cerebral palsy. *J Chin Med Assoc* 2020;**83**:323–4.
4. Niu X, Xu X, Luo Z, Wu, Tang J. The expression of Th9 and Th22 cells in rats with cerebral palsy after hUC-MSC transplantation. *J Chin Med Assoc* 2020;**83**:60–6.
5. Jiang M, Mishu MM, Lu D, Yin X. A case control study of risk factors and neonatal outcomes of preterm birth. *Taiwan J Obstet Gynecol* 2018;**57**:814–8.
6. Chen SN, Wang PH, Hsieh MF, Tsai HW, Lin LT, Tsui KH. Maternal pregnancy-induced hypertension increases the subsequent risk of neonatal candidiasis: a nationwide population-based cohort study. *Taiwan J Obstet Gynecol* 2019;**58**:261–5.
7. Chang WS, Lin LT, Hsu LC, Tang PL, Tsui KH, Wang PH. Maternal pregnancy-induced hypertension increases the subsequent risk of transient tachypnea of the newborn: a nationwide population-based cohort study. *Taiwan J Obstet Gynecol* 2018;**57**:546–50.
8. Woraboot W, Wanitpongpan P, Phaophan A. Correlation between lower uterine wall thickness measured by transabdominal ultrasonography and cervical length measured by transvaginal ultrasonography in Thai pregnant women. *J Chin Med Assoc* 2019;**82**:50–4.
9. Li HR, Li YH, Wang PH. Prediction of preterm labor by cervical length or lower uterine wall thickness. *J Chin Med Assoc* 2019;**82**:247.
10. Lee WL, Yeh CC, Wang PH. Risk to increase threatened abortion: deficiency of some essential trace elements and exposure of toxic heavy metals. *J Chin Med Assoc* 2019;**82**:607–8.
11. Hosny AEMS, Fakhry MN, El-Khayat W, Kashef MT. Risk factors associated with preterm labor, with special emphasis on preterm premature rupture of membranes and severe preterm labor. *J Chin Med Assoc* 2020;**83**:280–7.
12. Li YT, Li HR, Wang PH. Parameters to predict the pregnancy in assisted reproductive technology. *J Chin Med Assoc* 2019;**82**:249-50.
13. Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. *BMC Med* 2013;**11**:154.
14. Subtil D, Brabant G, Tilloy E, Devos P, Canis F, Fruchart A, et al. Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial. *Lancet* 2018;**392**:2171–9.
15. Li YT, Wang PH. The *Lactobacillus* and herpes simplex virus type 2 infection. *J Chin Med Assoc* 2018;**81**:757–8.