ORIGINAL RESEARCH

Value of Combined Bone Morphogenetic Protein-2/7 Testing in the Assessment of Infected Preterm Labor

Jinlai Zhan, MM; Nan Huang, BS; Wenbin Zhao, MM; Lin Qiu, MM; Yin Zhu, MM; Jieyu Chen, MM; Xiangjun Chen, BS

ABSTRACT

Objective • To analyze the clinical significance of bone morphogenetic protein-2 (BMP-2) and bone morphogenetic protein-7 (BMP-7), members of the bone morphogenetic protein family, in infectious preterm birth, to provide references for future prevention and management of IPB.

Methods • The study participants were 20 pregnant women with IPB admitted to between January 2022 and January 2023 (research group) and 20 concurrent normal pregnancies (control group). Serum BMP2, BMP-7 inflammatory factors were quantified. Differences in BMP2 and BMP-7 were identified. The Receiver Operating Characteristic curve analyzed the evaluation value of BMP2 and BMP-7 on infectious preterm birth and adverse pregnancy outcomes in pregnant women, and Pearson correlation coefficient determined the correlation of the two with inflammatory factors levels.

Results • The research group was higher in serum BMP2 and BMP-7 levels than control group ($P < .05$). The joint detection by BMP2 and BMP-7 had a sensitivity of 80.00% and a specificity of 90.00% in diagnosing infectious preterm birth ($P < .05$), and its sensitivity and specificity in predicting adverse pregnancy outcomes in infectious preterm birth pregnant women were 100.0% and 66.67%, respectively ($P < .05$). According to Pearson correlation coefficient analysis, there was an obvious positive relationship between BMP-2 and BMP-7 and inflammatory factors in research group ($P < .05$).

Conclusions • BMP-2 and BMP-7 are elevated in IPB and are linked to inflammatory factor levels. Joint detection of BMP2 and BMP-7 shows promising potential for evaluating infectious preterm birth. (*Altern Ther Health Med.* 2023;29(8):518-523).

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INTRODUCTION

Preterm birth (PTB) refers to delivery at 28 weeks of gestation but less than 37 weeks.[1] The earlier PTB babies are born, the lighter their weight, and the more serious the immature development of various organs, with statistics indicating that two thirds of infants who died within one year of birth are PTB babies. As one of the most common pregnancy complications, PTB is 11% in prevalence worldwide, increasing yearly in recent years.[2] Being asymptomatic in most cases, PTB usually happens accompanied by flatulence, pain and uterine contraction in the lower abdomen in the mother, as well as a small amount of vaginal bleeding. At this time, doctors need to judge whether to terminate the pregnancy according to the situation of the parturient to reduce the harm to the mother and fetus.[3] Currently, the specific etiology of PTB is not completely clear, and it is considered that intrauterine, systemic and pelvic infections play a particularly key role in PTB.[4] Studies have shown that infection can activate a variety of inflammatory pathways, promote the release of inflammatory factors (IFs), and induce the synthesis of prostaglandin and other substances in the body, thus increasing the possibility of developing PTB.[5] Moreover, infectious preterm birth (IPB) will further elevate the risk of congenital diseases in PTB infants and further threaten their life safety.[6] Therefore, effectively preventing and managing IPB is of great significance to maintain the normal pregnancy of mothers.

Bone morphogenetic proteins (BMPs) are a group of highly conserved functional proteins with similar structure, belonging to the TGF-β family.[7] BMPs can stimulate DNA synthesis and cell replication, thus promoting the directed differentiation of mesenchymal cells into osteoblasts.[8] With the deepening of research, BMPs have been gradually found to not only participate in the regulation of bones, but also

have an important impact on the development of fat, viscera and nervous system.[9] BMP-2 and BMP-7 have the most potent osteogenic-inducing activity in the BMP family and are also known as vital indicators of healthy bone development in newborns.[10] Meanwhile, recent studies have linked BMP-2 and BMP-7 to pregnancy behavior changes such as endometrial decidualization and abnormal expansion of trophoblast giant cells (TGCs) in the cavity wall.[11,12] Therefore, we suspected that BMP-2 and BMP-7 may be closely related to the occurrence of IPB, but there is no research to confirm our conjecture.

Therefore, by discussing the clinical implications of BMP-2 and BMP-7 in IPB and analyzing their relationship with inflammatory response in pregnant women, this study aimed to provide evidence and theoretical basis for future clinical prevention and treatment of IPB.

MATERIALS AND METHODS

Research location

This study was conducted in the Department of Obstetrics and Gynecology at the Affiliated Hospital of Hangzhou Normal University, and participants were recruited from January 2022 to January 2023.

Research target

Forty pregnant women who were admitted to the Department of Obstetrics and Gynecology of Affiliated Hospital of Hangzhou Normal University from January 2022 to January 2023 and met the inclusion criteria were selected as the research participants, of which 20 pregnant women with IPB were regarded as the research group (RG) and the other 20 normal pregnancies were regarded as the control group (CG). The guidelines of the Declaration of Helsinki were strictly followed. All pregnant women signed informed consent. Ethical approval for this study was obtained from the Affiliated Hospital of Hangzhou Normal University: 2021(B2)-HS-072.

Inclusion criteria

Complete clinical data; the criteria for PTB are women who have regular contractions (4 times/20min or 8 times/60 min) after 28 weeks of gestation and less than 37 weeks' pregnancy, but the cervix has not yet dilated, and the length of the cervix measured by transvaginal ultrasound is less than 20 mm; full-term delivery occurs when delivery is given after 37 weeks of pregnancy; the onset of labor is defined as regular contractions accompanied by cervical shortening and opening of the cervix by 2-3 cm; for full-term tissue samples, infection factors were excluded; age range: 18-40 years old; single live pregnancy; no obvious symptoms of vaginitis; those who have regular prenatal examinations at our hospital.

Exclusion criteria

those with pregnancy complications such as gestational obesity, gestational cardiovascular disease, pregnancy-induced hypertension, gestational diabetes mellitus (GDM) and intrauterine growth restriction (IUGR); those with hypertension and chronic diseases; a precious baby or test-tube baby, or a person with an adverse pregnancy history, such as fetal or neonatal malformation, stillbirth, and habitual abortion; suspected or confirmed threatened premature delivery; those with a history of cervical cerclage or trauma and iatrogenic PTB; premature or full-term infants who fail to resuscitate due to neonatal asphyxia or whose family members have abandoned treatment.

Data collection

When patients were admitted to the hospital, information on their age, race, education, family income, blood pressure, and reproductive history was collected and saved in a computer.

Specimen collection

From all subjects, 3 mL of venous blood was drawn upon admission, left at room temperature for 30 min, and centrifuged to obtain serum, which was then labeled and stored in a -80°C refrigerator for testing.

Enzyme-linked immunosorbent assay (ELISA)

Serum BMP-2, BMP-7, and IFs interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α were detected by ELISA following the operating manual of kits all supplied by China TransGen Biotech. The antigen used was diluted to 100 μg/mL with inclusion diluent, and 100 μl of antigen was added to each well.The liquid in the wells was discarded after incubation at 37°C for 4 h. The wells were blocked with 5% fetal bovine serum for 40 min (at 37°C), and washed three times with washing solution. The diluted sample was added into the enzyme reaction wells, 100μL per well, incubated at 37°C for 60min, washed for 3 times and then added into each well with 100 μL of TMB-hydrogen peroxide urea solution, incubated for 5min away from the light, and then added 50 μL of termination solution to develop the color. The optical density (OD) value at 490 nm was detected by an enzyme counter.

Quantitative real-time polymerase chain reaction (qRT-PCR)

After isolation with Trizol, the total serum RNA were validated by ultraviolet spectrophotometry for its purity and integrity, and then reverse-transcribed into complementary DNA as instructed by the reverse transcription kit. Using 2μL reverse transcription product as template, RT-PCR was carried out with the use of a ComSYBR qPcR kit. The relative expression levels of all the targeted substances were detected by TaqMan microRNA RT-PCR, which was performed using the Applied Biosystems 7500 Sequence Detection system from Ambion Inc. in strict accordance with instructions. BMP-2 and BMP-7 levels relative to U6 were detected by the $2^{-\Delta\Delta Ct}$ relative quantitative method.

Data collection

The clinical information of all parturients was collected, including age, ethnicity, education level, family income, systolic/diastolic blood pressure, and childbearing history.

Table 1. Comparison of clinical baseline data

		Control group	Research group	t or χ^2	P value
Age		28.50 ± 3.90	27.35 ± 5.24	0.787	.436
Ethnicity	Han Chinese / Ethnic Minority	17/3	19/1	1.111	.292
Education level	Below high school/high school and above	4/16	2/18	0.784	.376
Family income (year)	<100 000/≥100 000	9/11	8/12	0.102	.749
SBP (mmHg)		113.80 ± 11.29	111.95 ± 8.25	0.592	.558
DBP (mmHg)		75.55 ± 9.14	76.90 ± 4.25	0.599	.553
Types of Pregnancy	Primigravida/Menstrual	14/6	16/4	0.533	.465

Statistical methods

Data were statistically analyzed with SPSS 21.0, and the significance threshold was $P < .05$. All data were tested for normality by the Shapiro-Wilk test. The mean ± standard deviation ($\bar{x} \pm s$) was used to denote normally distributed continuous variables, for the inter-group comparison of which an independent sample t test was used. The nonparametric Mann-Whitney U test was used for data that did not conform to variance homogeneity, with α = 0.05 as the test level. Diagnostic value was analyzed by the receiver operating characteristic (ROC) curve [A coordinate plot consisting of False positive rate on the horizontal axis and True positive rate on the vertical axis. In the case of Area Under Curve (AUC) > 0.5, the closer the AUC is to 1, the better the diagnosis], and Pearson correlation coefficients identified correlation [Measures the correlation (linear correlation) between two variables (X) and (Y) with a value between -1 and 1.].

RESULTS

Comparison of clinical baseline data

Comparing the clinical baseline data between RG and CG (including age, ethnicity, family income, etc.), it was found that the inter-group difference was not statistically significant ($P > .05$), which proves that there is comparability between groups and the results of this study are accurate and reliable (Table 1).

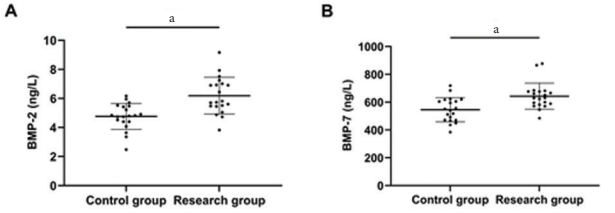
Comparison of BMP-2 and BMP-7 levels

In comparison with CG, the concentrations of BMP-2 and BMP-7 in RG increased markedly ($P < .05$), with statistical significance (Figure 1).

Diagnostic value of BMP-2 and BMP-7 in IPB

ROC analysis showed that when serum BMP-2 >5.44 ng/L, its sensitivity, specificity and area under the ROC curve (AUC) in IPB diagnosis were 80.00%, 75.00%, and 0.830, respectively, indicating a good diagnostic effect ($P < .05$). BMP-7 also showed favorable diagnostic effects, with its sensitivity, specificity, and AUC in diagnosing IPB being 90.00%, 60.00%, and 0.778 ($P < .05$), respectively, when BMP-7 >563.80 ng/L. Finally, through binary Logistic regression analysis, the formula of BMP-2 + BMP-7 detection: Log(P) = -16.045 + 1.420 × BMP-2 + 0.014 × BMP-7, was obtained. Further, ROC analysis showed that when the Log(P) was greater than 0.53, the sensitivity, specificity and ACU of the joint detection in diagnosing IPB were 80.00%, 90.00%, and 0.898 ($P < .05$), respectively, suggesting excellent diagnostic effects (Figure 2).

Figure 1. Comparison of BMP-2 and BMP-7 levels. **A.** BMP-2, **B.** BMP-7.



[a]$P < .05$

Figure 2. 2 Diagnostic value of BMP-2 and BMP-7 in IPB. **A.** ROC for BMP-2 diagnosis of IPB, **B.** ROC for BMP-7 diagnosis of IPB, **C.** ROC for BMP-2 combined with BMP-7 diagnosis of IPB.

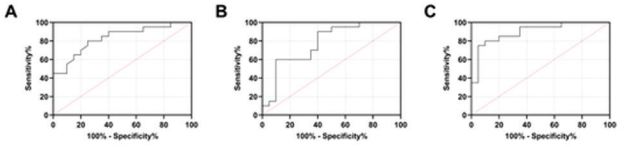
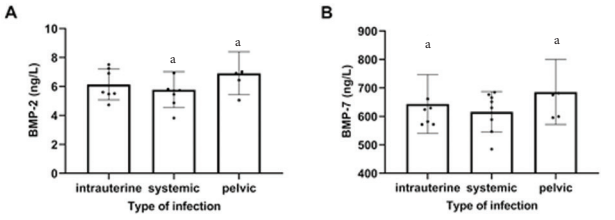
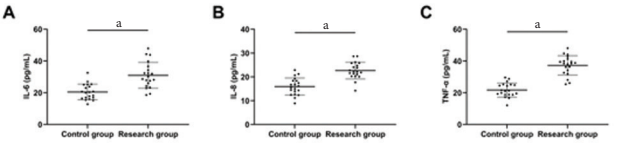


Figure 3. Correlation of BMP-2 and BMP-7 with infection types in RG. A) BMP-2, B) BMP-7.



[a]$P < .05$

Figure 4. Comparison of IF concentrations. **A.** IL-6, **B**. IL-8, **C.** TNF-α.



[a]$P < .05$

Patients in the RG were stratified based on their infection types

Patients in RG were grouped based on their infection types to comparatively analyze BMP-2 and BMP-7. Serum concentrations of BMP-2 and BMP-7 were found to differ insignificantly among pregnant women with intrauterine, systemic and pelvic infections ($P > .05$), suggesting that BMP-2 and BMP-7 have no obvious relationship with infection types of pregnant women with IPB (Figure 3).

Comparison of IF concentrations

The detection results of IFs in the two groups showed that the serum levels of IL-6, IL-8 and TNF-α in RG were (30.99 ± 8.19)pg/mL, (22.66 ± 3.49)pg/mL and (37.21 ±6.07) pg/mL, respectively, which were obviously increased compared with CG ($P < .05$, Figure 4).

Figure 5. Correlation of BMP-2 and BMP-7 with IFs in RG. **A.** Correlation of BMP-2 and IL-6, **B.** Correlation of BMP-2 and IL-8, **C.** Correlation of BMP-2 and TNF-α, **D.** Correlation of BMP-7 and IL-6, **E.** Correlation of BMP-7 and IL-8, **F.** Correlation of BMP-2 and TNF-α.

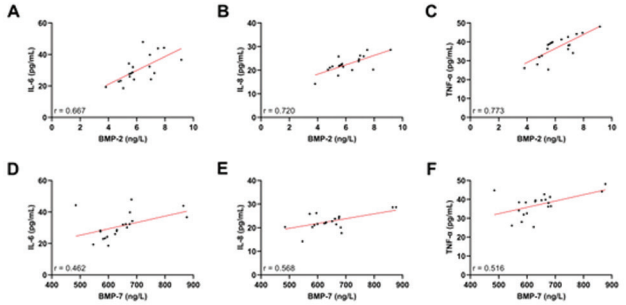
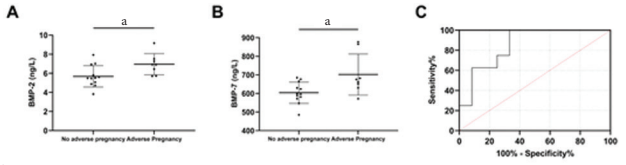
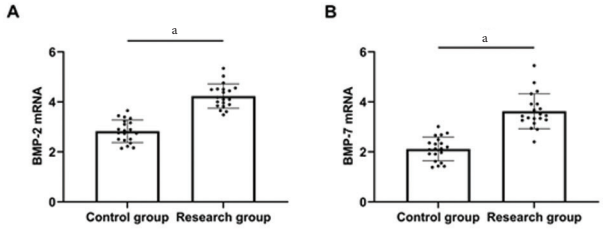


Figure 6. Correlation of BMP-2 and BMP-7 with childbirth in RG. A) BMP-2, B) BMP-7, C) Combined BMP-2 and BMP-7 assay for diagnosis of ROC in adverse pregnancies.



*$P < .05$

Figure 7. BMP-2 and BMP-7 expression by qRT-PCR. A) BMP-2 mRNA, B) BMP-7 mRNA.



[a]$P < .05$

Correlation of BMP-2 and BMP-7 with IFs in RG

According to Pearson correlation coefficient analysis, BMP-2 and BMP-7 were positively correlated with IL-6, IL-8 and TNF-α in RG ($P < .05$), that is, the levels of IFs increased with the increase of BMP-2 and BMP-7 concentrations (Figure 5).

Correlation of BMP-2 and BMP-7 with childbirth in RG

In RG, 10 pregnant women had adverse pregnancy outcomes (fetal malformation, fetal edema, fetal distress, congenital diseases, etc.), all showing higher BMP-2 and BMP-7 levels than those without adverse pregnancy outcomes ($P < .05$). Furthermore, ROC analysis revealed that when the Log(P) was greater than 0.23, the sensitivity, specificity and AUC of BMP-2 + BMP-7 detection in predicting IPB in pregnant women were 100.0%, 66.67%, and 0.854, respectively ($P < .05$), indicating a good diagnostic effect (Figure 6).

BMP-2 and BMP-7 expression by qRT-PCR

Finally, BMP-2 and BMP-7 levels were further detected by PCR to verify the above experimental results. BMP-2 and BMP-7 mRNA were higher in RG than in control CG. ($P < .05$, Figure 7).

DISCUSSION

The incidence of IPB has been on the rise worldwide in recent years.[13] It is shown that inflammation, which infectious and non-infectious factors can cause, is the primary cause of PTB, but the mechanism underlying the occurrence of PTB is not fully understood at present.[14,15] Therefore, the study of the etiology and associated molecular mechanisms of PTB has great clinical implications for the effective prevention and treatment of PTB and the reduction of its incidence. Current studies have confirmed that BMP-2 and BMP-7 play an important role in endometrial decidualization, embryogenesis, and development.[16,17] Therefore, the two are speculated to be involved in initiating labor and repairing fetal membranes, but the exact mechanisms need further study and discussion.

This study determined markedly higher concentrations of BMP-2 and BMP-7 in pregnant women with IPB than in those with normal pregnancies. The PCR results were also the same, suggesting the potential involvement of the two in IPB onset and progression. Among them, BMP-2 is mainly located in amniotic epithelial cells and also exists in a small amount of decidua stromal cells and trophoblast cells, which is the only member of BMP family whose expression in pregnant uterus is regulated by progesterone.[18] The loss of BMP-2 in the female reproductive tract can result in delayed embryonic development, abnormal uterine angiogenesis, and placental intrauterine growth restriction.[19] Another study found that BMP-2 expression in the fetal membranes may be associated with the repair and regeneration activities during the healing process of fetal membrane injury, suggesting that BMP-2 may participate in the healing process of fetal membrane injury.[20] The BMP-7 gene, located on chromosome 20, has a total length of 1293bp and ability to encode proteins containing 431 amino acids, which is expressed in tissues such as bone, kidney, adrenal gland, bladder and brain, and interferes with the development and formation of many organs in the whole body.[21] The counts of primary, preantral, and antral follicles increases, indicating that BMP-7 can facilitate the transformation of primordial follicles into primary, preantral, and antral follicles. In addition, BMP-7 increases the DNA synthesis of small antral follicles and the proliferation of granulosa cells in vitro, and exerts an inhibitory effect on ovulation rate and serum progesterone level.[22] Thus, BMP-2 and BMP-7 may play an essential role in the process of human childbirth. Through ROC analysis, we can see that the two had good diagnostic and evaluation value for the occurrence of IPB, and the AUC reached 0.898 when they were combined, which is of great significance for IPB, a condition without special clinical symptoms and lacking reliable evaluation indicators in clinical practice. We believe that in the future, monitoring BMP-2 and BMP-7

levels during pregnancy can effectively evaluate the occurrence of IPB, so that timely and early intervention can be carried out to maintain pregnancy and improve the safety of the mother and child.

Although the relationship between BMP-2, BMP-7 and IPB can be preliminarily understood through the above experiments, the specific mechanism of their action remains elusive. As we all know, inflammatory reaction is one of the important links in IPB, and the correlation of BMP-2 and BMP-7 with inflammation has also been mentioned in previous studies many times.[23,24] Therefore, we speculate that the participation of BMP-2 and BMP-7 in IPB may also be related to the modulation of inflammatory response. For validation, we further analyzed the relationship between the two and the levels of IFs in pregnant women. First, higher IL-6, IL-8 and TNF-α were found in pregnant women with IPB compared with those with normal pregnancies, similar to previous findings.[25] And in IPB patients, an obvious positive correlation of BMP-2 and BMP-7 with the above IFs were identified, confirming that the increase of BMP-2 and BMP-7 levels could aggravate the inflammatory reaction. Kaito et al. also indicated that the secretion of IL-1β and TNF-α can increase the production of BMP-2 in amniotic epithelial cells.[26] which is also consistent with our research results and can support our view. From this, we preliminarily speculate that after infection, the conduction capacity of BMP-2 and BMP-7 in endometrium, follicles and other organs and tissues is improved, and the release of the activated IFs accelerates the occurrence of IPB, which is transferred to the newborn through amniotic fluid, umbilical cord and other channels, increasing the adverse risk of newborns. Similarly, BMP-2 and BMP-7 were found to have good evaluation value for adverse pregnancy outcomes, which can also preliminarily support the above viewpoint, and once again confirmed the important clinical significance of the two for IPB. Later, no significant differences were observed in BMP-2 and BMP-7 contents among pregnant women with different infection types. This result suggests that although BMP-2 and BMP-7 have an excellent evaluation effect on IPB, they still cannot accurately identify the types of infection. In the future, we still need to use other means or conduct more in-depth research to further understand the pathological mechanism of IPB.

However, there may be some result bias due to the limited number of subjects included. Second, peripheral blood was the main test object in this study; given that the detection of uterus and placenta tissue may contribute to more accurate and representative results, a follow-up verification analysis of the above samples should be conducted in the future. But based on the consideration of BMP-2 and BMP-7 as future IPB evaluation indexes, blood samples are more advantageous for collection and preservation. Finally, we also need to carry out follow-up in vitro experiments to further confirm the specific mechanism of BMP-2 and BMP-7 in IPB to provide a more reliable reference for clinical practice.

CONCLUSION

BMP-2 and BMP-7 were elevated in IPB, and their combined detection were assessed to be effective in evaluating the occurrence of IPB and adverse pregnancy outcomes in pregnant women. In the future, the occurrence of IPB can be effectively prevented by monitoring the levels of BMP-2 and BMP-7 during pregnancy. In addition, BMP-2 and BMP-7 in pregnant women with IPB are positively correlated with inflammatory reaction, which may also be the mechanism of their involvement in IPB onset and progression. We will conduct in vitro experiments for validation and analysis as soon as possible.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Affiliated Hospital of Hangzhou Normal University: 2021(B2)-HS-072.

COMPETING INTERESTS

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Nan Huang and Yin Zhu: Methodology, Investigation, Data curation, original draft. Wenbin Zhao and Jieyu Chen: Methodology, Investigation, Data curation, original draft. Jinlai Zhan: Writing, review & editing. Lin Qiu: Review & editing. Xiangjun Chen: Idea, Supervision, review & editing.

AVAILABILITY OF DATA AND MATERIALS

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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