Combined quantitative detection of IGFBP--1/fFn for predicting premature rupture of membranes and preterm delivery

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Abstract: Objective: To evaluate the clinical value of IGFBP-1 and fFN in preterm birth prediction. Method: Second-trimester pregnant women who choose to come to our hospital for pregnancy check-screening. Results: The combined detection of IGFBP-1 and fFN was consistent with the clinical diagnosis .Conclusion: fFN and IGFBP-1 are effective indicators for predicting premature rupture of membranes and preterm birth, and the combined application can maximize the diagnostic coincidence rate.

Keywords: Insulin-like growth factor binding protein-1(IGFBP-1), Fetal fibronectin (fFN), Premature delivery, Premature rupture of membranes(PROM)

1. Introduction

Premature birth refers to the childbirth that reaches 28 weeks but less than 37 weeks. The newborn at this time is called premature babies. Some countries have defined the lower limit of premature birth time as 24 weeks or 20 weeks of pregnancy. Each organ development of premature babies is not good enough. The smaller the birth week, the lighter weight, and the worse the prognosis. Domestic premature birth accounts for 5%to 15%of the total number of delivery. About 2/3 of the babies who were born within 1 year old were premature infants. Premature production prevention and control is one of the main measures to reduce the mortality of the siege and improve the quality of the newborn.

At present, commonly used means are symptoms and cervical length assessment, as well as separate cervical length or biomarkers evaluation, and its specificity is not high.

Fetal fiber connection protein (fFN) detection is extremely negative in biomarkers, so it is extremely valuable. The Chinese Guide and the American Obstetrics and Gynecologist Association (ACOG) guide are recommended to diagnose conventional projects for premature birth.

fFN, that is, fetal fibrin connecting protein, is the substrate ingredients of the extracellular cell cells of the uterine chorion. It is a sugar protein. It exists between the choric membrane and the molt. It is mainly produced by nourishing layer cells. Between 22-35 weeks of pregnancy, the level of fFN in the cervical vaginal secretion has a great correlation with premature birth.

The " Guidelines for the diagnosis and treatment of premature rupture of membranes "[1] of premature birth pointed out: fFN negatives, the negative prediction value of no childbirth within 1 week is 98%, and 95%of no delivery within 2 weeks. Its significance is its negative prediction value and the significance of recent predictions.

Among the factors of conventional premature birth, the premature breakthrough of the fetal membrane occupies the main factors, so the diagnosis of premature breakthroughs in the fetal membrane is also of great significance for prediction prediction.

The natural rupture of the abnormal membrane before the birth is called premature fetal membrane breakthrough (PROM), and those who have reached and exceeded 37 weeks have said that the full moon membrane is broken; those who have not reached 37 weeks say that the firous membrane is broken early (PPROM). The incidence of a single PROM in full moon is 8%; the incidence of PPROM in a single

pregnancy is 2%to 4%, and the incidence of PPROM in the pregnancy is 7%to 20%. Premature breakthroughs in the perfection of the lunar membrane are one of the main reasons for premature birth. The smaller the fetal membrane breakfast, the worse the prognosis of the siege.

Premature diagnostic method of fetal membrane: Observation method (amniotic fluid out of the amniotic fluid); pH test (pH ≥6.5); vaginal fluid coating to check sheep-like crystals; ultrasonic examination; cervical vaginal fluid biochemical examination: insulin-like growth factor binding protein -1, etc. Essence

IGFBP-1, that is, insulin-like growth factors bind to protein -1, mainly exist in amniotic fluid, which is synthesized by molten cells. It is a iconic protein in amniotic fluid during pregnancy. When the fetal membrane is ruptured, the amniotic fluid leaks from the rupture of the fetal membrane to the cervical vagina, and the IGFBP-1 contained in the vaginal secretions becomes the symbol of the premature diagnosis of the fetal membrane. Due to its high content in the amniotic fluid, the sensitivity is Very high, you can detect the trace amniotic fluid that conventional means cannot be measured, and solve the problem that the premature breakthrough and high water breakthroughs are difficult to detect. It has high sensitivity and specificity, and is not interfered by body fluid.

Earlier abroad carried out the study of the premature breakthrough and fFN prediction of prediction of prediction of pre-birth of the vaginal secretion of vaginal secretions abroad, and transformed into a test agent, conducted relevant clinical value research, confirming that the value of IGFBP-1 diagnosis of fetal membrane breakdown is that the specificity lies in the specificity Both and sensitivity are high. The value of fFN predicting premature birth risk is that the negative prediction rate is high.

In 2018 ACOG's No. 188 Guide "Prelabor Rutture of Membranes"[2], IGFBP-1 is recognized as early breakthroughs and higher-specific fetal membrane assisted. Diagnostic indicators.

There are fewer related documents for the combined diagnostic value of these two indicators.

In terms of quantitative research, IGFBP-1 has less quantitative research. At present, theoretical analysis believes that the detection of IGFBP-1 in vaginal secretions means positive, so there is no quantitative detection IGFBP-1 and set the need for reference range. fFN has related quantitative studies. Study through sample segment statistics, it shows that the fFN content is related to the high and low risk of premature birth. : Based on a large number of evidence -based medical evidence, in addition to affirming the significance of the fFN negative results, it also mentioned and affirmed the advantages of fFN quantitative detection than the meaning of fFN negative results. Evidence -based medical evidence that occurs in different quantitative results at different quantitative results, which is of great significance for the guidance of medical institutions that can carry out fFN quantitative testing in my country.

In summary, there are fewer research on IGFBP-1 and fFN, and are currently limited to the study of single qualitative or a small amount of fFN single quantitative clinical value.

In the early days of domestic use of foreign import reagents such as Adeza, Aisu, and Haolojet, a single IGFBP-1 or fFN qualitative testing of the qualitative detection of fFN was consistent with foreign countries. The value of the premature breakdown of the diagnosis of the fetal membrane is that the specificity and sensitivity are high, and the value of fFN predicts the risk of premature birth is that the negative prediction rate is high.

In 2015, the "Guidelines for the diagnosis and treatment of premature rupture of membranes"[1], based on reference to foreign guidelines, further affirmed the detection value of IGFBP-1. Due to the premature breakthrough of the fetal membrane, the amniotic fluid leaked into the vaginal secretion, which also contains fFN, which makes the correlation of fFN positive testing unknown. Therefore, China 's" Premature Clinical Diagnosis and Treatment Guide "[12]in 2014 is no longer recommended for fFN testing alone.

Due to the innovation of domestic diagnostic reagents, in recent years, reagents that can use the same vaginal secretion samples to detect IGFBP-1 and fFN have been detected at the same time. At the same time, the premature breakthrough and premature birth risk of the fetal membrane are simplified, and the operation of the premature breakdown and simple premature birth can be provided to provide additional premature breakdown and simple premature birth. Therefore, it is of great significance.

At present, the research on fFN single quantitative testing has appeared in China. The research results show that the content of the fFN of the vaginal secretion is related to the risk of premature birth. The IGFBP-1 quantitative research is blank, which needs to be further studied.

"People" is the basic element and dynamic of economic and social development power. In recent

years, the width of the willingness to be educated in my country has decreased. The number of childcare women also shows a decline, resulting in big birth decrease. China's 2019 population outgive birthdropto14.65 million, outgive birthrate dropto1.048%, the lowest level since 1949. 2016, since the "Full of 2nd Children" policy, population out Birth rising to17.86 million in 2016, and then declined for two consecutive years, the policy effect has subsided significantly. Therefore, my country will enter the aging society in advance, resulting in series of economic and social issues [2]. Lifting the population quality and reduced the mortality rate of siege will contribute to partial will help part of the problem of alleviating aging society. But how to effectively Popularity of the population has become an urgent problem to be solved. Preterm birth, especially the premature birth of the fetal membrane is the main factors that affect the quality of the population and the mortality rate of the siege. [1.2.3].

Prevention and control of preterm birth is one of the main measures to reduce perinatal mortality and improve the quality of newborns[5]. Early broken fetal membrane is the main factor that leads to premature birth. With the continuous development of medicine, more and more evidence-based medicine proves that Strengthening the management of premature birth and health care during the perinatal period is important to reduce premature birth and improve the ending of premature babies. American, British, French and other national obstetrics and gynecology societies, European Society of Perinatal Medicine, Society for Maternal-Fetal Medicine, WHO have issued a guidelines for premature birth management [6-7].

However, precise predictions of preterm birth are still lacking. Fetal fibronectin(fFN) is the ingredient component of the outer cells of the puffy film, which is a glucose protein. It exists between the chorus membrane and the molt. The detection of negative predictive values in the signs logo is extremely valuable. China Guide and The American College of Obstetricians and Gynecologists(ACOG) Guide Recommended as a regular plan for premature diagnosis. [8-9].

Among the factors of conventional premature birth, the premature breakthrough of the fetal membrane occupies the main factors, so the diagnosis of premature breakthroughs in the fetal membrane is also of great significance for prediction. IGFBP-1, that is, insulin-like growth factor binding protein - 1, mainly exists in amniotic fluid, is synthesized by molten cells, is the iconic protein in amniotic fluid during pregnancy. When the fetal membrane is ruptured, the amniotic fluid is leaked from the broken cymbal of the fetal membrane to the cervical vagina. The IGFBP-1 contained in the vaginal secretions becomes the symbol of the premature diagnosis of the fetal membrane. Due to its high content in the amniotic fluid, it is extremely high. Therefore, the sensitivity is very high, and the trace amniotic fluid measured by the conventional means can be detected, which solves the problem of the premature breakthrough and high -level breakthrough. It has high sensitivity and specificity[10].

However, IGFBP-1 combined with fFN detection in the premature predictions still lacks research reports. In this study, IGFBP-1 and fFN are combined with cervical secretions of maternal cervical secretions in large samples to evaluate the value of prediction for prediction; dynamic and quantitative detection of IGFBP-1 and fFN for high-risk pregnant mothers, then intervene in time.

2. Objects and methods

2.1. Research objects

A total of 320 pregnant women in the second trimester of pregnancy were selected to come to our hospital for examination during pregnancy. There was no massive vaginal bleeding.The paper size must be set to A4 (210x297 mm). The margins must be set as the following:

2.2. Experimental method

For healthy and normal pregnant women, starting from 22 weeks, sampling every 4 weeks, and record the test results, until the diagnosis of threatened preterm labor or premature rupture of membranes. Among them, for pregnant women with fFN≥50ng/ml or IGFBP-1≥20ng/ml, sampling was performed once a week, and the test results were recorded. At the same time, treat and monitor those who have no contraindications and conditions to prolong the gestational age.

2.2.1. Sampling method

Use a disposable sterile swab to wipe 5-7cm from the vagina to collect vaginal secretions or vaginal effluent. If the sample is contaminated with blood, it will interfere with the test results. Insert the swab

into the sample diluent and rotate for about 60 seconds to extract the secretions. Discard the cotton swab. The collected sample solution should be tested within 1 hour.

2.2.2. Inspection method

The operation method is as follows: take out the aluminum foil bag in the kit and equilibrate at room temperature, open the aluminum foil bag, and take out the test card. Place the detection card flat on the table, and pipette 75 µl of the sample solution into the sample hole of the detection card. After 15 minutes, push the detection card to the supporting instrument to read the detection results of IGFBP-1 and fFN, and obtain the corresponding concentration value.

The combined quantitative determination kit of IGFBP-1 and fFN was provided by Anhui Huibang Bioengineering Co., Ltd.

2.2.3. Diagnosis

Diagnosis of premature rupture of membranes: Pregnant women complained of sudden vaginal discharge or invisible leakage, a few pregnant women only felt that the vulva was moister than usual, and the speculum test showed that amniotic fluid mixed with fetal fat flowed out of the cervix.

Diagnosis of preterm birth: Regular uterine contractions (4 times every 20 minutes or 8 times every 60 minutes) and progressive shortening of the cervical canal (cervical shortening $\geq 80\%$) accompanied by dilation of the cervix, clinical diagnosis of preterm labor; The presence of regular contractions (4 every 20 minutes or 8 every 60 minutes), but the cervix has not been dilated, and a $CL < 20$ mm measured by transvaginal ultrasonography is diagnosed as threatened preterm labor.

3. Results

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3.1. IGFBP-1

Within 34 weeks, IGFBP-1$\geq$20ng/ml, the number of cases is 45.

20ng/ml<IGFBP-1$\leq$50ng/ml, the number of cases is11, Combined with the clinical symptoms of pregnant women and the examination of blood inflammatory indicators, it is judged that it should be chorioamnionitis caused by infection, and early fetal membrane rupture may occur. continuous monitoring, which 3 example IGFBP-1 keeps increasing to >100ng/ml, eventually turned into premature rupture of membranes. 2 cases were finally diagnosed as threatened preterm birth.

50ng/ml<IGFBP-1$\leq$100ng/ml, the number of cases is10, after continuous monitoring, where6exampleIGFBP-1keep increasing to >100ng/ml, eventually turned into premature rupture of membranes. 2 cases were finally diagnosed as threatened preterm birth.

IGFBP-1>100ng/ml, the number of cases is 24, consistent with the diagnosis of premature rupture of membranes.

In the rest of the case of maintaining IGFBP-1 <20ng/ml, 1 case of premature rupture of membrane finally occurred.

Table 1: Test results of IGFBP-1.

IGFBP-1(ng/ml)	Number of cases	final >100ng/ml or number of cases of threatened preterm birth
$\geq$20	11	5
20 < IGFBP-1 $\leq$ 100	10	8
>100	24	24
Total	45	37

3.2. fFN

Of the 320 cases, 107 cases of 50ng/ml$\leq$fFN <200ng/ml. After treatment, 42 cases of fFN became smaller and the mutation coefficient (CV)> 20%, 58 fFN values changed CV $\leq$20%, and 2 cases gave birth 34 weeks ago.Seven cases of fFN became larger and changed CV> 20%, of which 6 of them gave

birth 34 weeks ago.

60 cases with 200ng/ml≤fFN<500ng/ml. After treatment, the fFN value of 13 cases became smaller and the CV>20%, the fFN value of 35 cases changed little (CV≤20%), and 1 case gave birth before 34 weeks. Twelve patients had larger fFN and changed CV >20%, 11 of whom delivered before 34 weeks.

23 cases with fFN≥500ng/ml. After treatment, the fFN value of 6 cases changed little (CV≤20%), and 1 case delivered before 34 weeks. Seventeen patients had larger fFN and changed CV >20%, of which seven delivered before 34 weeks.

4. Conclusions

4.1. fFN

fFN is an extra -matched component of the uterine choric membrane cells. It exists between the choric membrane and the molt, and it is mainly produced by the nourishing layer cells. Because after 21 weeks of pregnancy, the fusion of the fluff film and the molting prevents the release of the fFN, and the normal pregnant woman has a very low content when the 22-35 gestational week. When the extracellular matrix of the molt interface is damaged (such as uterine contraction) or protein hydrolytic enzymes, the fFN can be seen in the cervical vaginal secretion. Therefore, at 22-35 weeks of pregnancy, the level of fFN in the cervical vaginal secretion has a great correlation with premature birth, that is, excessive fFN in the cervical vaginal secretion in the late pregnancy is a symbol of premature birth. The results of this study are consistent with the relevant research. In addition, fFN indicates that the chance of premature birth is greater.

4.2. IGFBP-1

IGFBP-1 is mainly synthesized and secreted by molten cells, mother and child liver, ovarian particle cells, and separate mechanical pressure, protein hydrolysis and local inflammation of premature birth. Essence If IGFBP-1 is found in cervical mucus, the possibility of premature birth will increase significantly. This study shows good clinical application value. Compared with fFN, IGFBP-1 will not affect the test results due to vaginal bleeding, premature fetal membrane breakdown, and semen.

4.3. Combined detection

In this study, the results of fFN and IGFBP-1 combined detection and predicting prediction prediction are also relatively satisfactory. Two indicators have a high diagnostic compliance rate, which can effectively make up for the errors caused by a single indicator detection, and provide a more accurate and objective basis for clinical judgment and treatment of obstetricians

4.4. Screening

As a result of the screening of pregnant women, IGFBP-1, fFN joint testing is consistent with the results of clinical diagnosis. Among them, the fFN results are basically consistent with the "2016 Queensland Clinical Guidelines: Preterm Labor and Delivery"[11].

4.5. Total

Before and after the treatment of pregnant women with premature signs, the joint test results are consistent with the results of the clinical diagnosis.

In conclusion, dual quantitative dynamic monitoring IGFBP-1 and fFNs can be used to accurately predict the premature birth of the fetal membrane.

References

[1] Obstetrics Group, Obstetrics and Gynecology Branch of Chinese Medical Association(2015). Guidelines for the diagnosis and treatment of premature rupture of membranes[J]. Chinese Journal of Obstetrics and Gynecology, no.50(1), pp.3-8.
[2] American College of Obstetricians and Gynecologists(2018). Practice Bulletin No. 188: Prelabor

Rupture of Membranes. Clinical management guidelines for obstetrician-gy necologists[J]. Obstet Gynecol, no. 131(1), pp.e1-e14.

[3] Sun Sumei, Li Shouzhong(2016). The clinical value of insulin-like growth factor-binding protein-1 in the diagnosis of premature rupture of membranes[J]. Practical Clinical Medicine, no.17(2), pp.43-45.

[4] Schmitz T, Sentilhes L, Lorthe E, et al(2019). Preterm premature rupture of the membranes: Guidelines for clinical practice from the French College of Gynaecologists and Obstetricians(CNGOF). European Journal of Obstetrics & Gynecology and Reproductive Biology, no.236, pp.1-6.

[5] Zhang Luming, Sun Mingqiang, Chen Qiang, et al(2017). The value of fetal fibronectin and insulin-like growth factor-binding protein-1 in the prediction of preterm birth [J]. Frontiers in Chinese Medicine, no.8(18), pp.89-90 .

[6] Zeng Jingyan, Zhang Yuan, Kuang Xiaoling(2016). The application of insulin-like growth factor-binding protein-1 in the diagnosis of premature rupture of membranes [J]. Journal of Haer Medical College, no.037(002), pp.155 -157.

[7] Zhang Xiahui, Chen Yiwan, Hong Xiaoqian, et al(2017). Analysis of β-chorionic gonadotropin and C-reactive protein levels in predicting intrauterine infection and prognosis of premature rupture of membranes[J]. Zhonghua Hospital Infection Journal of Science, no.27(5), pp.1167-1170.

[8] Ilhan N, Celik E, Kumbak B(2015). Maternal plasma levels of interleukin-6, C-reactive protein, vitamins C, E and A, 8-isoprostane and oxidative status in women with preterm premature rupture of membranes[J]. The Journal of Maternal-Fetal & Neonatal Medicine, no.28(3), pp.316-319.

[9] Chaemsaithong P, Romero R, Korzeniewski SJ, et al(2016). A point of care test forinterleukin-6 in amniotic fluid in preterm prelabor rupture of membranes: a step toward the early treatment of acute intra-amniotic inflammation/infection[J]. The Journal of Maternal-Fetal & Neonatal Medicine, no.29(3), pp.60- 367.

[10] Yang Xing(2019). Research progress on diagnosis of premature rupture of membranes [J]. Handong Medicine, no.53(045), pp.100-102.

[11] Queensland Clinical Guidelines(2020). Queensland Clinical Guideline: Preterm labour and birth [EB/OL]. pp.12-13. https://www.health.qld.gov.au/__data/assets/pdf_file/0019/140149/g-ptl.pdf

[12] The Industrial Science Group of the Chinese Medical Association's Obstetrics and Gynecology Branch(2014). Premature clinical diagnosis and treatment guide [J]. China Mimin Magazine, no. 18(4), pp. 241-245.