Pathological staging of chorioamnionitis contributes to complications in preterm infants

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Abstract

Objective: To investigate the effect of pathological staging of chorioamnionitis (CA) on complications in preterm infants; Methods: A single-center, retrospective study was conducted to choose singleton preterm infants in our hospital from December 2016 to December 2017. The basic data and placental pathological results were retrospectively collected. The patients were divided into 4 groups according to the placental pathological results, the incidence of common complications in preterm infants in each group was compared, and analyzed the influence of pathological staging of CA on the complications. Further, CA 0/I phase was combined into non-amnitis group, CA II/III phase was combined into amnitis group, gestational age and birth weight were corrected, logistic regression was used to analyze the effects on complications whether inflammation infiltrated amnion according to odds ratio (OR) value. Results: A total of 221 preterm infants were enrolled, including 84 cases of non-chorioamnionitis(CA0), 102 cases of CAI, 30 cases of CAII, and 5 cases of CAIII. The gestational age of CA II and III groups was lower than CA 0 and I, birth weight was lower than that of CA 0 and I, and the hospital stay in CA II and III was longer (P<0.05); The incidence of intraventricular hemorrhage (IVH) in CAII/III group (26.7%, 60.0%) was higher than that in CA 0 and I (15.5%, 9.8%)(P = 0.007), and the early-onset IVH was more common(P=0.021). CA 0, I was divided into non-amnitis group according to whether the inflammation infiltrated the amniotic layer (placental fetal surface), CA II and III were divided into amnitis group, and the risk of IVH increased by amnitis(OR= 3.248, P value <0.05), and after correction of gestational age and birth weight, the risk of it still increased (OR = 3.236, P value <0.05), the difference was statistically significant. Conclusion: Intrauterine inflammation leads to a significant reduction in gestational age and birth weight in preterm infants, and it is also an independent risk factor for increasing the incidence of IVH;
Background

Chorioamnionitis, an inflammatory state of the intrauterine or fetal membrane, divided into histological chorioamnionitis and clinical chorioamnionitis\(^1\). It is well known that chorioamnionitis can increase the incidence of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), retinopathy (ROP), early-onset sepsis (EOS), late-onset sepsis (LOS), and necrotizing enterocolitis (NEC)\(^2\). Chorioamnionitis leads to an inflammatory response in the placenta, which is an important factor in preterm birth and neonatal adverse outcomes. Although, the effect of chorioamnionitis on complications in preterm infants has been widely studied, the pathological staging on it has rarely been published. Therefore, this study aimed to investigate the effect of pathological staging of chorioamnionitis on complications in preterm infants.

Methods

Study population
A single-center, retrospective study was conducted. Singleton infants (gestational age <37 weeks) who given birth in our hospital from December 2015 to December 2017 were selected as the study population, eliminate cases of genetic metabolic diseases, nervous system malformations, and stillbirth. The maternal routine placental pathology examinations with informed consent.

Histopathological Examination
After delivery, the whole placenta, fetal membrane and umbilical cord were fixed in 4% formaldehyde for 48 hours, evaluated the quality of the placenta, the length of the umbilical cord, the attachment and the number chorioamnionitis of blood vessels, and the placenta was cut at intervals of 1 cm. All specimens were embedded in paraffin, sectioned, and routine Hematoxylin-Eosin Staining (HE staining). The criteria for histological: Nonage (stage I) is mild chorioamnionitis, neutrophils are restricted to chioronic fibrin layer; Metaphage (stage II) is moderate chorioamnionitis, neutrophils infiltrate into the amnion and chorion; Advanced (stage III) is severe necrotizing chorioamnionitis, a large number of neutrophils infiltrate into the full layer of amnion and chorion with necrosis\(^4\).

Clinical characteristics
The gestational age, A\(^\prime\)'s score, birth weight, blood routine, C-reactive protein, procalcitonin and blood culture results of each premature infant were collected, and the disease of each system during hospitalization was observed. The relevant complications were defined as follows:

Intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) are common complications in preterm infants, which can be detected by serial head ultrasound and MRI, the first is recommended between 5 and 8 days, 21 and 28 days, between 34 and 36 weeks of corrected gestational age\(^5\). Those with IVH born \(\leq 3 \text{ d}\) were defined as early-onset intraventricular hemorrhage, and \(>3 \text{ d}\) were defined as late-onset intraventricular hemorrhage\(^6\).

The sepsis in this study requires a positive clinical or laboratory screen and a positive culture. Early-onset sepsis (EOS) occurred during the first 72 hours of life, Late-onset
sepsis (LOS) refers to sepsis that occurred between day of 4 and 120.
Bronchopulmonary dysplasia (BPD) is defined as oxygen dependency at 36 weeks of corrected gestational age.
Respiratory distress syndrome (RDS) is caused by a deficiency of pulmonary surfactant, with progressive dyspnea, bruising and respiratory failure several hours after birth.
NEC is a late complication, manifested as abdominal distension, vomiting, and Bloody stools, can be diagnosed by abdominal piece.
Retinopathy of prematurity (ROP) refers to retinal vasoconstriction, obstruction and retinal vascular hypoxia, leading to a large number of angiogenic factors, stimulating neovascularization form.

Statistical analysis:
The normal distribution data is represented as the mean ± standard deviation (SD), Non-parametric analysis tests (rank test) were used for differences between groups. Dichotomous data are expressed by the frequency and relevant percentage. Univariate analysis was performed using chi-square test or Fisher's exact probability test, and multivariate analysis was performed using logistic regression. Significance was accepted at p < 0.05, All analyses were performed by using SPSS version 19.0 software.

Results

General situation:
A total of 221 maternal placenta were detected in this study. 84 cases of non-chorioamnionitis(CA 0), 102 cases of CAI, 30 cases of CAII and 5 cases of CAIII. The gestational age of CA II and III groups (32.34±2.53 weeks, 29.20±1.79 weeks) was significantly lower than CA 0 and I (34.30±1.84 weeks, 34.03±2.23 weeks), the birth weight of CA II and III groups (1.96±0.6kg, 1.48±0.35kg) were significantly lower than those of CA 0 and I (2.27±0.55kg, 2.25±0.61kg), and the time of hospitalization in CA II and III group was significantly prolonged (23.00±18.67 days, 42.00±15.08 days VS 18.75±15.82 days, 18.91±17.64days) (P<0.05), CA II and III groups, CA 0 and I groups, there was no significant difference. However, there were no significant difference in maternal age, placental weight, Prenatal hormone , premature rupture of membranes, mode of delivery, gender, thrombocytopenia, and Apgar scores (P>0.05). (As shown in Table 1).

Neonatal outcome:
Among the 221 patients, the incidence of intraventricular hemorrhage (IVH) in CAII/III group (26.7%, 60.0%) was significantly higher than that in CA 0 and I (15.5%, 9.8%) (P=0.007) ), but the incidence of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), retinopathy of prematurity (ROP), early-onset sepsis (EOS), and late-onset sepsis (LOS), there was no difference between the four groups (P value > 0.05) (as shown in Table 2). According to whether the inflammation infiltrated the amnion (placental fetus), CA 0/I phase was combined into non-amnitis group, CA II/III phase was combined into amnitis group(Table 3 and 4), it can be found that the risk of intraventricular hemorrhage significantly increased in amnitis group (OR=3.248, P<0.05), and it is more likely to cause early-onset IVH (P value <0.05); After correction of gestational age and birth weight, the risk of intraventricular hemorrhage still
significantly increased (OR = 3.236, P value <0.05), the difference was statistically significant. Therefore, it can be seen that histological chorioamnionitis is an independent risk factor for intraventricular hemorrhage in premature infants, not affected by gestational age and birth weight. And also no significant effect on other common complications related to premature birth (P <0.05)

Discussion

Preterm birth is a global problem of perinatal medicine. Some evidence shows that intrauterine infection is one of the main causes of premature birth, accounting for over 40%\(^8\), 80% of preterm birth with gestational age less than 30 weeks is due to infection, over 90% of preterm birth of gestational age 24-28 weeks is related to intrauterine infection\(^9\). Intrauterine infection can induce a variety of tissue inflammatory reaction, some foreign studies have detected pathogenic microorganisms from specimens such as placenta in preterm infants with gestational age 31 weeks, which proves that intrauterine infection is closely related to preterm birth, and intrauterine infection often causes histological chorioamnionitis\(^10\). Some literature reports that the detection rate of histological chorioamnionitis in premature infants is 40%-70%, which is inversely proportional to gestational age, and preterm infants 28 weeks even reach 80%\(^11\). This indicates that chorioamnionitis is an important factor in triggering preterm birth.

However, the research on complications of preterm infants caused by chorioamnionitis in modern life, the results are almost the same. The incidence of RDS in this study was significantly higher in chorioamnionitis group (35.8%) than non-chorioamnionitis group (28.6%), while Watterberg \(^12\) et al found that intrauterine inflammation reduced the risk of RDS, and even some reports think there is no correlation between them. At present, many scholars believe that intrauterine inflammation will increase the incidence of IVH, BPD, ROP, NEC, EOS, etc. \(^2,14\), the results of this study are also different. In addition, the incidence of complications such as IVH, BPD, RDS, NEC, and LOS in chorioamnionitis III is too high, which may be too few cases of CAIII.

In this study, chorioamnionitis was divided into 4 stages according to the depth of neutrophil infiltration of placenta, and compared the incidence of complications in preterm infants. The results showed that the gestational age and birth weight in CAII and III were significantly lower than those in CA 0 and I, and the incidence of IVH was significantly higher than that in CA 0 and I. The incidence of other complications was not statistically significant among the groups. It suggests that the different histological stages of chorioamnionitis in premature infants are closely related to the occurrence of IVH. There are some studies have also shown that chorioamnionitis is an independent risk factor for increasing risk of intraventricular hemorrhage (IVH), and ventricular hemorrhage is often associated with gestational age and birth weight loss\(^15\). Except for postpartum factors, some prenatal factors may also cause intraventricular hemorrhage, such as placental vascular disease, hemodynamics, which our study did not evaluate.

For the staging of IVH, many studies have not specifically emphasized the role of chorioamnionitis \(^16-19\), and some studies suggest that chorioamnionitis may be more likely to trigger late-onset IVH\(^20\), that contrary to our study.

Conclusion
histological chorioamnionitis is closed to various complications of premature infants, especially intraventricular hemorrhage (IVH). Clinically, the effect of intrauterine inflammation on premature infants should be emphasized. For mothers with chorioamnionitis, focus on monitoring, especially that the placenta should be routine pathological examination, improve the detection rate of chorioamnionitis, reduce the sequelae of nervous system in premature infants.

Abbreviations

Bronchopulmonary dysplasia (BPD)
Chorioamnionitis (CA)
Early-onset sepsis (EOS)
Intraventricular hemorrhage (IVH)
Late-onset sepsis (LOS)
Necrotizing enterocolitis (NEC)
Periventricular leukomalacia (PVL)
Platelet (PLT)
Retinopathy (ROP)
Respiratory distress syndrome (RDS)

Declarations

Ethics approval and consent to participate
All mother have given their written informed consent for placental pathology, and that the study protocol was approved by Guangdong Women and Children Hospital ethics committee (No.201701046). We obtain the informed consent from study participants verbal, because some people can not sign the consent, the ethics committee approved this procedure.

Consent for publication
The manuscript have consent for publication

Availability of data and material
All data generated or analysed during this study are included in this published article [and its supplementary information files]

Competing interests
The authors declare that they have no conflict of interest.

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Authors’ Contributions
Jiayu Miao collected all data; Jiayu Miao and Zhuxiao Ren wrote the manuscript e and analysed the data, Yunbei Rao, Qi Zhang, Xin Xia, Fang Xu, Xiaoling Zhang, Jie Yang all contributed to conception and design.

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Tables

Table 1 Clinical characteristics of CAO, CAI, CAII, and CAIII

|                  | CAO[84] | CAI[102] | CAII[30] | CAIII[5] |
|------------------|---------|----------|----------|----------|
| Maternal age[yr] | 30.73±  | 30.59±   | 30.28±6.62 | 33.00±3.16 |
|                  | 5.57    | 5.24     |          |          |
| Gestational age[wk] | 34.30±  | 34.03±   | 32.34±2.53 | 29.20±1.79 |
| Placental weight[g] | 483.83±189.49 | 479.45±110.09 | 464.14±87.35 | 464.00±48.27 |
| Birth weight[kg] | 2.27±0.55 | 2.25±0.61 | 1.96±0.60 | 1.48±0.35 |
| Prenatal hormone,n,(%) | 19(22.6%) | 27(26.5%) | 8(26.7%) | 4(80%) |
| Premature rupture,n,(%) | 30(35.7%) | 34(33.3%) | 14(46.7%) | 2(40%) |
| Cesarean section,n,(%) | 45(53.6%) | 50(49.0%) | 13(43.3%) | 2(40.0%) |
| Male,n,(%)       | 47(56.0%) | 59(57.8%) | 11(36.7%) | 4(80.0%) |
| Apgar score 1min≤7,n,(%) | 3(3.6%) | 7(6.9%) | 3(10.0%) | 1(20.0%) |
| Apgar score 5min≤7,n,(%) | 0(0%) | 2(2.0%) | 1(3.3%) | 0(0%) |
| PLT,≤150×109/L ,n,(%) | 6(7.1%) | 6(5.9%) | 0(0%) | 1(20%) |
| Hospitalization | 18.7±15.82 | 18.91±17.64 | 23.00±18.67 | 42.00±15.08 |

Data are expressed as n (%) or mean ± standard deviation.*P < 0.05, the difference was statistically significant.
Table 2 Neonatal outcome

| Outcome parameter | N (%) | CA0 [84] | CA137 | CAI102 | CAI30 | CAIII 5 |
|-------------------|-------|----------|-------|--------|-------|--------|
| IVH n, %          |       | 1315.4%  | 2115.3% | 109.8% | 826.7% | 360.0% |
| BPD n, %          |       | 11.2%    | 107.3% | 76.9%  | 26.7%  | 120.0% |
| RDS n, (%)        |       | 24(28.6%)| 49(35.8%)| 33(32.3%)| 11(36.7%)| 5(100.0%) |
| NEC n, %          |       | 1416.7%  | 96.6%  | 65.9%  | 13.4%  | 240.0% |
| ROP n, %          |       | 67.1%    | 12(8.8%)| 109.8% | 26.7%  | 0(0)   |
| EOS n, %          |       | 11.2%    | 10.7%  | 0(0%)  | 0(0%)  | 120.0% |
| LOS n, (%)        |       | 22.4%    | 21.5%  | 2(2.0%)| 0(0.0%)| 0(0.0%)|

Data are expressed as n (%). Fisher's exact probability method is used.

Table 3 The clinical characteristics of non-amnitis group and amnitis group
### Table 4 Neonatal outcome of non-amnitis group and amnitis group

| Clinical characteristics | Non-amnitis group (186) | Amnitis group (35) | P    |
|--------------------------|--------------------------|---------------------|------|
| Maternal age (y)         | 30.62 ± 5.38             | 30.89 ± 6.80        | 0.797|
| Gestational age (d)      | 34.1 ± 2.06              | 32.0 ± 2.71         | 0.001|
| Placental weight (g)     | 480.71 ± 150.43          | 469.03 ± 112.85     | 0.659|
| Birth weight (kg)        | 2.27 ± 0.58              | 1.93 ± 0.64         | 0.002|
| Prenatal hormone (n, %)  | 46 (24.7 %)              | 12 (34.3 %)         | 0.239|
| Premature rupture (n, %) | 64 (34.4 %)              | 16 (45.7 %)         | 0.202|
| Cesarean section (n, %)  | 965 (51.6 %)             | 1645 (79.0 %)       | 0.583|
| Male (n, %)              | 107 (57.5 %)             | 1645 (79.0 %)       | 0.197|
| Apgar score 1 min ≤ 7 (n, %) | 73.8 %                  | 12 (8.6 %)          | 0.198|
| Apgar score 5 min ≤ 7 (n, %) | 42.2 %                  | 12.9 %              | 0.581|
| PLT, ≤ 150 x 10^9/L (n, %) | 126.5 %                 | 12.9 %              | 0.359|
| Hospitalization (d)     | 18.83 ± 16.80            | 25.71 ± 19.23       | 0.031|

Data are expressed as n (%) or mean ± standard deviation. *P < 0.05, the difference was statistically significant. The measurement data were analyzed by independent sample t test, and the count data were analyzed by chi-square test using Fisher exact probability method.
| outcome                  | non-amnitis group186 | amnitis group35 | P     | OR     | Adjusted P | Adjusted OR |
|--------------------------|-----------------------|-----------------|-------|--------|------------|-------------|
| IVH,n,[][%]              | 2312.4%               | 1131.4%         | 0.007 | 3.248  | 0.015      | 3.236       |
| BPD,n,[][%]              | 84.3%                 | 38.6%           | 0.029 | 0.479  | 0.0356     | 2.350       |
| RDS,n,(%)                | 57(30.6%)             | 16(45.7%)       | 0.085 | 0.525  | 0.052      | 3.086       |
| NEC,n,[][%]              | 2010.8%               | 311.4%          | 0.699 | 1.285  | 0.163      | 3.338       |
| ROP,n,[][%]              | 168.6%                | 25.7%           | 0.597 | 1.506  | 0.163      | 3.338       |
| EOS,n,[][%]              | 10.5%                 | 12.9%           | 0.235 | 0.184  | 0.992      | 0.000       |
| LOS,n (%)                | 4(2.2%)               | 0(0.0%)         | 0.253 | 0.363  | 0.998      | 0.000       |
| Death,n,[][%]            | 42.2%                 | 00%             | 1.000 | 0.363  | 0.998      | 0.000       |

OR=odds ratio; adjusted P=gestational age and birth weight, stage were included in the logistic regression to adjust the P value; Adjusted OR=gestational age and birth weight, stage were included in the logistic regression to adjust the OR value.

**Table 5 Comparison of pathological staging and IVH staging**

| staging              | CA0I186 | CAIIII35 | P value |
|----------------------|---------|----------|---------|
| Early-onset, n, (%)  | 8(4.3%) | 5(14.3%) | 0.021   |
| Late-onset, n, (%)   | 6(3.2%) | 3(8.6%)  | 0.155   |
The count data is expressed by frequency (percentage), and the count data is analyzed by chi-square test. Fisher's exact probability method is used, *P<0.05, the difference is statistically significant.

Supplementary Files

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