Significance of Mid-Pregnancy Down Syndrome Risk Screening in Predicting Adverse Maternal and Fetal Outcomes

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Abstract: Objective: To investigate the value of mid-pregnancy Down syndrome risk screening in predicting adverse maternal and fetal outcomes. Methods: 536 mothers who underwent mid-pregnancy screening for Down syndrome at Chengyang District Maternal and Child Healthcare and Family Planning Service Center from January 2021 to December 2022 were selected for retrospective analysis. The risk was calculated using the Asian population database in the American prenatal screening software PRISCA 4.0, combined with the age, gestational week, and body mass of the day of the pregnant women’s blood collection. Results: The screening results showed that there were 469, 54, and 13 cases in the low-risk, critical-risk, and high-risk groups, respectively, and there were no statistically significant differences in the age and body mass of each group (P > 0.05). However, there was a significant difference between the adverse fetal outcomes in low-risk, critical-risk, and high-risk groups (P < 0.05); and the screening results showed that there was a significant difference between the adverse maternal outcomes in the low-risk, critical-risk, and high-risk groups (P < 0.05). Conclusion: There is a relationship between the high risk of Down syndrome detected through screening and adverse maternal and fetal outcomes. Besides, the false positive and negative rates of Down syndrome screening results are positively correlated with adverse maternal and fetal outcomes.

Keywords: Down syndrome screening; Risk prediction; Adverse pregnancy outcome

1. Introduction
Mid-pregnancy Down syndrome screening is an early screening tool for specific chromosomal abnormalities that offers advantages like simplicity, non-invasiveness, low cost, and accuracy. Therefore, it has been widely used in China. However, mid-pregnancy Down syndrome screening cannot predict the occurrence of maternal and fetal adverse pregnancy outcomes (e.g., miscarriage, stillbirth, etc.) caused by chromosomal abnormalities[1]. Therefore, it is important to study the value of mid-pregnancy Down syndrome screening risk in predicting adverse maternal and fetal outcomes. In this study, we retrospectively analyzed the value of mid-pregnancy Down syndrome
screening risk in predicting maternal-fetal adverse pregnancy outcomes at the Maternal and Child Health and Family Planning Service Center of Chengyang District from January 2021 to December 2022, with the goal of reducing adverse maternal and fetal outcomes.

2. Information and methods

2.1. General information
A retrospective analysis of the value of mid-pregnancy Down syndrome screening risk in predicting adverse maternal-fetal pregnancy outcomes was performed on 536 cases from January 2021 to December 2022. The average maternal age was 26.98 ± 2.69 years, with an average of 1.58 ± 0.89 pregnancies per patient. All cases involved singleton pregnancies, and deliveries were followed up via case-finding and telephone recall at the end of one year.

2.2. Methods
3 mL of fasting blood samples were collected from the elbow vein of the patients using a standard negative pressure pro-coagulation serum tube. After static incubation for 30 minutes, the samples were centrifuged at 5000 r/min for 10 minutes to extract serum for the triple test: human chorionic gonadotropin (hCG), free estriol (uE3), and alpha-fetoprotein (AFP). Each test was conducted simultaneously with three levels of indoor quality control. Risk assessment was performed using the Asian population database in the American prenatal screening software PRISCA 4.0, considering factors such as the pregnant women’s age, gestational week, and body mass on the day of blood collection.

2.3. Criteria for determining the risk of Down syndrome
The risk of a fetus developing 21-trisomy syndrome or 18-trisomy syndrome is considered low if it is less than 1:1000 or if the value of the alpha-fetoprotein test is less than 2.5 AFP-MOM. A critical risk level is identified when the risk of developing 21-trisomy syndrome falls between 1:1000 and 1:270, or when the risk of 18-trisomy syndrome falls between 1:1000 and 1:350. High risk is defined as a risk of developing 21-trisomy syndrome higher than 1:270, a risk of 18-trisomy syndrome higher than 1:350, and an alpha-fetoprotein test value higher than 2.5 AFP-MOM.

2.4. Statistical methods
SPSS18.0 statistical software was used to analyze the data. Measurement data were expressed as mean ± standard deviation and compared using a t-test; count data were expressed as percentages (%) and compared using a χ²-test. P < 0.05 was considered statistically significant.

3. Results

3.1. Screening results
The screening results showed that there was no statistically significant difference between the age and weight mass of the low-risk, critical-risk, and high-risk groups (P > 0.05), as shown in Table 1.
Table 1. Statistics of screening results

<table>
<thead>
<tr>
<th>Group</th>
<th>Low-risk group</th>
<th>Critical-risk group</th>
<th>High-risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases ((n/%))</td>
<td>469 (87.50)</td>
<td>54 (10.07)</td>
<td>13 (2.43)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.01 ± 1.36</td>
<td>26.87 ± 1.65</td>
<td>27.02 ± 1.48</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.12 ± 2.69</td>
<td>62.06 ± 2.47</td>
<td>62.15 ± 2.58</td>
</tr>
</tbody>
</table>

Note: There was no statistical difference between the three groups in terms of age and body mass, i.e., \(P > 0.05\).

3.2. Correlation between labor screening risk and adverse fetal outcome

The results of the screening showed that there was a significant difference \((P < 0.05)\) between the three groups in terms of adverse fetal outcomes, as shown in Table 2.

Table 2. Correlation between labor screening risk and adverse fetal outcomes.

<table>
<thead>
<tr>
<th>Group</th>
<th>Stillbirth</th>
<th>Malformation</th>
<th>Neonatal asphyxia</th>
<th>Neonatal infection</th>
<th>Premature labor</th>
<th>(\chi^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group ((n = 469))</td>
<td>2 (0.43)</td>
<td>2 (0.43)</td>
<td>12 (2.56)</td>
<td>14 (2.99)</td>
<td>21 (4.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical-risk group ((n = 54))</td>
<td>3 (5.56)</td>
<td>4 (7.41)</td>
<td>8 (14.81)</td>
<td>7 (12.96)</td>
<td>12 (22.22)</td>
<td>105.017</td>
<td>0.000</td>
</tr>
<tr>
<td>High-risk group ((n = 13))</td>
<td>0 (0.00)</td>
<td>2 (15.38)</td>
<td>2 (15.38)</td>
<td>2 (15.38)</td>
<td>1 (7.69)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3 Correlation between labor screening risk and maternal adverse pregnancy outcomes

The results of the screening showed that there was a significant difference \((P < 0.05)\) between the adverse pregnancy outcomes of pregnant women in the low risk, critical risk and high risk groups as shown in Table 3.

Table 3. Correlation between labor screening risk and adverse pregnancy outcomes in pregnant women.

<table>
<thead>
<tr>
<th>Group</th>
<th>Cesarean section</th>
<th>Spontaneous abortion</th>
<th>Premature rupture of membranes</th>
<th>Premature exfoliation of membranes</th>
<th>(\chi^2)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group ((n = 469))</td>
<td>154 (32.84)</td>
<td>2 (0.43)</td>
<td>36 (7.68)</td>
<td>11 (2.35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical-risk group ((n = 54))</td>
<td>8 (14.81)</td>
<td>4 (7.41)</td>
<td>3 (5.56)</td>
<td>3 (5.56)</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>High-risk group ((n = 13))</td>
<td>2 (15.38)</td>
<td>2 (15.38)</td>
<td>0 (0.00)</td>
<td>1 (7.69)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Discussion

Currently, Down syndrome screening methods include serologic screening and noninvasive DNA testing, both of which are used to detect fetal chromosomal aneuploidy abnormalities by detecting indicators such as maternal serum levels of alpha-fetoprotein, chorionic gonadotropin, and free estriol. However, they cannot yet completely exclude the occurrence of maternal-fetal adverse pregnancy outcomes caused by chromosomal abnormalities. In recent years, a large number of studies at home and abroad have shown that the incidence of adverse maternal and fetal outcomes is similar in the high-risk and low-risk groups of Down syndrome screening. However, some studies have also pointed out that the risk of miscarriage, stillbirth, and neonatal severe congenital anomalies (such as neural tube malformations) is higher in the high-risk group of Down syndrome screening[2].

Although there are fewer studies related to Down syndrome screening, the probability of spontaneous
abortion in early pregnancy is significantly higher in the high-risk group than the low-risk group, and the probability of stillbirth and severe congenital anomalies of the newborn is higher in early pregnancy than in the low-risk group. The above results suggest that the risk of spontaneous abortion, stillbirth and severe congenital anomalies of the newborn in the Down syndrome high-risk group is higher than that of the low-risk group. It has been suggested that maternal serum concentration of alpha-fetoprotein is lower and free estriol level is higher during pregnancy in the high-risk group, and free estriol is most closely related to fetal chromosomal abnormalities, so it is hypothesized that high risk of Down syndrome screening may be related to abnormal maternal serum concentration of alpha-fetoprotein and free estriol level [3]. This may be because the detection rate of chromosomal abnormalities in the population of pregnant women in the high-risk group is higher than that in the low-risk group, and the same chromosomal abnormalities are present in the population of high-risk pregnant women; therefore, pregnant women with high-risk Down syndrome screening results are at a higher risk of adverse pregnancy outcomes than those with low risk.

A retrospective analysis by Li et al. showed that there was no statistically significant difference in the number of fetuses with chromosomal abnormalities in pregnant women in the high-risk group compared with those in the low-risk group [4]. Similarly, Gao et al. highlighted that there was no variance in the frequency of adverse maternal-fetal pregnancy outcomes between the high- and low-risk groups identified through Down syndrome screening. This lack of distinction could potentially stem from variations in the quality of data obtained during screening conducted within the same region, at similar gestational weeks, and following identical protocols, thereby rendering the conclusions incomparable [5]. In addition, neither study analyzed the correlation between abnormal screening results and indications for prenatal diagnosis.

In this study, significant differences were observed in adverse fetal outcomes among the low-risk, critical-risk, and high-risk groups (P < 0.05), as well as in adverse maternal outcomes (P < 0.05). Notably, the incidence of maternal-fetal adverse pregnancy outcomes was significantly lower in the low-risk group compared to the high-risk group (P = 0.000). Conversely, the high-risk group exhibited a significantly higher incidence of adverse maternal-fetal pregnancy outcomes compared to the low-risk group (P = 0.000). However, there was no significant difference in maternal-fetal adverse pregnancy outcomes between the high-risk and low-risk groups, indicating that Down syndrome screening may not fully predict such outcomes. Furthermore, pregnant women identified as high-risk through Down syndrome screening were more likely to experience low birth weight babies (P = 0.024), preterm births (P = 0.041), and low birth weight babies (P = 0.036) compared to low-risk pregnant women. Additionally, patients categorized as high-risk had poorer pregnancy outcomes, with a higher proportion of miscarriages, stillbirths, and malformations observed in the low-risk group compared to the high-risk group (P = 0.039). Moreover, the low-risk group had a higher proportion of preterm births (P = 0.007), and patients with a high risk of Down syndrome screening were more likely to experience preterm labor compared to those with low risk (P = 0.016). These findings suggest a correlation between false-positive Down syndrome screening results and the incidence of adverse pregnancy outcomes. Higher rates of false-positive and false-negative screening results are associated with an increased likelihood of preterm labor and malformations, highlighting the importance of minimizing false-positive results to mitigate the risk of maternal-fetal adverse pregnancy outcomes.

Zhang’s research revealed a significantly elevated risk of adverse pregnancy outcomes, including miscarriage, stillbirth, and malformation, among pregnant women identified as high-risk through Down syndrome screening compared to those classified as low-risk [6]. Similarly, Han’s findings indicated that all pregnant women experiencing adverse pregnancy outcomes in the low-risk group were identified as high-risk through Down syndrome screening. This suggests a higher false-positive rate of Down syndrome screening.
results in the low-risk group compared to the high-risk group, implying that Down syndrome screening may not entirely predict the occurrence of maternal and fetal adverse pregnancy outcomes \(^7\). Furthermore, Zhang et al. discovered that high-risk pregnant women identified through Down syndrome screening were more prone to adverse pregnancy outcomes such as preterm labor, stillbirth, and fetal developmental abnormalities compared to low-risk pregnant women \(^8\).

Down syndrome screening is a simple, effective, and safe means of early screening, and it is clinically valuable due to the high incidence and lethality of Down syndrome \(^9\). demonstrated a significant association between the risk identified through mid-pregnancy Down syndrome screening and the occurrence of adverse maternal and fetal pregnancy outcomes \(^10\). However, the predictive model for this risk is not yet perfected and cannot fully replace traditional Down syndrome screening. In recent years, an increasing number of studies have focused on the value of mid-pregnancy Down syndrome screening in predicting adverse maternal-fetal pregnancy outcomes, leading to the proposal of different theoretical models by scholars, such as ROC curve analysis, linear regression analysis, and logistic regression \(^11,12\). Nevertheless, these models have varying degrees of limitations in accurately predicting adverse maternal-fetal pregnancy outcomes.

5. Conclusion
There exists a correlation between a high risk identified through Down syndrome screening and adverse maternal-fetal pregnancy outcomes. Moreover, the rates of false-positive and false-negative results in Down syndrome screening are directly linked to adverse maternal-fetal pregnancy outcomes. As medical technology advances, more individuals may be categorized into the high-risk group for mid-pregnancy Down syndrome screening, potentially leading a better prediction of adverse maternal-fetal pregnancy outcomes among these high-risk groups. Consequently, further clinical research is necessary to investigate high-risk groups and incorporate them into Down syndrome screening for comprehensive analysis in the future. Additionally, researchers should strive to enhance and refine existing prediction models and explore new methods to better anticipate adverse maternal-fetal pregnancy outcomes. This endeavor aims to enhance the accuracy of Down syndrome screening and mitigate the risk of adverse maternal-fetal pregnancy outcomes in clinical practice.

Disclosure statement
The authors declare no conflict of interest.

References


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