Changes of hemorheological indexes, coagulation function and cytokines in women with intrahepatic cholestasis of pregnancy

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Objective: To explore the changes of hemorheological indexes, coagulation function and cytokines of women with intrahepatic cholestasis of pregnancy ICP. Methods: A total of 54 cases of ICP in our hospital were collected as study group, 54 cases of normal pregnancy period were collected as the control group. The changes of coagulation function, inflammatory cytokines and D- dimer of two groups were observed and compared. Results: The blood rheology indexes such as whole blood viscosity at high shear, whole blood viscosity at low shear, plasma viscosity, hematocrit and erythrocyte sedimentation rate of study group were (4.73±0.81) mPa•s, (6.67±1.40) mPa•s, (1.93±0.38) mPa•s, (46.34±4.25)% and (68.92±7.93) mm/h, respectively; they were significantly higher than those of control group (P<0.05). The difference between two groups in PT and APTT was not statistically significant (P>0.05). FIB, D-D of the study group respectively were (5.62±0.78) g/L, (0.45±0.11) mg/L, significantly higher than the control group. PLT was (168.44±16.35)×10⁹/L, and was significantly reduced compared with the control group (P<0.05). The levels of IL-18, IL-12, TNF-α of the study Group were (70.22±5.33) ng/L, (47.55±4.23) ng/L and (40.45±3.45) ng/L, respectively. Compared with normal pregnancy control they was significantly increased (P<0.05). The rates of premature delivery, amniotic fluid contamination, fetal distress, neonatal asphyxia and low birth weight infants were 20.37%, 37.04%, 18.52%, 11.11% and 9.26%, significantly higher than the control group (P<0.05). Conclusion: ICP patients have significantly high viscosity changes, high coagulation and has adverse effects on pregnancy outcome, which play important roles in the clinical diagnosis.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is one of the common complications occurring during the latter half of pregnancy and leading to fetal distress, growth restriction or even premature birth and sudden intrauterine death. While a few pregnant women show coagulation dysfunction and inflammatory cytokines release to occur postpartum hemorrhage due to the abnormal change of hemorheology which is one of the main causes of maternal death[1–5]. The etiology and pathogenesis of ICP remain in the research stage currently, and few reports are presented on the change of hemorheology, coagulation function and cytokines of pregnant women with ICP. Our study aims to make a preliminary study on these changes.

2. Materials and methods

2.1. General information

A total of 54 cases of ICP pregnant women in our hospital from January 2013 to July 2014 were collected as the research group. ICP diagnosis code with “Obstetrics and Gynecology”;
maternal age ranged from 22 to 36 years old, with a mean age of (28.34±6.45); 38 cases of primipara and 16 cases of multipara. Totally, 54 cases of normal pregnant women with the cesarean section operation indications were collected as the control group, with maternal age ranged from 23 to 38 years old [mean age of (29.72±7.13) years]. There were 41 cases of primipara and 13 cases of multipara in the control group. The above research objects were singleton pregnancies, and pregnant women with hypertension, diabetes, abnormal liver and kidney function, taking drugs that effect hemorheology and coagulation parameters were excluded. Pregnant women did not fit the clinical detection; fetus malformation. Two groups had no significant difference in maternal age and pregnancy times.

2.2. Detection method

Venous blood was collected when fasting and placed into heparinized tubes and citrate anticoagulation tube respectively, mixed and related indexes were detected. The blood rheology indexes including blood viscosity (high shear and low shear), plasma viscosity, hematocrit and erythrocyte sedimentation rate were detected by the full functional automatic blood rheometer. The blood coagulation function including platelet (PLT), two D-dimer level (D-D), fibrinogen (FIB), prothrombin time (PT) and partial thromboplastin time (APTT) was detected by the full automatic blood coagulation analyzer. TNF-α, IL-12 and IL-18 levels were detected by radioimmunoassay according to the kits operating instructions.

2.3. Statistical analysis

Data were analyzed by statistical software SPSS 17.00. The count data are showed as percentages and the measurement data as (x±s). The groups were compared using χ² and t test. P<0.05 was considered for the difference with significant difference.

3. Results

3.1. Comparison on the blood rheology indexes

The blood rheology index of high shear whole blood viscosity, whole blood viscosity at low shear, plasma viscosity, hematocrit and erythrocyte sedimentation rate of the research group are shown in Table 1. These indexes were significantly higher than those of the normal pregnant control group (P<0.05).

3.2. Comparison on the blood coagulation indexes

The difference between two groups in PT and APTT was not statistically significant. The FIB and D-D of the research group were (5.62±0.78) g/L, (0.45±0.11) mg/L respectively, both of which were significantly higher than the control group. The PLT was (168.44±16.35)×10⁹/L, which was significantly reduced compared with the control group, and the statistical analysis showed significant difference (P<0.05) (Table 2).

Table 1

Comparison on the blood rheology indexes between two groups pregnant women (x±s).

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Whole blood viscosity (mPa/s)</th>
<th>Plasma viscosity (mPa/s)</th>
<th>Hematocrit (%)</th>
<th>Erythrocyte sedimentation rate (mm/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High shear</td>
<td>Low shear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>54</td>
<td>3.51±0.78</td>
<td>5.23±1.18</td>
<td>1.49±0.23</td>
<td>36.45±3.88</td>
</tr>
<tr>
<td>Research group</td>
<td>54</td>
<td>4.73±0.81a</td>
<td>6.67±1.40a</td>
<td>1.93±0.38a</td>
<td>46.34±4.25a</td>
</tr>
</tbody>
</table>

aP<0.05 vs the control group.

Table 2

Comparison on the blood coagulation indexes between two groups pregnant women (x±s).

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>PT (s)</th>
<th>APTT (s)</th>
<th>FIB (g/L)</th>
<th>D–D (mg/L)</th>
<th>PLT (×10⁹/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>54</td>
<td>11.73±1.28</td>
<td>30.84±2.79</td>
<td>4.67±0.65</td>
<td>0.23±0.08</td>
<td>217.02±18.54</td>
</tr>
<tr>
<td>Research group</td>
<td>54</td>
<td>12.04±0.81</td>
<td>32.01±2.46</td>
<td>5.62±0.78</td>
<td>0.45±0.11</td>
<td>168.44±16.35</td>
</tr>
</tbody>
</table>

aP<0.05 vs the control group.
3.3. Comparison on inflammatory factors IL-18, IL-12 and TNF-α level

The levels of IL-18, IL-12, and TNF-α of the research group were significantly increased compared with the normal pregnant control group, and the statistical analysis showed significant differences ($P<0.05$) (Table 3).

Table 3
Comparison on inflammatory factor level between two groups pregnant women ($\bar{x}\pm s$).

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>IL-18 (ng/L)</th>
<th>IL-12 (ng/L)</th>
<th>TNF-α (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>54</td>
<td>37.47±3.44</td>
<td>13.44±1.75</td>
<td>27.42±2.22</td>
</tr>
<tr>
<td>Research group</td>
<td>54</td>
<td>70.22±5.33$^a$</td>
<td>47.55±4.23$^a$</td>
<td>40.45±3.45$^a$</td>
</tr>
</tbody>
</table>

$^a$P<0.05 vs the control group.

3.4. Comparison on the outcomes

The rates of premature delivery, amniotic fluid contamination, fetal distress, neonatal asphyxia and low birth weight infants of the research group were 20.37% (11/54), 37.04% (20/54), 18.52% (10/54), 11.11% (6/54) and 9.26% (5/54) respectively. Those rates in the normal control group were 3.70% (2/54), 9.26% (5/54), 7.40% (4/54), 1.85% (1/54) and 3.70% (2/54) respectively. The rates were significantly higher than the normal pregnant control group, and the statistical analysis showed significant differences ($\chi^2=10.447$, 12.301, 8.093, 5.567, 5.009, $P<0.05$).

4. Discussion

ICP is a bile secretion or eduction disorder disease caused by a variety of reasons which is characterized by jaundice, cholestasis and pruritus. It is a pregnancy-specific disease usually occurring during the third trimester and have a great threat to the maternal and perinatal health and life. The etiology and pathogenesis of ICP are still in the exploration clinically[6-8]. Studies have suggested that abnormal indexes of blood rheology and coagulation function may contribute to the local microcirculation disorder, which caused fetal hypoxia or acidosis in the uterus and thus had adverse effects on pregnancy outcome[9].

The blood rheological indexes can reflect the blood viscosity and liquidity with the increasing viscosity and decreasing liquidity. There should be a dynamic balance between the viscosity and liquidity to maintain the normal operation of blood in the vessels. In ICP patients, hypercoagulable state blood slows down the blood flow, and placenta appears to ischemia and hypoxia, while the high concentrations of cholic acid will stimulate the contraction of placental villous vessels and umbilical vascular, aggravate the placental hypoperfusion and cause severe consequences for the fetus such as fetal hypoxia, neonatal asphyxia or even death. So clinically we should pay more attention to it[10,11].

Clinical studies have demonstrated that the blood will be in hypercoagulable state to prevent intrapartum hemorrhage in the middle and later pregnancy of normal pregnant women[12,13]. In pregnant women with ICP, hemorheological indexes are obviously varieties compared with normal pregnant women. Our study shows that the blood rheology indexes whole blood viscosity at high shear, whole blood viscosity at low shear, plasma viscosity, hematocrit and erythrocyte sedimentation rate of the study group were significantly higher than the normal pregnant women, which indicated that ICP patients red cell deformability decreased and aggregation ability enhanced to enhance whole blood viscosity.

In ICP patients, the dynamic balance between the coagulation system and fibrinolytic system become disordered because of the damage of vascular wall epithelial cell[14]. Our study shows that FIB and D-D were significantly higher while PLT was significantly reduced compared with normal control group. High concentration bile acid will cause placenta ischemia or necrosis, endothelial cell damage; large amounts of prothrombin were released and lead to the formation of coagulation and microthrombi.

Clinical studies have suggested that inflammatory factor levels can be used to determine the degree of liver function abnormality[15]. Our study shows that IL-18, IL-12 and TNF-alpha levels of the research group were significantly increased compared with the normal control group. Inflammatory factors involved in the damage process of liver destroy the immune balance between mother and fetus and can be used to reflect the severity of disease.

Both high coagulation and high viscosity will cause microthrombosis which hinder local microcirculation, resulting in a decline of placental perfusion ability, coupled with the increasing release of inflammatory factors. All those lead to adverse pregnancy outcomes. Our study shows that in the research group, the incidence of premature delivery, amniotic fluid pollution, fetal distress, neonatal asphyxia and low birth weight infants were significantly higher than the normal control group. The elevated blood viscosity will increase peripheral vascular resistance, slow the blood flow and cause placenta hypoxia and ischemia to affect fetus. In addition, ICP will decrease the fetal red blood cells oxygen uptake capacity to stimulate peristalsis which is the main cause of turbid amniotic fluid and fetal distress.

In summary, ICP women with high viscosity, high coagulation and increased inflammatory cytokine release have adverse effects on pregnancy outcome, which plays an important role in the clinical diagnosis.
Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgment

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References


