Successful combination therapy of low-dose aspirin and unfractionated heparin in recurrent pregnancy loss: A case report

Adhi Pribadi*1
1Division of Maternalfetal, Department of Obstetrics and Gynecology, Universitas Padjadjaran, Bandung, Indonesia
*Corresponding author: priana1001@gmail.com

ABSTRACT

Habitual abortion, defined as more than two consecutive pregnancy losses, affects approximately 1% to 2% of women. This pathological condition undoubtedly frustrates a woman, yet this condition still has a chance to be treated and achieve a favorable pregnancy outcome. This case report aims to describe the success of a pregnancy with a history of recurrent miscarriages (five times of baby loss). The administration of a combination of low-dose aspirin and unfractionated heparin offers a 72-80% chance of having a good pregnancy outcome. We present a P2A5 woman with Thalassemia Minor and thrombocytosis. Preventive treatment, prenatal diagnosis, pregnancy outcomes, and complications were reviewed. Combination therapy of 80 mg aspirin and 2 x 5000 U unfractionated heparin subcutaneously during the last two pregnancies were able to maintain the pregnancy and prevent early pre-eclampsia or Fetal Growth Restriction (FGR) but not late-onset one. In the 6th pregnancy, the patient experienced late-onset FGR with a minor congenital anomaly. In the 7th pregnancy, severe pre-eclampsia appeared. However, administration of combination of heparin and aspirin could maintain pregnancy and fetal viability in Thalassemia Minor patients with recurrent abortus and thrombocytosis.

INTRODUCTION

Recurrent pregnancy loss (RPL), or habitual abortion, was defined as three pregnancy losses, consecutive or not, within 20 weeks of the last menstrual period, which affects approximately 1% to 2% of women.1 The etiologic of RPL involves
immunological and blood component disorders, including antiphospholipid antibody syndrome (APS) and thrombophilia. Sticky platelet syndrome (SPS) or platelet-hyper aggregation is associated with RPL and thrombophilia. Besides, high platelet counts and hypercoagulable states may lead to thrombocytosis in thalassemia cases, thereby increasing the risk of thrombosis and possibly exacerbating thrombophilia.

Heparin as a preventive therapy appears to have a beneficial effect on pregnancy outcomes in women with thrombophilia. Combination therapy of heparin and aspirin before 12 weeks of gestation can prevent hypertension. This case report discusses the success of using heparin in combination with aspirin in maintaining pregnancy for fetal survival in patients with minor Thalassemia accompanied by thrombophilia who have had recurrent miscarriages. In addition, to see pregnancy complications that may occur. The patient had permitted her health problem to be published.

**CASE DESCRIPTION**

We report two pregnancies in a 30-year-old woman with a history of 5 times abortions (P0A5), with all previous abortions occurring before ten weeks gestation. Data were collected prospectively at the Maternalfetal Medicine Division High-Risk Pregnancy Clinic, Department of Obstetrics & Gynaecology, Padjadjaran University, Bandung Indonesia, from 2018 to 2020 (two pregnancies). The data described include laboratory results, preconception medication, preventive medication, prenatal diagnosis, pregnancy outcomes, and complications.

The pregnancy diagnosis was made at five weeks of gestation based on the last menstrual period. Several examinations included a complete blood test, anticardiolipin antigen antibodies, b-2 glycoprotein antibodies, liver and kidney function, and blood sugar. The previous test showed thyroid function within normal limits. Liver function, kidney function, and blood glucose levels were within normal limits. The Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin (MCH) were below normal limits, and thrombocytosis, suspected Thalassemia, which then confirmed as Thalassemia Beta minor using hemoglobin electrophoresis (Table 1).

The presence of platelet hyper aggregation and thrombocytosis led to the decision to give a combination therapy of aspirin 80 mg and unfractionated heparin 2 x 5000 U per day subcutaneously. Based on the literature, Unfractionated heparin is equally effective and more affordable for the patient. We found fetal heart rate at the 7th week of gestation through transabdominal ultrasonography. At the 14th and 18th weeks, a Doppler examination revealed a notching on the bilateral artery uterine that was more pronounced on the left side (Figure 1).

**Table 1. Laboratory result**

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Value</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>11.0 mg/dl</td>
<td>Normal</td>
</tr>
<tr>
<td>Mean Corpuscular Volume*</td>
<td>62 fl</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Mean Corpuscular Hemoglobin**</td>
<td>19.4 pg</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Platelets***</td>
<td>488x103/ml</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Ig M Anti Cardiolipin Antigen</td>
<td>1.2 Unit/ml</td>
<td>Normal</td>
</tr>
<tr>
<td>Ig G Anti Cardiolipin Antigen</td>
<td>2.0 Unit/ml</td>
<td>Normal</td>
</tr>
<tr>
<td>Ig M b-2 Glycoprotein 1</td>
<td>1.2 Unit/ml</td>
<td>Normal</td>
</tr>
<tr>
<td>Ig G b-2 Glycoprotein 1</td>
<td>2.5 Unit/ml</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemoglobin A2****</td>
<td>4.7%</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Ferritin</td>
<td>278 ng/ml</td>
<td>Normal</td>
</tr>
<tr>
<td>Platelets Hyperaggregation</td>
<td>Positive</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

Note: Normal: * > 80 fl, ** > 26 pg, *** < 450x103/ml, **** < 3.5%
In addition, unilateral mild clubfoot was detected. The patient then followed every month. From the 28th week of gestation onwards, biweekly growth monitoring was performed using ultrasound which showed a suboptimal fetal growth was not optimal. At the gestational age of 35 weeks, we discovered a late-onset FGR because of a stagnant fetal weight based on the growth chart on the ultrasound device compared to the previous week (Figure 2). An elective Cesarean section was planned five days after aspirin and heparin discontinuation 12 hours before the surgery. The newborn weighed 1900 g with a favorable APGAR score. We confirmed a unilateral mild clubfoot, treated using a specific brace. The growth and development of the child were within normal limits.

Six months after delivery, 7th pregnancy was confirmed. The identical therapy was administered based on the history of previous successful pregnancy outcomes. Ultrasound of the uterine arteries in the 21st week showed notching on both sides, with a more pronounced left side (Figure 3). Fetal growth looked good and optimal until the gestational age of 35 weeks and the fetal weight reached 2761 g. Delivery was planned at the 38th week by elective cesarean section.

![Figure 1. Left uterine artery. Ultrasound examination results for the 6th pregnancy, left uterine artery persistent notching at 18th weeks of pregnancy (white arrow).](image1)

![Figure 2. Growth chart. Ultrasound examination results for the 6th pregnancy. The fetal growth chart showed that fetal weight decreased at 35 weeks (red arrow).](image2)
following aspirin discontinuation at week 36, and heparin continued until 12 hours before delivery. We observed a new onset of hypertension and diagnosed the patient with severe (late onset) pre-eclampsia. The decision to terminate the pregnancy at 37th weeks is unavoidable. A healthy baby was born by cesarean section; the newborn’s weight was 2800 g, with a good APGAR score and no congenital abnormalities. The mother and the newborn were discharged in healthy condition.

Figure 4 shows the survival resume of the last two pregnancies that managed to get a live baby even though the mother had pregnancy complications in the 3rd trimester, and the baby at 6th gestation had a mild clubfoot abnormality. Unlike the previous pregnancy, no congenital abnormality was seen in this 7th pregnancy.

**DISCUSSION**

Administration of heparin to pregnant women
with thrombophilia in early pregnancy reduces the number of miscarriages, cases of FGR and Haemolysis, Elevated Liver Enzymes, and Low Platelets (HELLP) syndrome. However, the use of heparin does not affect Pre-Eclampsia incidence.⁷ The combination of low-dose aspirin and heparin is superior to the use of aspirin only, with the combination of aspirin and heparin having a 72%-80% chance of having successful pregnancy outcomes.⁸

In these two pregnancies, the combination of heparin and low-dose aspirin was successful, resulting in delivery after 34 weeks of gestation with vigorous babies, although minor congenital abnormalities were found in the 6th pregnancy. Even though using similar treatment, two different types of complications arose in late pregnancy. In the 6th pregnancy, FGR appeared late in gestation, whereas the late onset of severe pre-eclampsia appeared in the 7th pregnancy. Low-dose aspirin is more effective in preventing the early onset of FGR and pre-eclampsia.⁹ Aspirin only reduces the risk of early-onset pre-eclampsia when started before 16 weeks of gestation and at a daily dose of >100 mg; Meanwhile, the recommendation of the American College of Obstetricians and Gynecologists (ACOG) is 81 mg aspirin/day.¹⁰,¹² In this case, although the dose of aspirin administered was 80 mg, it prevented pre-eclampsia, probably because the treatment was given early in pregnancy and combined with heparin. The occurrence of abnormal MCV and MCH with a high platelet count is a condition that is often found in patients with Thalassemia.¹³ Due to a tendency for thrombocytosis; therefore, low-dose aspirin alone is ineffective because of previous failed pregnancies. In the 6th pregnancy, laboratory values showed a platelet count of 488,000/mL, which indicated thrombocytosis. Pregnancy in patients with Thalassemia major or intermedia showed the dynamic multiple system changes and metabolic disturbances caused by chronic anoxia and iron overload. Those events are associated with an increased risk of thromboembolic events.¹⁴ The first-trimester uterine artery can be used to predict newborns small for gestational age (SGA), especially early-onset SGA newborns.¹⁵ During the 6th pregnancy, an ultrasound of the uterine arteries was performed at the 14th week and repeated at the 18th week showing a bilateral notching with the left side more prominent. During the 7th pregnancy, the uterine arteries were examined at the 21st week and a bilateral notching with the left side was also more clearly observed. The notching appearance in the 2nd and 3rd trimesters of pregnancy indicated an increased uterine vascular resistance and impaired uterine circulation. Whereas in the first trimester, the notching in non-pregnant women was normal and should begin to disappear at 13 weeks until 16 weeks. Bilateral notching of the uterine artery assesses the risk of developing FGR or pre-eclampsia. In these cases, the combination of heparin and aspirin prevented the recurrent loss but did not prevent late-onset complications such as late-onset FGR and pre-eclampsia. The safety issue of aspirin use has been questioned for a long time, and it is a clinician’s first consideration when deciding to administer aspirin early in pregnancy. In the 6th pregnancy, a minor congenital abnormality of clubfoot was found; it remains a question whether this is due to the administration of aspirin early in pregnancy. The meta-analysis by Kozer of receiving low-dose aspirin was not evidence of association with a congenital abnormality. Nevertheless, some literature reports an association with gastroschisis.¹⁶ Clubfoot is associated with gene abnormalities, and repeated microduplication of chromosome 17q23.1q23.2 has been identified.¹⁷ Diagnose parental clubfoot and smoking, confirm possible association with clubfoot in offspring, especially smoking in the first trimester.¹⁸ Several genes are involved in the occurrence of clubfoot syndrome, particularly those affecting peroxisomal matrix proteins and enzymes required for the sulfation of proteoglycans, which are essential for connective tissue.¹⁹ Further investigation is needed to confirm the association of clubfoot with aspirin. Meanwhile, heparin does not affect the fetus because it does not cross the placental barrier; so the frequency of occurrence is not different from normal pregnancy without heparin administration.²⁰ The limitations of this report are that we did not obtain accurate and complete medical and therapeutic data from 5 cases of abortion handled by previous clinicians. Therefore, all patients must always store medical data for future needs regarding previous medical conditions.
CONCLUSION

The combination of 2 x 5000 U unfractionated heparin subcutaneously and 80 mg aspirin can maintain pregnancy and fetal viability especially when administered from early gestational age. However, late-onset preeclampsia and FGR cannot be prevented by using these drugs in combination. Thrombocytosis in pregnant patients aggravates platelet hyper aggregation, therefore a therapy combination is needed. Heparin and aspirin could maintain pregnancy and fetal viability in Thalassemia minor patients with recurrent abortus and thrombocytosis.

CONFLICT OF INTEREST

None declared

ACKNOWLEDGEMENT

None declared.

REFERENCES

17. Alvarado D, Aferol H, McCall K, Huang J, Techy

