รายงานผู้ป่วย

Maternal warfarin and fatal neonatal hemorrhage

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Oral anticoagulant therapy with warfarin in the first trimester of pregnancy is associated with fetal anomalies,while that in the last trimester causes neonatal hemorrhage. Our case was a near-term infant whose mother had been given warfarin for her atrial fibrillation during the last half of pregnancy. Although her coagulation was carefully monitored, the infant still succumbed from bleeding in the lungs, liver, kidneys,spleen,brain and scalp. Heparin, which does not cross the placenta, has been recommended to replace warfarin prior to delivery to prevent the bleeding tendency of both the mother and the infant.

Key words : *Warfarin, Hemorrhage, Neonates, Newborn infants.*

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หญิงมีครรภ์อาจมีความจำเป็นต้องได้รับการรักษาด้วยยาต้านการแข็งตัวของเลือด warfarin ซึ่งเป็นยาชนิดที่ใช้รับประทาน สามารถผ่านรกเข้าสู่กระแสโลหิตของทารกในครรภ์ได้ ทำให้เกิดรูปวิปริตในไตรมาสแรก และภาวะเลือดออกในไตรมาสที่สองและสาม ผู้ป่วยมารดาและทารกในรายงานนี้ แสดงถึงภาวะแทรกซ้อนของ warfarin ที่มีต่อทารก ถึงแม้มารดาจะได้รับการตรวจ PT และ INR และระวังให้อยู่ในระดับต่ำ ๆ ในระหว่างการรักษา atrial fibrillation ด้วย warfarin แต่ก็ไม่ใช่ดัชนีที่จะประกันได้ว่าทารกจะไม่มีภาวะเลือดออก การที่ไม่ได้เปลี่ยนยาจาก warfarin เป็น heparin ซึ่งเป็นยาต้านการแข็งตัวของเลือดชนิดฉีดที่ไม่ผ่านรกเข้าสู่ทารก ทำให้ทารกเสียชีวิตเนื่องจากเลือดออกในสมอง ในปอด ตับ ม้าม และไต การอธิบายให้มารดาเข้าใจถึงปัญหาจากการรักษา ภาวะเสี่ยงที่มีต่อทารกในครรภ์ และความจำเป็นในการปรับเปลี่ยนยาในไตรมาสสุดท้าย รวมถึงการที่ต้องอาศัยความร่วมมือจากผู้ป่วยในการติดตามผลการรักษาอย่างใกล้ชิด อาจช่วยป้องกันภาวะแทรกซ้อนที่จะเกิดแก่ทารกแรกเกิดได้

Oral antiboagulant therapy in a pregnancy is associated with mobidity and mortality to the offspring. The first such fatal hemorrhage was reported in 1949[1]. However in some life threatening conditions administration of anticoagulant to the pregnant woman is unavoidable. The following case represents an example of the devastating effect of maternal warfarin to a fetus.

Case report

A male infant, 2170 grams (10^{th} percentile) was born to a G_2P_1, 29 years old mother at 37 weeks of gestational age by prophylaxis forcep extraction. The Apgar scores were7 and 8 at 1 and 5 minutes respectively.

The mother had taken diuretic and digoxin for rheumatic heart disease prior to this pregnancy. Upon her first prenatal visit at 18 weeks of gestational age, she was found to have severe mital stenosis, mild mitral and tricuspid regurgitation and atrial fibrillation for which warfarin was added to her medications. The dose of warfarin was adjusted to the maximum of 4-5 mg alternate with 6 mg. per day, while her PT was kept at 15-19 sec. (control 13 sec.) and INR 1.2 - 1.4. Intrauterine growth retardation was ruled out by ultrasonography at 26 weeks of gestational age. The fetal movement was good throughout pregnancy but maternal dyspnea increased and admissions were adviced twice by the obstetrician at 31 and 35 weeks of gestational age, however, the mother refused, citing her personal problem. Warfarin had been continued until 37 weeks when the labor began, and lasted 10 hours during which the fetal heart rates were 140-154/ minute. Maternal PT was 24.5/12.5 sec, PTT 29.4/27 sec., and Vitamin K 10 mg. was given intravenously 25 minutes prior to delivery.

Physical examination of the infant at 15 minutes after birth revealed body temperature 35.8 °C,RR 40/min, BP 52/25 Torr, head circumferece 37 cm. (+4 S.D.), anterior fontanel 3.5 x 3.5 $cm.^2$, not bulging, saggital suture 1.5 cm. in width. He was marked pale, lethargic and hypotonic. Generalized soft tissue swelling of the scalp with some ecchymosis was noted. Heart and lungs were normal, abdomen was soft, without hepatosplenomegaly. The other systems were within normal limit. The central venous pressure was 3.5 cm., and 0.9 % normal saline was given initially, while awaiting blood transfusion. Complete blood count at 3 and a half hours old was Hb 6.9 gm/dl, Hct 19.5 %, Wbc 17,700, PMN 51 %, E 4%, M 10 %, B 5 %, L 30 % platelets 242,000/mm^3. PT 84.1/13.2 sec PTT > 150/ 32.7 sec.

At 4 hours of age, his BP dropped to 38/29 Torr ,the swelling of the scalp increased in size and extended down to the neck. Subgaleal hematoma was diagnosed, and whole bood, packed red cell, fresh frozen plasma, and Vitamin K were given. Mechanical ventilation was required at 20 hours old because of hypoxia, respiratory distress, and apnea, which were

imposed on by the swelling of the neck. Fresh bloody secretion was detected in the trachea before the endotracheal tube was inserted.

On day 2 he developed seizure and gross hematuria,which progressed to renal failure on day 3. Ultrasound of the head discovered intraventricular hemorrhage with huge blood clot and venticular dilalation. The head circumference increased 0.8 cm. Treatment included multiple doses of fresh frozen plasma, whole blood, packed red cell, Vitamin K intravenously, and other supportive and symptomatic managements. The prothrombin time was within normal limit on day 4, but prolonged PTT and bleeding continued. His clinical condition deteriorated and he expired at the age of 4 days old.

Autopsy revealed subgaleal and intracerebral hemorrhage. There were recent hemorrhage of lungs,liver,spleen and kidneys.

The mother's postnatal course was uneventful.

Discussion

Conditions such as prosthetic heart valve, thromboembolism, arrythmia, necessitate the pregnant woman to require anticoagulant therapy. Warfarin is the oral anticoagulant most frequently prescribed. Bleeding, it's major toxicity, was first recognized in cattles which resulted from the ingestion of spoiled sweet clover silage in 1924.[2] The responsible agent was identified as bishydroxycoumarin (dicoumarol).[2] 4 hydrocoumarin and it's derivatives, such as warfarin, phenprocoumon, dicoumarol and acenocoumarol, are vitamin K antagonist, thus depress the vatamin K-dependent coagulation factors II,VII,IX,X, protein C and protein S. Warfarin crosses placenta and causes fetal morbidity and mortality. Of 418 reported cases of warfarin treatment one-sixth of pregnancy resulted in abnormal liveborn infants, one-sixth in abortion or stillbirth and two-thirds in apparently normal.[3] Lecuru observed only one coumarin embryopathy but no neonatal death or fatal intracranial hemorrhage in 54 pregnancies.[4] Warfarin administering in the first trimester of pregnancy causes embryopathy, manifested as nasal bone hypoplasia, stippling of the epiphyses, deformities of the bones, optic atrophy, delayed psychomotor development, mental retardation,[5] dextrocardia and situs inversus.[6] However, exposure to warfarin in the 2 nd and 3 rd trimesters of pregnancy is equally dangerous to the fetus and massive hemorrhage in multiple organs that causes fetal and neonatal death[1,7] are reported. Congenital schizencephaly, cerebral damage, microcephaly, hydrocephalus, blindness, and mental retardation were held as the consequences of hemorrhage in the growing organs.[8] Delivery is the critical time that causes both maternal[4] and infant bleeding.[9] Because heparin doses not enter the fetal circulation, it is recommended to replace warfarin during the first 12 weeks of gestational period to prevent the untoward effects during organogenesis, and the last 2 weeks of

pregnancy to prevent hemorrhagic disorder.[10,11] Fixed mini-dose warfarin was offered as a safe ulternative for the fetus.[12]

The patient in this report had been prescribed warfarin for the last half of her pregnancy. Even her prothrombin time and INR were monitored, they did not reflect the safety of the fetus.[7] Vatamin K given prior to the delivery had some benefits for the mother who did not have excessive bleeding, but effect on the fetus was insufficient to prevent massive hemorrhage. Serial ultrasonography for early detection of the hemorrhagic evidence in the fetus should be done while the mother is given warfarin during pregnancy. Considering intrauterine tranfusion of fresh frozen plasma and Vitamin K to reverse the anticoagulant effect in a high risk fetus has been proposed.[7] Oral warfarin should be replaced by heparin which doses not cross the placenta during the last two weeks of pregnancy. Treating the patient as a whole, including counselling and educating the mother are needed to obtain her compliance and cooperation.

Conclusion

Oral anticoagulant therapy in a pregnant woman carries a small but serious risk to the fetus and the infant. Bleeding in mutiple organs of this infant was the result of 11 weeks of maternal warfarin treatment during the last half of pregnancy. Although maternal coagulation was kept in acceptable ranges, the infant was still subjected to massive hemorhage perinatally and postnatally. Vitamin K, blood, fresh frozen plasma and other supportive treatments did not save the infant's life. To prevent perinatal and neonatal bleeding, oral anticoagulant should be replaced by heparin which does not cross the placenta during the last two weeks of pregnancy. Counselling and maternal compliance are necessary.

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