

Subchorionic hematomas are increased in early pregnancy in women taking low-dose aspirin

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Objective: To determine the frequency of subchorionic hematomas (SCH) in first-trimester ultrasound examinations of patients with infertility and recurrent pregnancy loss (RPL) and in patients from a general obstetric population. To determine if the method of assisted reproduction utilized or the use of anticoagulants, such as heparin and aspirin (ASA), influenced frequency of SCH.

Design: Prospective, cohort study.

Setting: Fertility clinic and general obstetrics clinic.

Patient(s): Five hundred and thirty-three women who were pregnant in the first-trimester.

Interventions: Not applicable.

Main Outcome Measure(s): Frequencies of subchorionic hematomas in women based on diagnosis, use of anticoagulants, and fertility treatment.

Result(s): SCH were identified in 129/321 (40.2%) in the study group compared to 23/212 (10.9%) in the control group. Fertility diagnosis and the use of heparin did not appear to affect the frequency of SCH in the first trimester; however, SCH occurred at an almost four-fold increase in patients taking ASA compared to those not taking ASA, regardless of fertility diagnosis or method of fertility treatment.

Conclusion(s): The use of ASA may be associated with an increased risk of developing a SCH during the first trimester. The increased frequencies of SCH in pregnancies of patients attending a fertility clinic compared to women from a general obstetrical practice was highly correlated with the use of ASA. (Fertil Steril® 2016; ■:■-■. ©2016 by American Society for Reproductive Medicine.)

Key Words: subchorionic hematomas, aspirin, infertility, anticoagulants, recurrent pregnancy loss

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The incidence of SCH in first-trimester pregnancies has been estimated to be from 0.46% to 22% in the general obstetric population within the last decade (1–3). SCH are defined as a collection of fluid in the uterine cavity, and they are thought to be the result of subchorionic bleeding caused by a partial detachment of the

trophoblasts from the uterine wall (2). Small echogenic structures are also found in these areas, and these are thought to be blood clots. SCH are generally diagnosed by ultrasonography. The patterns of SCH were first described in 1981 by Mantoni and Pedersen, and since then ultrasonographic equipment has improved

tremendously leading to more accurate findings and diagnosis (4).

The clinical significance of the finding of a SCH in early pregnancy has long been controversial. Adverse outcomes in early pregnancies with detected SCH include spontaneous abortions, fetal demise, and preterm deliveries. In patients with threatened abortions, a SCH is correlated with increased risk in miscarriage (5). SCH are also shown to be associated with preterm birth through unknown physiological mechanisms, and the presence of a SCH in early pregnancy correlates with a two-fold increase in pregnancy loss (6, 7).

Aspirin, or acetylsalicylic acid (ASA), is a widely utilized vasoactive

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substance that irreversibly inhibits the enzyme cyclooxygenase in platelets, preventing the synthesis of thromboxane (8). ASA has been shown to increase intra-ovarian vascularity, improve uterine perfusion, and subsequently increase endometrial receptivity and ovarian response to gonadotropin stimulation in assisted reproductive treatment (ART) cycles (9). In some programs, ASA is frequently administered during ovulation induction. Both heparin and ASA have been utilized in the treatment of recurrent pregnancy loss (RPL) by affecting both the immune and coagulation system (9). The effects of ASA on inhibition of platelet aggregation are thought to work together with heparin to promote and enhance implantation.

ASA is also often prescribed during pregnancy as an effective method to treat pre-eclampsia without harm to mother or fetus (10). Studies have also shown that, along with treatment for pre-eclampsia, use of ASA lowers the risk of preterm birth (11, 12). After the report by Weckstein et al. suggesting that low-dose ASA improved endometrial receptivity in oocyte receptors (13), many programs began to routinely use ASA as a part of their IVF protocols. We anecdotally observed that the frequency of SCH increased in some of these patients and were concerned that either medicine or treatment being used might indirectly be related to this observation. We suspected that use of ASA might be correlated with increased SCH.

We were unable to identify studies in the literature that describe the association between SCH and ASA. The purpose of our study was to determine the frequency of SCH during the first trimester in patients with infertility and recurrent pregnancy loss (RPL) versus the general obstetric population. We hypothesized that pregnancies in women with infertility and RPL may be associated with an increased risk for SCH. Furthermore, we sought to determine whether the method of assisted reproduction treatment or the use of anticoagulants, including ASA 81 mg, influenced the frequency of SCH.

MATERIALS AND METHODS

We compared the frequency of SCH among a study group consisting of patients attending a fertility clinic and a control group of general obstetric patients. The prevalence of SCH was further categorized based on patient diagnosis (infertility or RPL), treatment, and use of anticoagulants.

This study was a prospective, cohort study of the frequency of first-trimester SCH in early pregnancies. This study was approved by the Institutional Review Board at the University of Tennessee Health Science Center involving the collection and study of data recorded by the investigators in such a manner that the subjects could not be identified either directly or indirectly, although identifiers were linked to the subjects. All pregnant patients who had a viable pregnancy on initial ultrasound evaluations from 6 to 12 gestational weeks were asked to participate in the study. Patients were recruited from two centers, Fertility Associates of Memphis and Memphis Obstetrical and Gynecologic Association. All 533 women underwent first-trimester ultrasound examinations between August 2005 and August 2007. Demographic data collected included age, gravity, diagnosis, medications, and method of conception.

This information was confirmed by extensive and careful review of medical records. Inclusion criteria were the presence of a viable gestation between 6 and 12 weeks gestation. Infertility was defined as the failure to conceive after one year of trying without the use of contraceptives. Recurrent pregnancy loss was defined as three or more documented pregnancies that failed to progress to delivery. Patients with pregnancies <6 or >12 weeks gestation, non-viable pregnancies, or those who refused to participate were excluded from the study.

ASA 81 mg was initiated prior to pregnancy in women with RPL and continued throughout pregnancy until 36 gestational weeks. Aspirin 81 mg was initiated at the start of any ovulation induction or IVF cycle and continued throughout pregnancy to 13 weeks. Heparin was administered at 5,000 units subcutaneously twice-daily starting with a positive pregnancy test in women with RPL. If the patient was undergoing IVF and had a history of RPL, heparin was initiated the night before embryo transfer. Medical records of patients were reviewed. Patients were asked about any current medications taken at the beginning of each visit. Medications were subsequently recorded. All Patients were instructed not to use any additional aspirin or aspirin-like products during pregnancy but rather to use acetaminophen for pain relief.

Detection of Subchorionic Hematomas

All ultrasounds were performed by the same two Registered Diagnostic Medical Sonographer (RDMS) certified ultrasonographers at each clinic. Gestational age was calculated based on last menstrual period, date of conception, date of embryo transfer, or was corrected when the crown-rump length measurements were more than 5 days different from the last menstrual period. Measurements were recorded from the ultrasound evaluations as follows: crown-rump length, yolk sac diameter, gestational sac diameter, fetal heart rate, presence of subchorionic hematoma. Gestational age was based on last menstrual period in women who conceived naturally or with timed intercourse and was corrected based on first ultrasound when crown-rump length was more than 5 days different from last menstrual period. Last menstrual period was also used in women who underwent ovulation induction with intrauterine insemination and was corrected to date of insemination if the crown-rump length on ultrasound was more than 5 days different from last menstrual period. In women who were undergoing IVF, the date of embryo transfer was used to calculate gestational age.

SCH were defined as crescent-shaped, sonoluscent fluid collections located between the chorion and the uterine wall. The location of the hematoma was recorded as fundal, anterior, posterior, lateral, or lower uterine segment. All sonographic measurements were made by Toshiba Nemio 20 (Toshiba America, Chicago, Illinois) with a 6.0 MHz transvaginal probe. Images were then carefully reviewed in a blinded fashion and interpreted by the investigators WHK and RWK.

STATISTICAL ANALYSIS

Statistical analyses were performed using the Fisher's exact two-sided test for significance to compare the presence or absence of SCH in each group. The one-way analysis of

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