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;105:1241–6. ©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 receptive 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

variance (ANOVA) and the Tukey-Kramer multiple comparison test were used to compare the frequency of SCH among the multiple treatment groups. This study was designed to detect a 10% difference in the frequency of SCH with a significance level of α=0.05 and a power of 80% (β=0.80) with the inclusion of 200 patients in each group.

RESULTS

Patient Demographics and the Prevalence of Subchorionic Hematomas in Pregnant Patients

A total of 533 women met the inclusion criteria and were enrolled. Of the 533 women, 321 fertility patients were included in the study group and 212 general obstetrical patients were included in the control group. The study group included 233 women diagnosed with infertility and 88 diagnosed with RPL. The mean maternal age for the study group was 34.6 ± 4.9 (range 22–48) and greater than that of the control group 30.6 ± 5.1 (range 16–44) (Table 1). The mean gestational age was 8.1 ± 1.7 weeks for the study group and 8.3 ± 2.0 weeks for the control group. There were more miscarriages in the study group due to the inclusion of 88 women diagnosed with RPL (Table 1). SCH were identified in 129/321 (40.2%) women in the study group but only in 23/212 (10.9%) women in the control group ($P<.0001$) (Fig. 1). SCH were identified in 41/88 (46.6%) of women with RPL versus 88/233 (37.8%) with infertility ($P=.1618$) (Fig. 1).

We also sought to determine if the method of fertility treatment used affected the frequency of SCH. Regardless of method of treatment, including spontaneous pregnancies, Clomid, Letrazol, Follicle Stimulating Hormone (FSH), and IVF, there was no significant difference in SCH frequency between these methods of conception ($P=.4345$) (data not shown).

Effect of Aspirin Use on the Frequency of Subchorionic Hematomas in Fertility Clinic Patients

Of the 321 women in the study group, 233 women were on ASA and 88 women were not on ASA. 12/88 (13.6%) of the women not on ASA had SCH, while 117/233 (50.2%) of women on ASA had SCH ($P<.0001$). These results demonstrated that there is a significant increased frequency in SCH with the use of ASA. Conversely, there was not a significant difference in SCH frequency with or without use of heparin (Fig. 2). No women in the control group were on ASA or heparin.

Effect of Aspirin and Method of Conception on Frequency of Subchorionic Hematomas

Of the 321 women in the study group, 233 were diagnosed with infertility and 88 were diagnosed with RPL. Among the 233 infertile women, 155 were on ASA 81 mg; of these, 77 (49.7%) had SCH. In comparison, 78 were not on ASA; among these, only 11 women (14.1%) had SCH. Of the 88 women diagnosed with RPL, 78 were on ASA and 40 (51.3%) had SCH. Of the 10 not on ASA, only 1 woman (10.0%) had SCH (data not shown).

Of the 321 pregnancies in the study group, 122 of those pregnancies were spontaneous, 28 pregnancies used Clomid, 13 pregnancies used Letrozol, 17 pregnancies used follicle-stimulating hormone (FSH), and 141 pregnancies were from IVF. Of the spontaneous pregnancies, 76 women were on ASA and 34/76 (44.7%) had SCH (Fig. 3). Of the 46 spontaneous pregnancies not using ASA, 10/46 (21.7%) had SCH. 13 out of the 28 (76.9%) pregnancies using Clomid while on ASA had SCH, while none (0.0%) of the 15 pregnancies without ASA had SCH. Similarly, 4 out of the 6 (66.7%) patients using ASA who conceived on Letrozol had SCH, while none out of 7 (0.0%) of the non-ASA Letrozol pregnancies had SCH. 4 out of the 6 (66.7%) FSH pregnancies also on ASA had SCH, while only 2 out of the 11(18.2%) non-ASA FSH pregnancies did not have SCH. Finally, 65 out of the 132 (49.2%) IVF pregnancies also on ASA had SCH, while none (0.0%) of the 9 non-ASA IVF pregnancies had SCH (Fig. 3).

DISCUSSION

SCH are presumably caused by low pressure bleeds resulting from tears in the marginal veins of the placenta (14). Although SCH have been associated with abnormal pregnancy outcomes, the relationship is unclear, with SCH reported to be present in 20% to 70% of these abnormal outcomes (14, 15). The overall incidence of hematomas in the 2003 study by Nagy et al. was 3.1% in a general obstetrics population which was 230 of 7405 singleton pregnancies (1). In a large retrospective study, Norman et al. reported of 1,081 out of 63,966 (1.7%) women before 22 weeks gestation had SCH (16). Their frequency of SCH is lower than what is reported here and is probably because their period of recording, 1994–2008, began at a time where sonographic technology was not as sensitive at detecting SCH. Our observational study suggests that SCH are detected four times more frequently in patients seeking fertility treatment compared with those patients who have a normal obstetrical history. Previous reports have suggested patients undergoing assisted reproductive technologies (ART) may have an increased risk of developing a SCH during early pregnancy (17). Asato et al. in 2014

TABLE 1

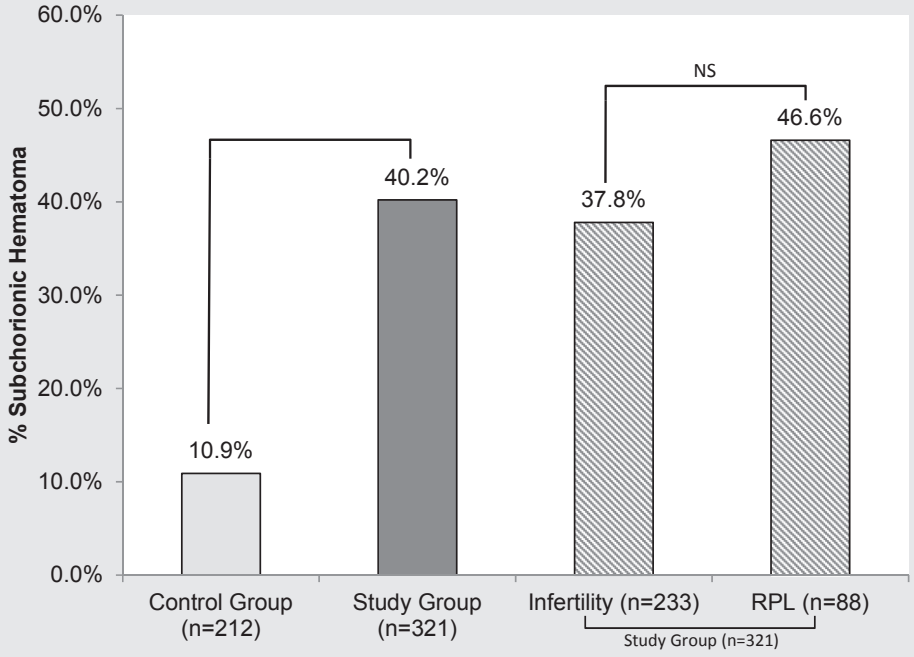
Demographics for patients in the study and control group.

Variable	Study group	Control group	*P* value
N	321	212	
Age (y), mean (±SD)	34.6 (±4.9)	30.6 (±5.1)	<.0001
Gravity	2.4	2.1	NS
Parity	0.4	1.0	NS
Miscarriage	1.0	0.1	<.001
Gestational age (y), mean (±SD), weeks at ultrasound	8.1 ± 1.7	8.3 ± 2.0	NS
No. of subchorionic hematomas (%)	129 (40.2)	23 (10.9)	<.0001

Note: NS = not significant.

Truong. Subchorionic hematomas and aspirin. Fertil Steril 2016.

FIGURE 1



Percentage of subchorionic hematomas in control group versus study group and compared to the diagnosis of infertility and recurrent pregnancy loss. *Solid bars* demonstrate the comparison of percentage of patients in control group with SCH versus percentage of study patients with SCH ($P<.0001$). *Striped bars* indicate the comparison of the percentage of SCH in patients of the study group, subdivided based on diagnoses of infertility or recurrent pregnancy loss ($P=.1618$). NS = not significant.

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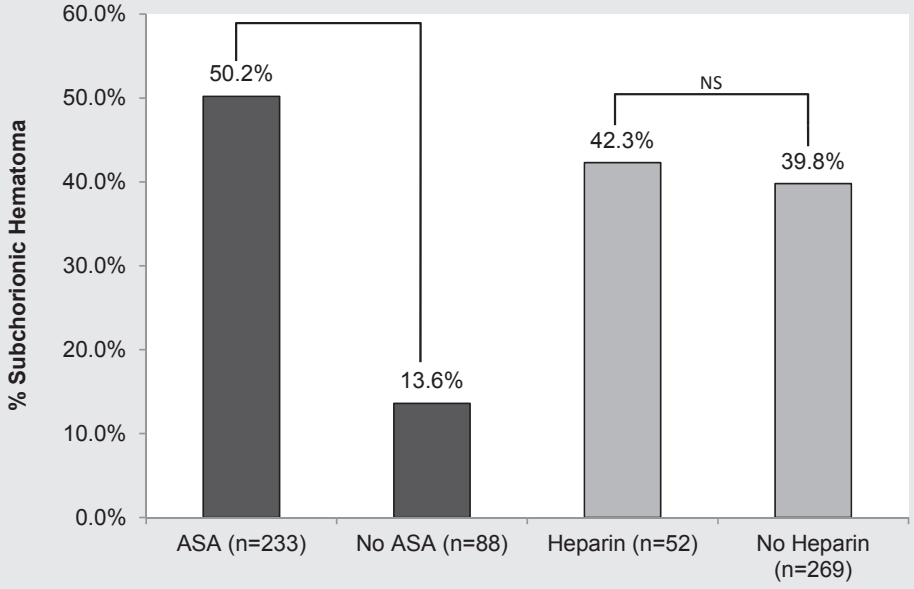
demonstrated that there is a significant increased frequency of SCH in IVF patients compared to non-IVF patients; however, they did not report on the frequency of SCH associated with aspirin. In our study, we reported an incidence 40.2% SCH in the study group compared to 10.9% in the general obstetric population. Interestingly, the increased frequency in

FIGURE 2



Percentage of SCH in study group using anticoagulants. Both ASA (*dark grey*) and Heparin (*light grey*) data groups are derived from the study group (n=321). 50.2% of women on ASA compared to 13.6% of women not on ASA had SCH ($P<.0001$). NS = not significant.

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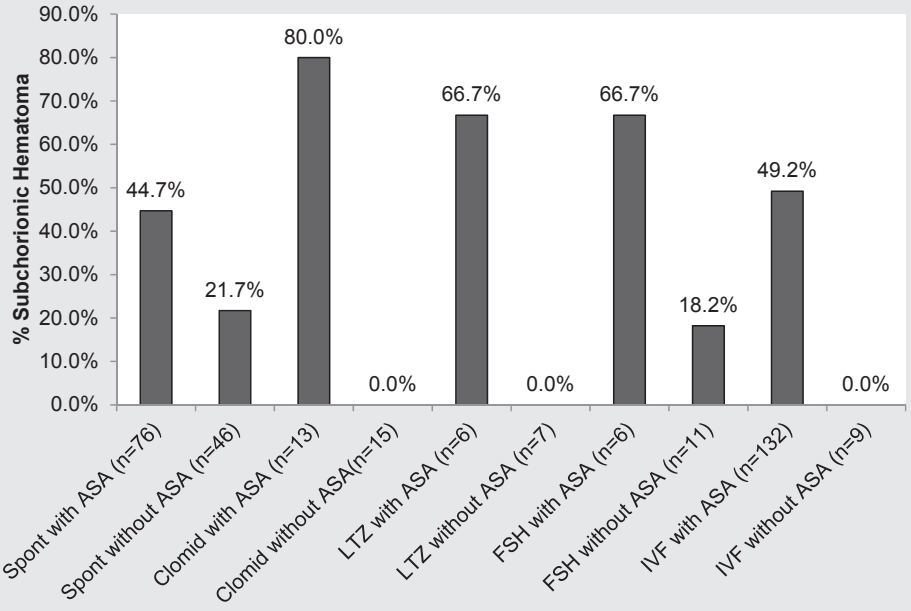
FIGURE 3



Percentage of SCH in study group with respect to fertility treatment and use of ASA. SCH frequency is significantly ($P<.05$) increased in those taking ASA compared to those who are not taking ASA, regardless of fertility treatment.

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SCH appeared to be due to ASA and not necessarily the patients' infertility treatment or diagnoses. The increased relative risk of developing a SCH may be in fact an indicator of increased risk of an adverse pregnancy outcome in this specific population.

ASA is now commonly prescribed to patients with pre-eclampsia (11), but the use of ASA may be associated with an increased risk of developing a SCH during the first trimester according to our study. Based on these data, we suggest that ASA should not be initiated in women with a history of pre-eclampsia until the start of second trimester. The U.S. Preventative Services Task Force has recommended the use of low-dose ASA (81 mg) in women with a history of pre-eclampsia, those with multiple gestation, chronic hypertension, diabetes mellitus, renal disease, or autoimmune disease (18). A recent cost-benefit analysis of low-dose ASA prophylaxis for prevention of pre-eclampsia suggested that universal prophylaxis for all pregnant women in the U.S. would reduce morbidity (19). This theoretical model, however, did not take into account the increased morbidity from the expected four-fold increase in SCH. Therefore, our data support the recommendation of the U.S. Preventative Services Task Force to delay the initiation of prophylactic low-dose ASA until the start of the second trimester.

The use of ASA in order to improve uterine blood flow and thus potentially improving implantation was originally advocated after a report of higher pregnancy rates in recipients of oocyte donor IVF cycles (13). Additionally, it has been demonstrated that endometrial and subendometrial vascularity is significantly higher in pregnant patients with live births than those with miscarriage making the argument for the use of ASA even more appealing (20). Moreover, in the past, many programs recommend the administration of low-dose ASA for patients undergoing IVF to improve implantation. Studies have shown that given the lack of proven efficacy and the actual potential for harm, ASA should not be routinely recommended to women undergoing assisted conception (9, 21-23). In support of this, our study has demonstrated a potential associated risk to pregnancy with the administration of ASA.

Limitations of this Study

A potential limitation in our study was the fact that the ultrasonographers were aware of the study and therefore, may have been more prone to finding SCH. In order to reduce this bias, the images of all the ultrasounds were reviewed by the physician investigators in a blinded fashion to confirm the presence or absence of SCH. Further studies in the pathophysiology of SCH will perhaps explain and/or clarify the significance of these findings. SCH may serve as markers for adverse perinatal outcomes such as miscarriage, preterm delivery, abruption, and fetal demise. The findings of our study are significant; however, they need to be correlated with pregnancy outcomes. When considering what factors are different about our two populations, we can see that there is a statistical difference in the ages of the two groups. Patients in our fertility clinic were older than those in the general obstetric population. Advancing maternal age has been found to play an important role in the factors increasing the incidence of SCH along with other independent variables such as earlier gestational age and hematoma size (23).

We determined that the overall frequency of SCH is increased in women attending fertility clinics making these

women significantly more likely to develop SCH when compared to the general obstetric population. However, the use of ASA, rather than the actual fertility diagnosis or treatment, was found to be directly associated with risk of SCH in this specific population compared to the general obstetric population. Prior to 2009 we routinely used ASA 81 mg as a part of our IVF protocol. Subsequent to this study, indicating an increased frequency of SCH associated with the use of ASA 81 mg, and several studies that did not detect a benefit from the use of ASA 81 mg (19, 20), we discontinued the routine use of ASA for these patients. We continue to routinely use ASA 81 mg pre-conceptually up to 36 weeks as well as in women with antiphospholipid syndrome and RPL (24). If women develop SCH while on ASA 81 mg and heparin, we discontinue the ASA. Regardless of initial diagnosis of infertility, RPL, or control status, patients in this study showed an increased frequency in SCH when using ASA. This newfound association between ASA and SCH requires further investigation in future studies. Previous studies have shown a relationship between SCH and adverse outcomes, thus appropriate counseling, treatment, and patient care may be advised. Patients should be counseled about the risks and benefits of ASA use in pregnancy.

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