ORIGINAL ARTICLE

The Role of Prophylactic Use of Low Dose Aspirin and Calheparin in Patients with Unexplained Recurrent Abortion

Taher M. M. Hassan, Abdelrahman R. Rashed, Mostafa M. R. Ali *

Department of Obstetrics and Gynecology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: ***Two or more miscarriages occurring within a 20-week window constitute recurrent pregnancy loss (RPL). A small percentage of pregnancies (1% to 5%) involve RPL. The causes of miscarriage are unknown in 40% of cases, which is categorized as an unjustified RPL (URPL), even though many factors are involved in approximately 60% of RPLs. These factors include environmental factors, stress, chromosomal abnormalities, coagulation protein defects, anatomic endocrine disorders, and the autonomic immune system.***

Aim and objectives: ***To assess the efficacy of low-dose aspirin and calheparin used as a preventative measure in women experiencing unexplained recurrent abortions.***

Patients and methods: ***The study was a prospective interventional study that included 60 patients who were selected from attendee of out-patient Obstetrics and Gynecology clinics of Al-Azhar at Al-Hussien and Sayed Gala University Hospitals from January 2024 till December 2024. Samples were collected using a random systematic method.***

Results: ***Regarding the outcome, 46 (76.67%) patients passed the first trimester, whereas abortion occurred in 14 (23.33%) patients.***

Conclusion: ***For women experiencing unexplained repeated abortions, a safe and effective treatment option is a combination of low-dose aspirin and calheparin, which can reduce the abortion rate and help them safely pass the first trimester. There is a small risk of temporary thrombocytopenia, gastrointestinal problems, bruising at the injection site, epistaxis, and bleeding gums when women with unexplained recurrent abortions take a low dose of aspirin and calheparin.***

Keywords: Calheparin; Recurrent abortion; Low dose aspirin

1. Introduction

At least half of the RPL cases have their roots in environmental, immunological, genetic, endocrinological, or coagulation-related variables. On the other hand, idiopathic abortion occurs in half of all cases where the reason is unclear. Five percent of reproductive-age women suffer from RPL, making it a serious health concern. Economic, emotional, and societal issues disproportionately affect women of childbearing age because of RPL.[1]

Multiple pregnancies in a row, chromosomal abnormalities in the parents, disorders affecting the mother's ability to clot, and uterine structural abnormalities are all considered to be risk factors for recurrent losses. Lastly, it is widely acknowledged that the most significant risk factor for future abortion, both for women experiencing repeated miscarriages and for the general population, is the mother's age. There is currently no known cause for recurrent miscarriage, which accounts for around half of all occurrences.[2]

Low-dose aspirin, progesterone, prednisolone, intravenous immunoglobulins, and calheparin are some of the experimental treatments being considered for unexplained RPL. This is because treatments for RPL with known causes are logically designed to compensate for the pathogenic defects or relevant risk factors. For RPLs with established causes, such as thrombophilic or immunologic-induced RPLs, the majority of these treatments have been effective.[3]

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* Corresponding author at: Orthopedic Surgery, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt.
E-mail address: mostafamamdoh450@gmail.com (M. M. R. Ali).

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Most drug prescriptions for unexplained RPL are based on assumptions about comparable reasons and are thus considered to be empiric. This is why it is crucial to conduct well-designed studies to evaluate each intervention independently. The use of calheparin to explain RPL has been the subject of several recent investigations, the majority of which have produced contradictory findings.[4]

Aspirin and low-dose heparin have shown average to extremely high success rates in treating patients with recurrent miscarriages; however, this treatment is limited to cases where antiphospholipid syndrome is present. There was a high proportion of live births and minimal late pregnancy problems in women who took low doses of aspirin and calheparin for unexplained repeated pregnancy losses, according to previous research.[5]

The purpose of this research is to determine whether or not women who experience unexplained repeated abortions benefit from using low-dose aspirin and calheparin as a preventative measure.

2. Patients and methods

The study was a prospective interventional study that included 60-patients who were selected from attendee of out-patient Obstetrics and Gynecology clinics of Al-Azhar at Al-Hussien and Sayed Gala University Hospitals from January 2024 till December 2024. Samples were collected by the systematic random method. Following clearance from Cairo's Al-Azhar University's Research Ethics Committee. Before any patient could be enrolled, they were required to sign an informed consent form.

Inclusion criteria:

Participants must be between the ages of 18 and 35 and have a history of at least two consecutive miscarriages. They must also be currently pregnant and within the first eight weeks of gestation, and they must have a history of unexplained recurrent miscarriage, which was defined as two or more miscarriages occurring within the first twenty weeks of gestation.

Exclusion criteria:

Known causes of recurrent foetal loss include patients with abnormalities in either the parents' chromosomes or in the mother's endocrinology, such as a luteal-phase defect (as confirmed by a timed endometrial biopsy), or uterine anomalies (such as an incompetent uterine septum or an internal cervical os). Polycystic ovarian disease (PCOD), thyroid disease, hyperprolactinemia, maternal thrombophilia (e.g., Factor V Leiden deficiency, protein C deficiency, protein S deficiency, antithrombin III deficiency, Maternal antiphospholipid antibody syndrome), systemic lupus erythematosus, and patients diagnosed with pregnancy after 8 weeks of gestation are all eligible for this clinical trial. If you have a history of peptic ulcer disease or are sensitive to aspirin, you should not use aspirin. Caution should be exercised while administering calheparin in cases of extremely low platelet counts or active bleeding.

Here is what all patients went through:

Demographic information: age, parity, race/ethnicity, and occupation; menstrual history: when did menarche begin, how long her periods are, how regular they are, and any problems with her periods; gestational age verification (GA): low-dose prenatal testing or ultrasound; obstetric history: total number of pregnancies, number of live births, number of miscarriages, details of previous abortions, whether or not fetal pulsations were present, when the abortions occurred, and whether or not surgical evacuation was necessary. Present complaints include any physical symptoms, emotional concerns, or issues specifically related to pregnancy.

Factors related to one's lifestyle, such as smoking, alcohol consumption, recreational drug use, dietary habits, and physical activity levels, as well as environmental exposures, such as occupational hazards, and one's mental health, including a history of depression, anxiety, psychiatric disorders, and support systems, as well as one's medical history, medications, and allergies.

Examination:

Vital signs(blood pressure, heart rate, respiration rate, temperature); signs of(pallor, cyanosis, jaundice, and lymph node enlargement); The formula to determine height, weight, and body mass index (BMI) was weight (kg) divided by height (m)^2 6 Overall appearance: well-nourished, well-developed, no apparent distress; skin: color, lesions, bruising; eyes: conjunctiva, sclera, pupils; ears: hearing, tympanic membranes; nose: sinuses, nasal septum; mouth: teeth, gums, tongue, throat; neck: lymph nodes, thyroid, carotid arteries; chest: breath sounds, percussion notes; heart: heart sounds, rate, and rhythm; abdomen: inspection, palpation, bowel sounds; pelvis: uterus, ovaries, adnexa; extremities: edema, pulses, capillary refill; neurological: cranial nerves, motor strength, sensation, reflexes.

Laboratory investigations:

Please ensure that the following prenatal laboratory tests are completed: complete blood count (CBC), random blood glucose level (RBGL), urine analysis, liver function tests (AST and ALT), kidney function tests (serum urea and creatinine), and fasting blood glucose levels. TORCH screening includes testing for toxoplasmosis, other viruses (such as HIV), rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), lupus anticoagulant,

anticardiolipin antibodies, protein C levels, protein S levels, antithrombin III levels, and karyotyping.

Methods:

Evaluation of antiphospholipid antibodies (APAs) using ELISA:

All selected women were evaluated for the presence of antiphospholipid antibodies(APAs) using the ELISA method. Ninety-six well microtiter plates(Immulon-2, Dynatech, Chantilly, VA) were coated with 30µL of either cardiolipin or phosphatidylserine at a concentration of 50µg/mL(Sigma, St. Louis).

Treatment procedure:

Calheparin (5000 IU subcutaneously every 12 hours) and low-dose aspirin (75 mg) were administered to all patients. As a preventative step against neural tube abnormalities, all women in the trial were instructed to take 400 µg of folic acid daily, beginning before conception and continuing until ten weeks into the pregnancy. Among the usual services provided by the participants' obstetricians during their pregnancies was structural fetal ultrasonography, which was done between the ages of 18 and 22 weeks.

Additionally, platelet counts were conducted at 12 and 30-weeks of gestation to monitor any potential complications. To ensure adherence to the protocol and to address any side effects, women were contacted by a dedicated research nurse every three months throughout the study until the completion of their first pregnancy. These interactions utilized a structured form to systematically gather information on compliance and any adverse effects experienced.

Follow up:

Until the first trimester came to a close, all participants were followed up with every two weeks. The patient's vitals, including weight and blood pressure, were measured during these follow-up appointments. Furthermore, to check on the mother's and the fetus's health, an ultrasound assessment of the pregnancy was conducted to track the fetal development.

Outcomes:

The primary outcome was to assess the continuation of pregnancy beyond the first trimester. While, the secondary outcomes included the assessment of any complications associated with the treatment administered.

Sample size:

Mohammed et al.,[7] The following assumptions were taken into account when using Epi Info STATCALC to determine the sample size: A power of 80% and a two-sided confidence level of -95%. This results in an odds ratio of 1.115 with a margin of error of 5%. The Epi-Info output yielded a maximum sample size of 53 in the end. Therefore, in order to account for potential cases of dropout during follow-up, the sample size was raised to 60 participants.

Ethical considerations:

Al-Azhar University Hospitals' Research Ethics Committee gave its stamp of approval to the study, which was conducted in Egypt.

Statistical analysis:

We used SPSS v26 (IBM Inc., Armonk, NY, USA) to complete all of our statistical analysis. Mean and standard deviation (SD) were used to show quantitative variables, and an unpaired Student's t-test was used to compare the two groups. Qualitative variables were examined using the Chi-square test or Fisher's exact test when appropriate, and were provided as frequency and percentage (%). It was deemed statistically significant if the two-tailed P-value was less than 0.05.

3. Results

Table 1. Baseline characteristics of the studied patients.

		TOTAL (N=60)
AGE(YEARS)	Mean±SD	26.83±5.25
	Range	20-35
WEIGHT(KG)	Mean±SD	76.97±11.32
	Range	58-96
HEIGHT(M)	Mean±SD	1.67±0.05
	Range	1.58-1.73
BMI(KG/M^2)	Mean±SD	27.75±4.05
	Range	20.04-35.93
RESIDENCE	Urban	31(51.67%)
	Rural	29(48.33%)

BMI:Body mass index

In terms of the patients' initial characteristics, their ages varied from 20 to 35 years old, with a mean (±SD) of 26.83±5.25 years. The subjects' height varied from 1.58 to 1.73 meters with a mean of 1.67±0.05 meters, their body weight varied from 58 to 96 kg with a mean of 76.97±11.32 kg, and their body mass index (BMI) varied from 20.04 to 35.93 kg/m2 with a mean of 27.75±4.05 kg/m2. Thirteen patients (or 51.67%) lived in urban regions, whereas twenty-nine (or 48.33%) lived in rural areas, (table 1; figure 1).

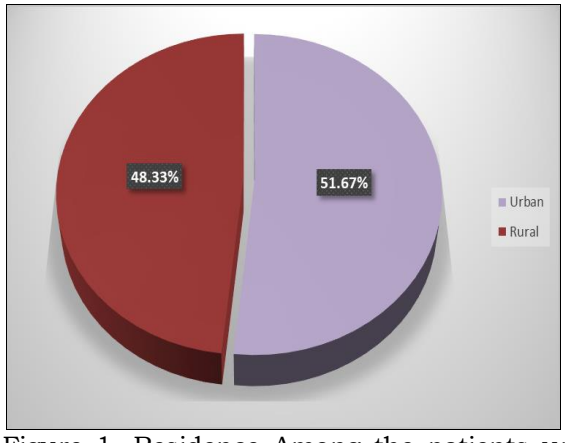

Figure 1. Residence Among the patients under study.

Table 2. Comorbidities Among the patients under study.

	TOTAL (N=60)
HTN	10(16.67%)
DM	12(20%)

HTN:hypertension, DM:diabetes mellitus

Regarding the associated comorbidities, 10(16.67%) patients had HTN and 12(20%) patients had DM, (table 1; figures 2&3).

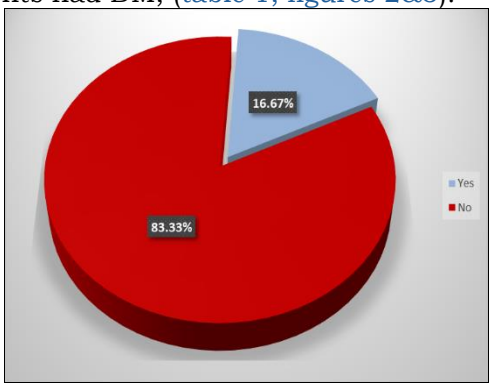

Figure 2. HTN Among the patients under study.

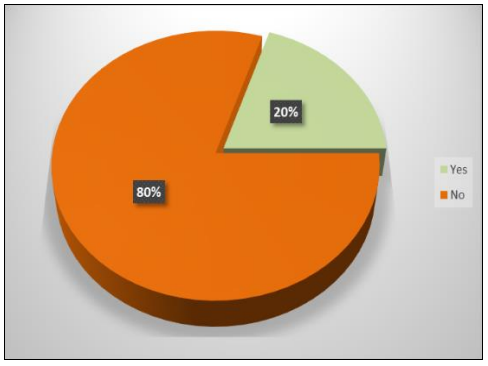

Figure 3. DM Among the patients under study.

Table 3. Vital sings of the studied groups.

		TOTAL (N=60)
HR(BEATS/MIN)	Mean±SD	81.38±8.04
	Range	70-95
SBP(MMHG)	Mean±SD	125±14.44
	Range	100-150
DBP(MMHG)	Mean±SD	76.17±10.27
	Range	60-90

HR:heart rate, SBP:systolic blood pressure, DBP:diastolic blood pressure, RR:Respiratory rate.

Regarding vital signs, HR ranged between 70-95 beats/min with a mean(±SD) of 81.38±8.04 beats/min, SBP ranged between 80-95mmHg with a mean(±SD) of 125±14.44 mmHg and DBP ranged between 40-60mmHg with a mean(±SD) of 76.17±10.27mmHg, (table 3).

Table 4. Obstetrical data of the studied patients.

		TOTAL (N=60)
GESTATIONAL AGE (WKS.)	Mean±SD	11.48±2.21
	Range	8-15
PARITY	Primipara	16(26.67%)
	Multipara	44(73.33%)
MENSTRUAL HISTORY	Regular	37(61.67%)
	Irregular	23(38.33%)
NO. OF PREVIOUS MISCARRIAGE	Mean±SD	5.2±2
	Range	2-8
NO. OF PREVIOUS LIVE BIRTH	Mean±SD	1.53±1.02
	Range	0-3
FAMILY HISTORY OF ABORTION		28.33%

The GA of the studied patients ranged between 8-15 wks. with a mean(±SD) of 11.48± 2.21 wks. 16(26.67%) patients were primipara and 44(73.33%) patients were multipara. The menstrual history was regular in 37(61.67%) patients and was irregular in 23(38.33%) patients. The number of previous miscarriages ranged between 2-8 with a mean(±SD) of 5.2±2 miscarriage. The number of previous live birth ranged between 0-3 birth with a mean(±SD) of 1.53±1.02 birth and 28.33% patients had family history of abortion, (table 4; figure 4).

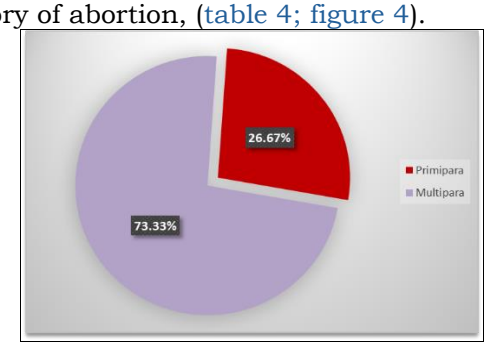

Figure 4. Parity of the studied patients.

Table 5. Vital sings of the studied groups regarding the outcome.

		PASS 1ST TRIMESTER (N=46)	ABORTED(N=14)	P-VALUE
HR(BEATS /MIN)	Mean±SD	81.07±8.07	82.43±8.15	0.583
	Range	70-95	70-95	
SBP(MMHG)	Mean±SD	123.26±14.92	130.71±11.41	0.091
	Range	100-150	110-150	
DBP(MMHG)	Mean±SD	77.39±9.76	72.14±11.22	5.25
	Range	60-90	60-90	

HR:heart rate, SBP:systolic blood pressure, DBP:diastolic blood pressure.

HR, SBP and DBP were insignificantly different between both groups, (table 5; figures 5-7).

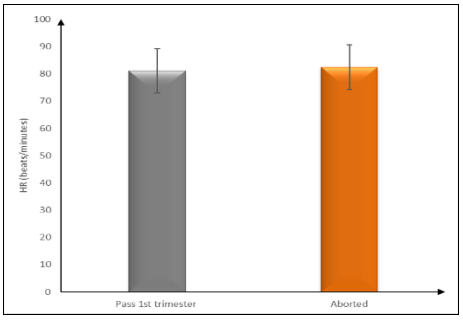

Figure 5. HR of the studied patients

regarding the outcome.

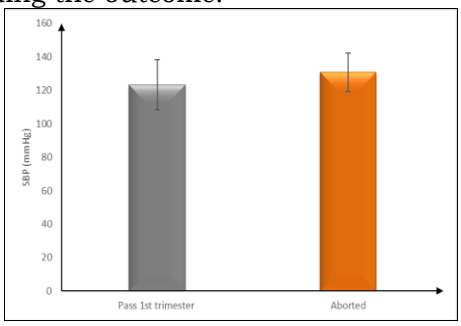

Figure 6. SBP of the studied patients regarding the outcome.

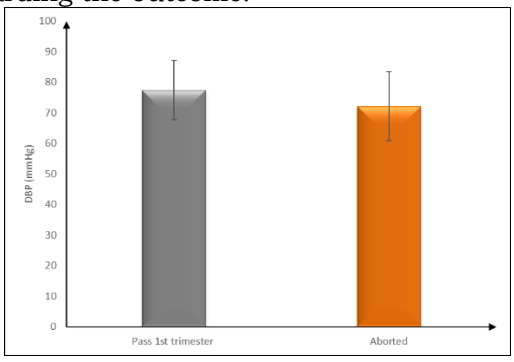

Figure 7. DBP of the studied patients regarding the outcome.

Table 6. Outcome of the studied patients.

	TOTAL (N=60)
PASS 1ST TRIMESTER	46 (76.67%)
ABORTION	14 (23.33%)

Regarding the outcome, 46 (76.67%) patients passed the 1st trimester, whereas abortion occurred in 14 (23.33%) patients.

4. Discussion

A significant concern for women's health is the occurrence of repeated miscarriages; between one and two percent of reproductive-age women have gone through three or more consecutive miscarriages, and about five percent have gone through two consecutive miscarriages.[1]

In women who have experienced several miscarriages, aspirin is being used more and more to lessen the chances of miscarriage and enhance the outcome of the pregnancy. The balance between prostacyclin (which has vasodilatory qualities) and thromboxane A2 (which has platelet-aggregating and vasoconstrictor effects) is a key component in regulating tissue perfusion. Regular dosing with LDA causes a change in the ratio of prostacyclin to thromboxane A2, which in turn causes vasodilatation and improved blood flow.[8]

In terms of the patients' initial characteristics, their ages varied from 20 to 35 years old, with a mean (±SD) of 26.83±5.25 years. With a mean (±SD) of 76.97±11.32kg, the body weight varied from 58 to 96 kg, the height from 1.51.73m to 35.93 kg/m2 varied from 20.04 to 35.93 kg/m2, and the BMI from 20.04 to 35.93 kg/m2 varied from 20.04 to 35.93 kg/m2. Thirteen patients (or 51.67%) lived in urban regions, whereas twenty-nine (or 48.33%) lived in rural areas.

Dongarwar & Salihu et al.,[9] echoed the findings, revealing that 66.4% of those who took the study called a village home. After controlling for other factors, rural women were more likely than urban women to have a miscarriage, stillbirth, early neonatal death, late neonatal death, or infant mortality. Abortions were 22% more common among urban women than rural ones (PR=1.22, 95% CI=1.10-1.35).

Regarding the co-morbidities, 10 patients (16.67%) had hypertension, and 12 patients (20%) had diabetes. One possible explanation for the correlation between hypertension and repeated miscarriages is the role that inflammation, oxidative stress, and endothelial dysfunction play in the aetiology of essential hypertension. Furthermore, women who have experienced a miscarriage are more likely to have thrombotic factors, such as increased platelet activation, which in turn increases the production of pro-inflammatory cytokines, and endothelial dysfunction, which is a symptom of essential hypertension. This suggests that an abnormal thrombotic response could be linked to the risk of miscarriage.[10]

Regarding vital signs, HR ranged between 70-95 beats/min with a mean(±SD) of 81.38±8.04 beats/min, SBP ranged between 80-95mmHg with a mean(±SD) of 125±14.44mmHg and DBP ranged between 40-60mmHg with a mean(±SD) of 76.17±10.27mmHg.

Nobles et al.,[10] the same findings as 1228 pregnant women who had experienced previous miscarriages; the average systolic blood pressure (SBP) was 111.6 (SD 12.1) mm Hg and the average diastolic blood pressure (DBP) was 72.5 (SD 9.4) mm Hg. There was a mean MAP of 85.5 (SD 9.6) mmHg. About a quarter of the sample, 307 people, fulfilled the criterion for stage I hypertension, while nearly half, 53 people, satisfied the criteria for stage II hypertension.

Our study shows that the gestational age of the studied patients ranged between 8 and 15 weeks, with a mean(±SD) of 11.48±2.21 wks. 16(26.67%) patients were primipara and 44(73.33%) patients were multipara. Of the patients surveyed, 37 (61.67%) had regular menstrual periods, while 23 (38.13%) reported irregular periods. With a mean (±SD) of 5.2±2 miscarriages, the number of previous miscarriages varied from 2 to 8. The average number of previous live births was 1.53, with a standard deviation of 1.02, and 28.33% of

the patients had a history of abortion in their family. The number of births ranged from 0 to 3.

Elmahashi al.,[11] according to the results, 75 pregnant women who had experienced previous miscarriages and were taking low-dose aspirin had an average of 4.1 weeks of gestational age, 8.3 weeks of GA, and 1.1 parity. In contrast, 75 pregnant women who had experienced previous miscarriages and were taking low-dose aspirin with LMWH had an average of 3.9 weeks of GA, 8.3 weeks of GA, and 0.08 parity.

Regarding complications, transient thrombocytopenia occurred in 3(5%) patients, gastrointestinal troubles occurred in 7(11.67%) patients, bruising at the injection site occurred in 23(38.33%) patients, epistaxis occurred in 7(11.67%) patients, and bleeding gums occurred in 8(13.33%) patients.

These outcomes are on the same line as Maged et al.,[12] They proved that 60% of patients experienced aspirin and calheparin-related problems. Injury to the i-axis was the most common side effect. Age, weight, height, body mass index (BMI), and place of residence were not substantially different between the two groups at baseline, according to our study. Also, when it came to factors like parity, gestational age, menstruation history, number of previous miscarriages, number of previous live births, and family history of abortion, there was no significant difference between the two groups.

In agreement with our results, Maged et al.,[12] revealed in a study that divided 180 pregnant women into two equal groups. Sixty percent of patients in Group 1 had injection site complications, fourteen percent had bleeding gums, twelve percent had gastrointestinal issues, ten percent had epistaxis, and two and a half percent experienced transient thrombocytopenia. Group 2 did not receive any treatment. Both groups were given low-dose aspirin 75 mg and heparin 5000 IU subcutaneously every twelve hours. There was no correlation between age, body mass index, or number of prior abortions and the outcomes of the first trimester.

Regarding the outcome, 46(76.67%) patients passed the 1st trimester, whereas abortion occurred in 14(23.33%) patients.

Zhang et al., [13] Maged et al.[12] Our results were supported by their conclusion that women with a recurrent abortion rate are less likely to have an abortion when they use LMWH plus low-dose aspirin.

4. Conclusion

For women experiencing unexplained repeated abortions, a safe and effective treatment option is a combination of low molecular weight heparin and low-dose aspirin, which can reduce the abortion rate and let them safely pass the first trimester. When women with unexplained recurrent abortions take modest doses of aspirin and low molecular weight heparin, they run the risk of experiencing transitory thrombocytopenia, gastrointestinal problems, injection site bruises, epistaxis, and bleeding gums.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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