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Bemiparin as a Prophylaxis After an Unexplained Stillbirth: Open-Label Interventional Prospective Study

Ariana Khalis Jawad, CABAG, FICMS[1], Shahla Kareem Alalaf, MD[2], Mahabad Salih Ali[3], and AbdulKader Ahmad Bawadikji, MSc[4]

Abstract

Stillbirth is a devastating event to the parents, relatives, friends, and families. The role of anticoagulants in the prevention of unexplained stillbirths is uncertain. An open-label interventional prospective cohort study was conducted on 144 women with a history of unexplained stillbirths. The intervention group had a high umbilical artery resistance index (RI) and received bemiparin. The nonintervention group had a normal RI and did not receive any intervention. We measured the adjusted odds ratio (OR) and 95% confidence interval (CI) of the main outcome for these variables using logistic regression analysis. Fresh stillbirth and early neonatal death rates were lower ($P = .005$, OR = 11.949 and 95% CI = 2.099-68.014) and newborn weight was higher ($P = .015$, OR = 0.048, 95% CI = 0.004-0.549) in the group that received bemiparin. Bemiparin is effective in decreasing the rate of stillbirth in women with a history of previous unexplained stillbirths.

Keywords

low-molecular-weight heparin, stillbirths, Doppler ultrasound, resistant index

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Background

Stillbirth is a devastating event, with profound emotional, social, and psychiatric effects on parents, relatives, friends, and families.[1-3] About 30% to 50% of all late-term stillbirths are unexplained, that is, no specific cause is identified.[4] Unexplained stillbirth is the largest single contributor to perinatal mortality.[5] The Stillbirth Collaborative Research Network (SCRN) examined more than 500 stillbirths in 59 medical centers around the United States. In almost one quarter of the cases, the researchers could not determine a probable or even possible cause of death.[6]

Besides the devastating psychological and emotional effects of a stillbirth, parents also fear having a subsequent stillbirth. Women who have had a previous stillbirth are known to be at increased risk of stillbirth in subsequent pregnancies.[7] A systematic review and meta-analysis on studies from high-income countries investigated the association between stillbirth in one pregnancy and risk of stillbirth in a subsequent pregnancy. The study concluded that the risk of stillbirth in subsequent pregnancies is higher in women who experience a stillbirth in their first pregnancy, and this increased risk remained after adjusting the analysis.[8] To improve the prediction and prevention of stillbirths, it is necessary to identify specific risk factors. These should be modifiable and targeted. In clinical practice and published observational studies, the primary target is maternal risk factors such as maternal smoking, obesity, and medical conditions.[9] However, there are other factors that may affect stillbirth risk, such as fetal vulnerability and stressors or placental problems.[9] Placental abnormalities or dysfunctions are associated with a significant proportion of stillbirths.[10,11]

Placental insufficiency placing fetuses at increased risk of stillbirth is not restricted to those born small for gestational age. Nearly half of normally formed stillbirths are reported to be

[1] Department of Obstetrics and Gynecology, Kurdistan Board of Medical Specialty, Erbil, Kurdistan, Iraq
[2] Department of Obstetrics and Gynecology, College of Medicine, Hawler Medical University, Erbil, Kurdistan, Iraq
[3] Department of Obstetrics and Gynecology, Ministry of Health, Maternity Teaching Hospital, Erbil, Kurdistan, Iraq
[4] School of Pharmaceutical Science, University Sains Malaysia, Penang, Malaysia

Corresponding Author:
Shahla Kareem Alalaf, Department of Obstetrics and Gynecology, College of Medicine, Hawler Medical University, Erbil, Kurdistan, Iraq.
Email: shahla_alaf@yahoo.com

adequate for gestational age. There may be a subgroup of fetuses whose weight is adequate for gestational age but who have placental insufficiency; this may be an important under-recognized group with suboptimal placental function and at increased risk of stillbirths.[12]

It is not clear what role anticoagulants might play in the prevention of placental-mediated pregnancy complications, including unexplained stillbirths. A pilot study examined the effectiveness of a low-molecular-weight heparin (LMWH) in preventing the recurrence of placental-mediated complications in women with known risk factors or previous unexplained stillbirths. The study concluded that LMWH is effective in decreasing the recurrence of placental-mediated complications in women without thrombophilia.[13]

Umbilical artery Doppler ultrasound is a noninvasive method for monitoring fetoplacental circulation during pregnancy. It is safe in pregnancy and hence can be repeated whenever indicated. It can predict adverse perinatal outcomes and is considered a sensitive tool for the early detection of fetal compromise and therefore to support timely intervention.[14]

Early antenatal detection, treatment where appropriate, and timely delivery could minimize the risks of unexplained stillbirth. We propose that unexplained stillbirth may be because of placental pathology that predisposes to increased umbilical artery resistance index (RI) and placenta thrombosis; furthermore to prevent recurrence of placental-mediated complications, the use of an antithrombotic agent in the aim to prevent placental thrombosis and increase placental perfusion may prevent fetal and neonatal deaths.

The primary aim of this study was to determine the effect of prophylactic dose of bemiparin to decrease the rate of stillbirth in pregnant women with a history of unexplained stillbirth and having a high umbilical artery RI in their current pregnancy.

Methods

Study Design and Site

We conducted an open-label interventional prospective cohort study between August 1, 2015, and December 6, 2018, at the Maternity Teaching Hospital in the city of Erbil, Kurdistan region, Iraq. It examined the effect of bemiparin on pregnant women with a history of unexplained stillbirth and high umbilical artery RI.

Study Population and Sampling

Inclusion criteria for cases were (1) gestational age 19 + 6/7 weeks, (2) normal congenial and acquired thrombophilia screening test, (3) one or more episodes of unexplained intrauterine death after 19 + 6/7 weeks in a previous pregnancy, (4) an umbilical artery RI of 0.6 or more for inclusion in the intervention group, and (5) not having any comorbidity at the time of inclusion (diabetes, hypertension, renal diseases, heart disease, epilepsy).

A normal congenital thrombophilia screen required all of the following: (1) absence of heterozygous or homozygous factor V Leiden or prothrombin 20210A mutations; (2) normal levels of antithrombin III, protein C, and protein S; and (3) normal level of homocysteine or absence of the homozygous MTHFRC677 T mutation. A normal acquired thrombophilia screen required both of the following: (1) negative testing for lupus anticoagulant and (2) absence of moderate or high levels of anticardiolipin antibodies and β2 glycoprotein 1.

Participants were excluded if they had a history of known causes for previous stillbirth, including fetal structural or chromosomal abnormalities, medical disorders in a previous or current pregnancy, multiple pregnancy, uterine malformation, placental or cord pathologies, or cytomegalovirus infection. They were also excluded if they had a previous history of venous or arterial thrombotic events and any known allergies or contraindications to heparin for the intervention group. Any pregnancies with structural and chromosomal anomalies were excluded by a standard 20-week anomaly scan and soft marker ultrasound findings. Uterine malformations were identified by 4-D ultrasound or hysterosalpingogram. Placental and cord pathologies were diagnosed by ultrasound scanning and appearance after delivery.

Grouping

The intervention group was women with unexplained stillbirth in a previous pregnancy and a high umbilical artery RI in their current pregnancy (0.6 or more). This group received bemiparin from 20 weeks of pregnancy.

The nonintervention group was women with the same inclusion and exclusion criteria but with a normal umbilical artery RI. They did not receive bemiparin but instead received ordinary pregnancy supplements.

Sample Size Estimation

The sample size was calculated to be 80 women with a high RI and 60 women with a normal RI. The calculation used a level of significance of 5%, power of study of 80%, and an estimated incidence of primary outcome of 5.5% versus 23.6%.[13]

Intervention

Women in the intervention group received bemiparin (bemiparin sodium; Hibor, Ivor, Zibor, Badyket; Laboratorios Farmacéuticos Rovi SA, Madrid, Spain). Bemiparin is a second-generation LMWH. It has a lower mean molecular mass (3600 Da) and a higher antifactor Xa–FIIa ratio (8:1) than other LMWHs. It is supplied as a prefilled syringe containing 2 mL of 2500 IU of bemiparin in 0.2 mL of water. Women were taught how to self-administer the medication daily by subcutaneous injection.

Bemiparin was started in the intervention group immediately after confirming the high umbilical artery RI. It was taken on a daily basis and stopped at least 24 hours before delivery. The nonintervention group did not receive any interventions

apart from routine antenatal care and ordinary maternal supplements throughout their pregnancy.

Follow-Up and Data Collection

We compared baseline maternal characteristics (age, body mass index [BMI], gestational age at birth, and mode of delivery) between the 2 groups. All information about the women was recorded in a questionnaire designed for the study that was completed in a face-to-face interview after written informed consent had been obtained.

The clinical management of women in both groups included antenatal care throughout the course of pregnancy conducted by a professional obstetrician and certified nurse-midwives. All pregnant women in both groups were assessed regarding their obstetrics history, family history, medical history, and pregnancy risk factors during the initial prenatal doctor visit. Regular obstetric examinations and obstetric ultrasound for fetal well-being were conducted. Weekly Doppler ultrasound for the umbilical artery was performed until the RI became normal for women in the interventional group, then fortnightly after that. For woman in the normal RI group, Doppler ultrasound for the umbilical artery was repeated fortnightly assuring that it remained normal throughout the pregnancy.

The noninterventional group included women who remained having normal RI throughout the study period. Three women within the noninterventional group develop high RI after 32 weeks' gestation and were excluded from the study. Assessment for the development of preeclampsia or abruptio placentae was also recorded and managed accordingly. Deliveries of the newborn being vaginal or cesarean section due to obstetric indications were conducted in a well-equipped labor room and theater. Information in relation to mode of delivery, gestational age at the time of delivery, newborn weight, indications for cesarean section, and perinatal outcome were recorded and coded for each woman.

Outcome Measures

The primary outcomes were one or more of the following: fetal death after 20 weeks of gestation, early neonatal death, newborn weight less than fifth percentile, and admission to the neonatal newborn intensive care unit (NICU). The secondary outcomes were development of severe preeclampsia, major abruption placentae resulting in delivery before 34 weeks of pregnancy, and preterm labor.

Severe preeclampsia was defined as having a systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 110 mm Hg or greater with significant proteinuria (more than 300 mg in a 24-hour urine collection).[15] Newborn weight less than fifth percentile was identified using the World Health Organization Child Growth Standards chart.[16] Preterm birth was defined as delivery of fetus after 20 weeks' gestation and before 36 6/7 weeks of pregnancy.[17]

Assessment of newborns regarding Apgar score was conducted in first and fifth minutes after delivery. A normal Apgar score was defined as 7 to 10, and the newborn was regarded to be in good to excellent condition and only routine postdelivery care was applied for them. Babies scoring between 4 and 6 in fifth minute of life were regarded as in fair condition and required some resuscitation measures. All in this group were admitted to the neonatal intensive care unit.[18]

Obstetric ultrasound examinations including umbilical artery RI were all carried out by 1 professional ultrasonographer in the hospital. An RI of 0.6 or more was regarded as high in a woman at 20 weeks' gestation.[19] Gestational age was confirmed either by date of last menstrual cycle and first-trimester ultrasound. The mode of delivery was classified as vaginal (spontaneous or induced), elective cesarean section, or emergency cesarean section. After delivery, the newborn was weighed and Apgar scores obtained at 1 and 5 minutes.

Statistical Analysis

Statistical analyses included demographics, frequency, χ^2 test, and logistic regression. Mean, standard deviations, odds ratio (OR), and the difference in the means with the 95% confidence interval (CI) were calculated. We adjusted the OR and CI of the main outcome for relevant variables in the logistic regression analysis. A P value of $<.05$ (2 sided) was considered to indicate statistical significance. Statistical analyses used Statistical Package for Social Sciences (SPSS) software, version 21.0 (SPSS Inc, Chicago, Illinois).

Results

Figure 1 shows the trial profile of the 171 women interviewed for eligibility, of whom 23 did not meet the inclusion criteria and 2 refused to participate because they had not previously heard of receiving heparin during pregnancy without a definite cause for treatment. Two women were already on LMWH because they had tested positive for antiphospholipid antibody syndrome and had a history of recurrent miscarriages. The study therefore recruited 144 women, 82 with high umbilical artery RI who received bemiparin (intervention group) and 62 with normal umbilical artery RI who did not received any interventions (nonintervention group). No women dropped out before assessment of outcome until delivery and follow-up of the newborns at up to 7 weeks postpartum.

Table 1 shows the characteristics and variables across the 2 groups. The mean age of the noninterventional group (31.13 $\pm$ 4.82 years) was higher than the intervention group (29.39 $\pm$ 5.00 years). The number of women older than 35 years was also higher in the nonintervention group (18, 30.0% vs 13, 16.3%). The mean prepregnancy weight was slightly higher in the nonintervention group (78 $\pm$ 12.0 kg vs 77 $\pm$ 11.28 kg). In contrast, the BMI was slightly higher in the intervention group (29.19 $\pm$ 4.99 kg/m^2 vs 28.48 $\pm$ 4.65 kg/m^2). The mean gestational age at the time of delivery in current pregnancy was slightly higher in the intervention group (35.54 $\pm$ 1.00 weeks vs 34.72 $\pm$ 1.35 weeks). The numbers of spontaneous vaginal deliveries and elective cesarean sections were higher in the

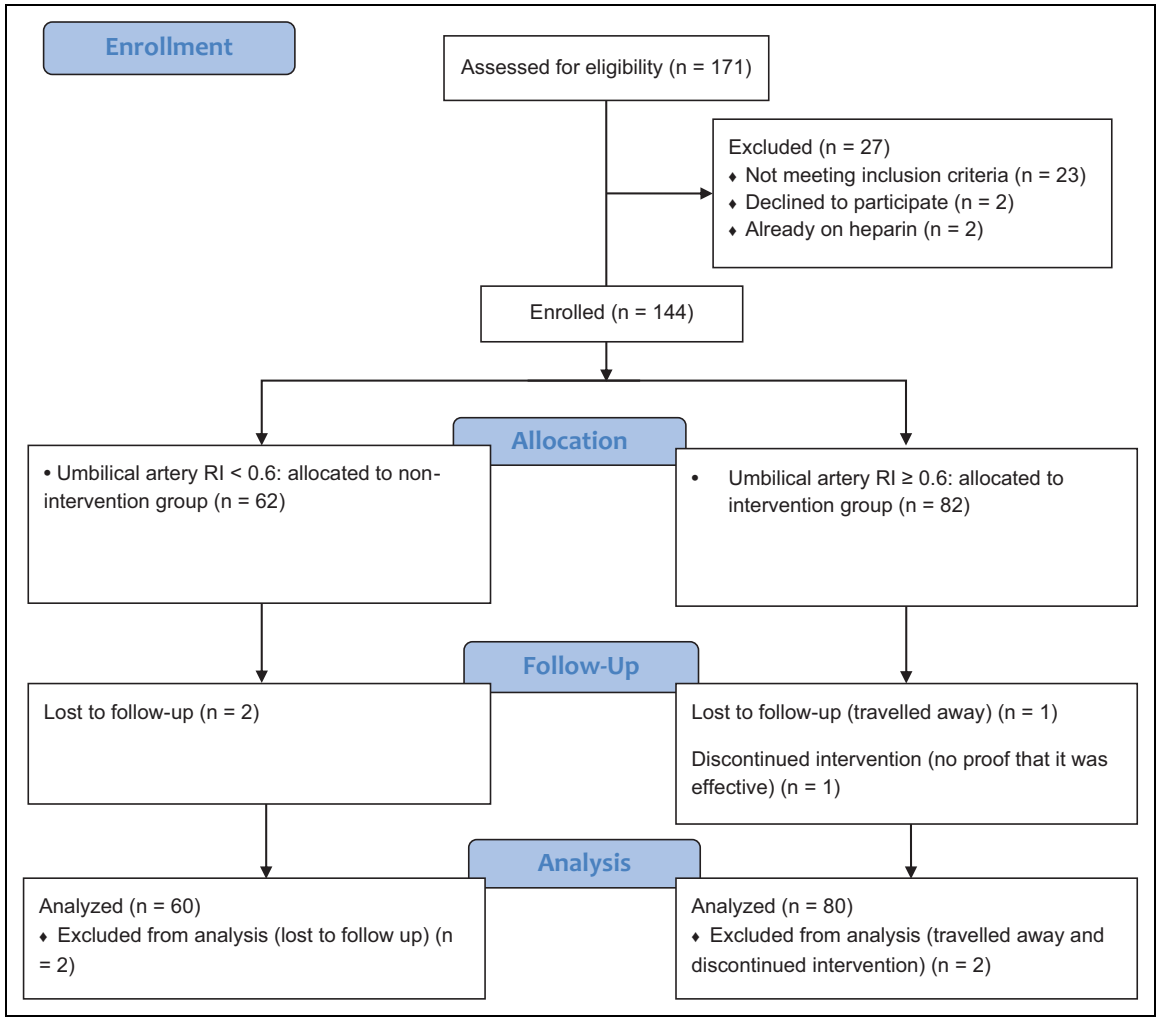

Figure 1. CONSORT 2010 flow diagram. RI indicates resistance index.

intervention group (11, 13.8% vs 8, 13.3%, and 66, 82.4% vs 42, 70%). However, induction of labor and emergency cesarean section were higher in the nonintervention group (5, 8.3% vs. 3, 3.8% and 5, 8.3% vs 0). The most common mode of delivery was elective cesarean section in both groups.

Induction of labor and cesarean sections were all obstetrical indication in both groups, although the noninterventional group had more emergency and induction of labor, which was related to non-reassurance fetal well-being.

Unexplained previous newborn weight <5th centile, 11 (13.8%) in bemiparin group was higher than 4 (6.7%) in no bemiparin group. Similarly, 2 previous unexplained fetal deaths at 12 to 20 weeks, 32 (40.0%) in bemiparin group was higher than 6 (10.0%) in no bemiparin group.

There were only 2 variables that were significantly different between the 2 groups. These were fetal outcome (fresh stillbirth, early neonatal deaths, alive with normal Apgar score, low Apgar score and admission to NICU; $P = .005$, OR = 11.949 and 95% CI = 2.099-68.014) and newborn weight ($P = .015$, OR = 0.048 and 95% CI = 0.004-0.549). These 3 variables were all in the favor to the intervention group. The model explained between 0.377 (Cox and Snell R^2) and 0.506 (Nagelkerke R^2) of the variation, and χ^2 was 66.305 (Table 2).

We saw only 3 cases in the intervention group with local bruising at injection sites. These resolved spontaneously and did not need any treatments. There were no major side effects such as hemorrhage, wound dehiscence, or separation in the group that received bemiparin.

Discussion

In this open-label interventional prospective cohort study, fetal outcomes (fresh stillbirths, newborns with normal Apgar score, newborns with low Apgar score plus admission to neonatal intensive care, and early neonatal deaths) were significantly better in the intervention group ($P = .005$). We observed a decrease in stillbirth rates in pregnant women with a history of unexplained stillbirth who received a daily prophylactic dose of bemiparin starting at 20 weeks of gestation, when the diagnosis of high umbilical artery RI was confirmed by Doppler ultrasound.

Table 1. Demographic/Clinical Data of Patients in the Intervention and Nonintervention Groups.

Demographic/Clinical Data	Bemiparin Group, n = 80	No Bemiparin Group, n = 60	*P* Value
Mean age, mean (SD), years	29.39 (5.00)	31.13 (4.82)	.04
No. of women aged >35 years	13 (16.3%)	18 (30.0%)	.05
Pre-pregnancy weight, mean (SD), kg	77 (11.28)	78 (12.0)	.98
BMI, kg/m^2 (SD)	29.19 (4.99)	28.48 (4.65)	.53
BMI $\geq$30 kg/m^2, n (%)	32 (40.0%)	24 (40.0%)	1.00
Smoker, n (%)	4 (5.0%)	2 (3.3%)	.63
History of living babies, mean (SD)	0.85 (1.12)	0.85 (0.95)	.61
Parity	–	–	.39
Multiparous	45 (56.3%)	38 (63.3%)	
Grand multiparous	35 (43.7%)	22 (36.7%)	
[a]Gestational age at the time of delivery, weeks, mean (SD)	35.54 (1.00)	34.72 (1.35)	
[a]Mode of delivery	–	–	.03
Spontaneous vaginal delivery	11 (13.8%)	8 (13.3%)	
Elective cesarean section	66 (82.4%)	42 (70.0%)	
Induction of labor	3 (3.8%)	5 (8.3%)	
Emergency cesarean section	0 (0.0%)	5 (8.3%)	
Unexplained previous newborn weight <5th centile	11 (13.8%)	4 (6.7%)	.10
Two previous unexplained fetal deaths at 12-20 weeks	32 (40.0%)	6 (10.0%)	.00

Abbreviations: BMI, body mass index; SD, standard deviation.
[a]In current pregnancy.

Table 2. Logistic Regression Model for the Intervention and Nonintervention Groups in Relation to Outcomes.

Variables	Bemiparin Group, n = 80	No-Bemiparin Group, n = 60)	*P* Value	Odds Ratio	95% Confidence Interval for Odds Ratio
Developed preeclampsia in current pregnancy	1 (1.3%)	4 (6.7%)	.711	2.057	0.046-93.012
Indication for cesarean section			.120	1.646	0.879-3.083
Fetal distress	55 (68.8%)	35 (58.3%)			
CPD	15 (18.8%)	19 (31.7%)			
Previous scar	10 (12.5%)	6 (10.0%)			
Fetal outcome			.005	11.949	2.099-68.014
Fresh stillbirth	1 (1.3%)	5 (8.3%)			
Alive with normal Apgar score	76 (95.0%)	33 (55.0%)			
[a]Low Apgar score + admission to NICU	2 (2.5%)	21 (35.0%)			
Early neonatal death	1 (1.3%)	1 (1.7%)			
Apgar score 1 minute after delivery			.909	0.851	0.053-13.686
Apgar score 5 minutes after delivery			.661	0.651	0.095-4.436
Newborn weight, kg	2.94 (0.74)	2.86 (0.19)	.015	0.048	0.004-0.549
Newborn weight <2.5kg	7 (8.8%)	4 (6.7%)	.651	1.92	0.374-4.813

Abbreviations: CPD, cephalo-pelvic disproportion; NICU, neonatal intensive care unit.
[a]Apgar score 4 or less was admitted to NICU.

Our results are consistent with the pilot study by Rey et al,[13] which included women with a history of unexplained stillbirths with normal thrombophilia screening tests. The women received dalteparin injections, and their primary outcome was a composite including one or more of severe preeclampsia, newborn weight less than fifth percentile, and major abruptio placentae resulting in delivery before 34 weeks of pregnancy or fetal death after 20 weeks of gestation. The authors observed a decrease in these complications with the use of prophylactic doses of dalteparin, from 23.6% to 5.5%.

Doppler ultrasound indices have been used extensively in obstetrics. Our study aimed to identify abnormal blood flow state before it affected the fetus, to allow treatment to prevent stillbirth. Other trials have mostly aimed to assess fetal well-being among high-risk women. The precise Doppler indices also varied between trials.

For example, a study by Akolekar et al[20] used uterine artery pulsatility index alone or in combination with fetal biometry and maternal factors in the second trimester as a screening method to predict a high proportion of stillbirths and, in particular, those due to impaired placentation. A review of trials identified 18 studies involving over 10 000 women comparing the use of Doppler ultrasound of the umbilical artery with no Doppler or cardiotocography.[20] The review concluded that current evidence suggests that the use of Doppler ultrasound on the umbilical artery in high-risk

pregnancies reduces the risk of perinatal mortalities and may result in fewer obstetric interventions.[21] Our findings, however, suggest that the results of Doppler ultrasound used to identify umbilical artery resistance at 20 weeks could be a good predictor of need for LMWH during pregnancy.

Other published articles have specified the use of Doppler ultrasound indices to identify growth-retarded fetuses or preterm labor[22] or in high-risk groups generally.[23] A study by Valiño et al[24] used several Doppler indices to predict stillbirth. These indices included uterine artery pulsatility index, umbilical artery pulsatility index, fetal middle cerebral artery pulsatility index, and mean arterial pressure in combination with other biomarkers such as estimated fetal weight, serum placental growth factor, and soluble FMS-like tyrosine kinase. All measurements were taken at 30 to 34 weeks.[23] Values of third-trimester cerebroplacental ratio and uterine artery Doppler indices have, however, been used to predict stillbirth and perinatal losses.[25] Our findings, however, suggest that the results of Doppler ultrasound used to identify umbilical artery resistance at 20 weeks could be a good predictor for late fetal death and a good way to prevent perinatal mortality using a preventive method.

A recent meta-analysis of randomized controlled trials examined the use of LMWH for the prevention of recurrent placenta-mediated pregnancy complications.[26] The authors identified 6 trials that included a total of 848 pregnant women with prior placenta-mediated pregnancy complications. The primary outcome was a composite of preeclampsia, birth of a small-for-gestational-age newborn (<10th percentile), placental abruption, or pregnancy loss >20 weeks. There were relative risk reductions with LMWH for individual outcomes, including any preeclampsia, severe preeclampsia, birth weight <10th percentile, birth weight <5th percentile, and preterm delivery. The authors concluded that LMWH may be a promising therapy for recurrent, especially severe, placenta-mediated pregnancy complications, but they recommended that further research is required.[26] These trials differed from our study because they used abnormal Doppler indices as a sign that the pregnancy should be terminated in an attempt to deliver the fetus in a viable state before the fetal death in uterus. Our study, however, aimed to identify abnormal blood flow state before it affected the fetus and then provided treatment to prevent stillbirth. The rate of stillbirths was significantly lower in the treatment group in our study. There was also a significant difference in birth weight between the 2 groups ($P = .001$).

A retrospective study by Kupferminc et al[27] examined the effect of LMWH on pregnant women without thrombophilia with severe pregnancy complications and placental vasculopathy in a previous pregnancy. The birth weights were significantly higher in the group receiving heparin than the control group ($P < .001$). This finding is very similar to our result.

We found no difference in gestational age at the time of delivery between the groups. This is comparable to the results of Rey et al[13] who also found no difference in gestational age at delivery between the 2 groups. We also found no difference between the 2 groups in history of unexplained previous newborn weight <5th centile and development of preeclampsia in current pregnancy. However, history of 2 previous unexplained fetal deaths in late first trimester and second trimester (12-20 weeks) was significantly higher in the intervention group. This suggests that we might need to provide LMWH to this group earlier in pregnancy. This might require earlier use of uterine artery Doppler ultrasound for those with recurrent second-trimester fetal death to assess the blood flow so that heparin can be prescribed earlier. This question needs to be addressed in future studies.

Only 1 woman in the intervention developed preeclampsia in the last stage of pregnancy, compared with 4 in the nonintervention group, but this difference was not statistically significant. This was also comparable with the results of Rey et al.[13] It is plausible that bemiparin might decrease preeclampsia because it could have antithrombotic effects on placental developments. It is becoming increasingly clear that heparin could play a role in prevention of preeclampsia, mainly because of its antithrombotic and anti-inflammatory effects, similar to those of aspirin.[28] Vascular resistance can also be decreased by using LMWHs, both in vitro and in vivo.[29,30]

The most common mode of delivery was elective cesarean section in both groups, while induction of labor and emergency cesarean section were higher in the nonintervention group. Most indications were obstetrically indicated; although in noninterventional group, the fetal well-being was deteriorated that faced the author to terminate the pregnancy in an attempt to save the fetus.

The principal strength of our study was that it was the first of which we are aware to look for a screening method to identify suspected risk factor for recurrent stillbirth in women with previous unexplained stillbirths. Doppler ultrasound is a safe and a noninvasive method of screening in women with no known risk factor for abnormal high umbilical artery RI.

Another strength is that to our knowledge, this is the first published trial on the effectiveness of a LMWH in women without thrombophilia and with a history of previous unexplained stillbirth and having high umbilical artery RI. Although it was not a large trial, the difference between the 2 groups for the primary outcome was both clinically and statistically significant.

This study had several limitations. First, as mentioned earlier, it was not a randomized clinical trial. These are regarded as statistically the best method of testing interventions, but we could not deprive women who might benefit from the intervention, so we used an open-labeled trial. Future researchers may consider preparing the same injection in 2 forms, one with a placebo container and the other to be the active component.

Second, although our study had a comparison group, it was not double blinded. However, the primary outcome was based on highly objective outcomes, and the comparison group already had a normal RI. We therefore suspect that lack of blinding for the intervention will not have any substantial effect on the findings.

The third limitation was that we grouped the fetal outcomes in the results as one variable rather than to analyze each

outcome separately. This was because we regarded the outcomes (fresh still birth [FSB], early neonatal death, admission to NICU, and normal Apgar scores) as all related to the outcome of the fetus and the newborns as a group also the number of one outcome in the sample size was so small that by itself it will not give any significant changes. We also ask future researches to adapt analysis for each outcome separately in one condition and their sample size should be large enough to have increased number of bad outcomes.

The fourth limitation in the article was that some differences were observed between the 2 groups in terms of mean maternal age and maternal weight, although these differences were assumed to be a result of small sample size in both groups and there was no match in relation to these characters as we included all of them, and the only exclusion was the high RI in the interventional group.

The last limitation is the nonavailability of published article screening for high RI in women with unexplained previous stillbirths and receiving LMWH to decrease the rate of subsequent fetal deaths to compare it with current study.

In conclusion, in this study, bemiparin revealed to be an effective prophylactic treatment in decreasing the recurrence rate of stillbirths in women with previous unexplained stillbirths. Our results may require confirmation in further randomized trials and a larger sample size in order to generalize its benefit.

Authors' Note

A.J. designed the study and drafted the manuscript. S.A. was responsible for project development and manuscript drafting and revision. M.A. was responsible for drafting and revising the manuscript and supervising the study. A.B. was responsible for acquisition, analysis, and interpretation of data and drafting the manuscript. The majority of the data supporting the findings of this article are available within the article. Other data and findings are available upon request from the first correspond author. The data are not available publicly as they may compromise the privacy and confidentiality of the participant.

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Declaration of Conflicting Interests

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ORCID iD

Shahla Kareem Alalaf https://orcid.org/0000-0003-1259-0338

Ethics approval and Compliance With Ethical Standards

We were unable to conduct a double-blind, randomized, placebo-controlled trial in patients with at least 1 previous stillbirth and elevated umbilical artery RI. The relevant ethics committee decided that it could not approve a randomized trial depriving women with high umbilical artery RI and a history of unexplained stillbirths of a potentially effective intervention. We therefore chose to compare the high-risk group receiving the intervention with a group at lower risk that did not receive the intervention. This trial was conducted in accordance with the ethical standards of the Research Ethics Committee of Hawler Medical University, College of Medicine (approval Number: 7/02/26-6-18) and with the Helsinki Declaration of 1975, as revised in 2000. Written informed consent to participate in the study was obtained from each woman. Women who participated in the research were assured that their confidentiality would be maintained and that their information would be used for research purposes only. The data safety and monitoring committee of the Maternity Teaching Hospital, consisting of 3 independent obstetricians from the hospital, ensured continued safety and monitoring of patients throughout the trial. The Clinical Trials.gov ID is NCT03601338.

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