Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial

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To assess whether antithrombotic prophylaxis with low-molecular-weight heparin effectively prevents recurrence of late pregnancy complications, 135 women with previous history of preeclampsia, hemolytic anemia, elevated liver enzymes and low platelet count syndrome, intrauterine fetal death, fetal growth restriction, or placental abruption who had been referred within the 12th gestational week were randomized to medical surveillance alone (n = 68) or combined to open-label nadroparin (3800 IU daily subcutaneous injections) treatment (n = 67) in the setting of a randomized, parallel-group, superiority trial, run in Italy from April 2007 to April 2010. Primary outcome was a composite end point of late-pregnancy complications. Analysis was by intention to treat. The study was stopped for futility at the time of the first planned interim analysis. Among the 128 women eventually available for final analyses, 13 of the 63 (21%) randomized to nadroparin compared with 12 of the 65 (18%) on medical surveillance alone progressed to the primary end point. The absolute event risk difference between treatment arms (2.2; −1.6 to 16.0) was not statistically significant (*P* = .76). Thus, nadroparin did not prevent late-pregnancy complications in women at risk of recurrence. This finding challenges the role of antithrombotic prophylaxis with low-molecular-weight heparin in the prevention of recurrent late pregnancy complications The trial was registered at http://ricerca-clinica.agenziafarmaco.it as EudraCT 2006-004205-26. (*Blood*. 2012;119(14):3269-3275)

Introduction

Preeclampsia, eclampsia and the hemolytic anemia, elevated liver enzymes, and low platelet count (HELLP) syndrome, intrauterine fetal death, fetal growth restriction (FGR), and placental abruption are observed in more than 10% of women in the second half of pregnancy, when placental implantation is completed.[1,2] These late pregnancy complications are a major health problem because preeclampsia, eclampsia, and the HELLP syndrome are the most common causes of maternal and infant morbidity and mortality in the world,[3] and infants who are small for gestational age are at increased risk of premature mortality and developmental problems during infancy and childhood.[4]

Evidence that the aforementioned complications are almost invariably associated with ischemic lesions and infarctions of the placenta, as well as thrombi in the placental blood vessels of the maternal side,[5] suggest that placental thrombosis with insufficient uteroplacental circulation may play a central role in the sequence of events that eventually result in late pregnancy complications.[6] Accordingly, interventions aimed to limit placental vascular thrombosis might be instrumental to prevent placental dysfunction and related sequelae in women at risk. However, results of clinical trials of antithrombotic prophylaxis with heparin or heparin analogues have been conflicting and largely inconclusive so far,[7,8] or may only apply to specific clinical conditions.[9] Of 2 trials suggesting some benefit for antithrombotic treatment, one was unreliable because of major bias in study conduction and data handling and analyses,[7] and the other one was a nonregistered pilot study suggesting some efficacy only in a highly selected population of women with previous placental abruption, but no fetal loss.[8]

Over the last 10 years obstetricians started to adopt antithrombotic prophylaxis in the majority of women considered at risk of events because of any history of late pregnancy complications. A plausible explanation of this attitude is that the consequences of placental-related complications may be so devastating that physicians are emotionally induced to administer antithrombotic therapy despite lack of proven efficacy. This is further encouraged by the common belief that the use of heparin in pregnancy is safe. However, besides minor side effects such as local skin reactions and bruising at the site of subcutaneous injections, placental

Submitted November 10, 2011; accepted January 19, 2012. Prepublished online as *Blood* First Edition paper, January 30, 2012; DOI 10.1182/blood-2011-11-391383.

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There is an Inside *Blood* commentary on this article in this issue.

The online version of this article contains a data supplement.

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bleeding or abruption has been seldom observed in women on heparin therapy during pregnancy,[10] and osteopenia and severe thrombocytopenia are also occasionally reported.[10] Moreover, treatment is costly and requires approximately 300 daily subcutaneous injections over the whole gestational period.[11] Thus, the potential benefits of heparin administration need to be examined in adequately powered and methodologically sound randomized clinical trials.[12] With this as background, we designed the Heparin in pregnant women with Adverse Pregnancy outcome to improve the rate of successful PregnancY (HAPPY) trial, a fully academic, independent, multicenter, prospective, controlled, open-label study aimed to compare event recurrence in women considered at increased risk because of previous late pregnancy complications, who were randomly allocated to treatment with a low-molecular-weight heparin in addition to medical surveillance or to medical surveillance alone.

Methods

HAPPY was an academic and fully independent superiority, parallel trial conducted by 8 Obstetric and Gynecology Units, all in Italy, in cooperation with the A. Bianchi Bonomi Hemophilia and Thrombosis Center of the Department of Medicine and Medical Specialties of the Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico of Milan and the Clinical Research Center for Rare Diseases Aldo & Cele Daccò of the Mario Negri Institute for Pharmacologic Research. The protocol was in accordance with the Declaration of Helsinki as revised in 1996, and was approved by the study Ethics Committee and the local Ethics Committees at each center according to Italian regulations. Calcium nadroparin (a low-molecular-weight heparin recommended by the Italian Society for Hemostasis and Thrombosis[13] for the prophylaxis of thrombotic complications of pregnancy at the suggested dose of 3800 IU/day) was donated and packaged by Italfarmaco SpA (Seleparina) and GlaxoSmithKline SpA (Fraxiparina). No pharmaceutical company was involved in any phases of the trial, including protocol design, study conduction, coordination and monitoring, data handling and analysis, and manuscript writing. All the authors had access to all the data of the study and take responsibility for the integrity of data and accuracy of the analysis. The trial (EudraCT 2006-004205-26) was prospectively submitted to the Registry of the Agenzia Italiana del Farmaco of the Italian Health Ministry (http://ricerca-clinica.agenziafarmaco.it; accessed October 10, 2011).

Study population

Pregnant women who from April 2007 through April 2010 had been referred to the participating centers at a gestational age less than 12 weeks were screened for any of the following events complicating previous pregnancies: (1) mild preeclampsia, defined by blood pressure higher than 140/90 mmHg on 2 or more occasions after the 20th gestational week plus proteinuria more than or equal to 0.3 g/24 hours or more than 2+ on dipstick testing; severe preeclampsia, defined by blood pressure higher than 160/100 mmHg plus proteinuria more than or equal to 0.5 g/24 hours or 3+ on dipstick testing, or concomitant placental abruption, FGR, or fetal loss; eclampsia, defined by the occurrence of new onset seizures in a preeclamptic woman; (2) HELLP syndrome, defined by the concomitant presence of signs of hemolysis (lactate dehydrogenase $>$ 600 IU/L or serum bilirubin $>$ 1.2 mg/dL or presence of schistocytes in the peripheral blood), serum aspartate transaminase more than 70 IU/L and thrombocytopenia (platelet count $<$ 100 000/mm^3); (3) spontaneous fetal loss after the 15th gestational week; (4) FGR, defined by birth weight below the 10th percentile for gestational age together with a percentile reduction from the growth curve of the abdominal circumference more than 40% by ultrasound; and (5) placental abruption, defined by vaginal bleeding with or without uterine tenderness and fetal distress followed by emergency delivery after 24 gestational weeks. Women with at least one of these events who provided written informed consent were included in the study. When preeclampsia or HELLP syndrome was observed in combination with placental abruption, FGR, or fetal loss, the event was categorized as preeclampsia or HELLP, respectively. When placental abruption was associated with FGR, the event was classified as placental abruption.

Women were not included when previous pregnancy complications were most likely explained by anatomic, chromosomal, endocrine, immunologic abnormalities or intercurrent traumatic or infectious events or, if at the time of screening evaluation, they reported previous venous or arterial thrombotic events or were found to have a multiple pregnancy, diabetes mellitus, immunologic disorders, abnormal placental insertion, alcohol or drug abuse, less than 50 000 platelets/mm^3, renal impairment, or any medical condition requiring continued anticoagulant or antiplatelet treatment, including low-dose aspirin, during pregnancy. Occasional use of aspirin as anti-inflammatory drug was discouraged throughout the whole study period.

Study design

Consenting women fulfilling the selection criteria with a positive pregnancy test and a confirmatory ultrasound evaluation were randomly assigned to receive daily subcutaneous administrations of 3800 IU of nadroparin combined to medical surveillance (monthly visits and controls of maternal weight, blood pressure, aspirin intake, abdominal growth, and ultrasound evaluation of fetal biometry) or to medical surveillance alone and were actively followed up to delivery and/or to complete resolution of any intercurrent adverse event.

Randomization and masking. A computer randomization list was generated by the Laboratory of Biostatistics of the Mario Negri Institute (Ranica, Italy). After stratification for the referral hospital, within each block of varying size, patients were assigned to the 2 treatment arms using a 1:1 ratio. The patient randomization number and study arm were requested by phone or fax and centrally assigned by the treatment secretariat at the Mario Negri Institute. Participants and care providers were not blind to study treatments.

Measurements. Before randomization, 4 weeks after, and at the 28th and 36th gestational week, blood and urine samples were obtained for routine hematochemistry and urinalysis, carried out at the participating centers. Blood samples collected before randomization were promptly centralized at the tertiary referral Hemophilia and Thrombosis Center for thrombophilia screening, including factor V Leiden and prothrombin G20210A gain-of-function mutations, measurement of antithrombin, protein C, and protein S plasmatic activities, and the search of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and anti–β2-glycoprotein I antibodies IgG and IgM). Deficiencies of the naturally occurring anticoagulant proteins were diagnosed when functional activities were below the lower limit of the normal laboratory values (80% for antithrombin, 63% for protein C, and 62% for protein S). Antiphospholipid antibodies were tested in fresh unfrozen plasma within 24 hours since blood sampling, and their results were promptly communicated to the participating centers; women who tested positive were excluded from the study. Results of other centralized tests were supplied at the end of the pregnancy. At the 20th gestational week, fetal and placental morphology were evaluated by ultrasonography. Uteroplacental blood flows were serially measured by Doppler ultrasounds at 20th, 28th, and 36th gestational weeks, respectively.

Monitoring. The study was monitored according to Good Clinical Practice (DL no. 191, July 15, 1997) and Standard Operating Procedures by the Drug Monitoring Unit of the Clinical Research Center. Compliance to treatment was assessed by accountability of prefilled syringes supplied to women and returned at each visit. Threshold to define adequate compliance was set at 80% consumption of supplied medication. Exposure to forbidden medications, including antiplatelet agents, was verified and recorded.

Outcomes. The primary outcome was a composite end point of preeclampsia, eclampsia, HELLP syndrome, intrauterine fetal death, FGR, or placental abruption. These outcomes were allocated on the basis of the same criteria used at screening evaluation by an independent adjudicator (P.R.) who was blinded to treatment allocation.

Secondary outcomes included adverse events possibly related to the study and any maternal, fetal, or newborn serious adverse event. Among

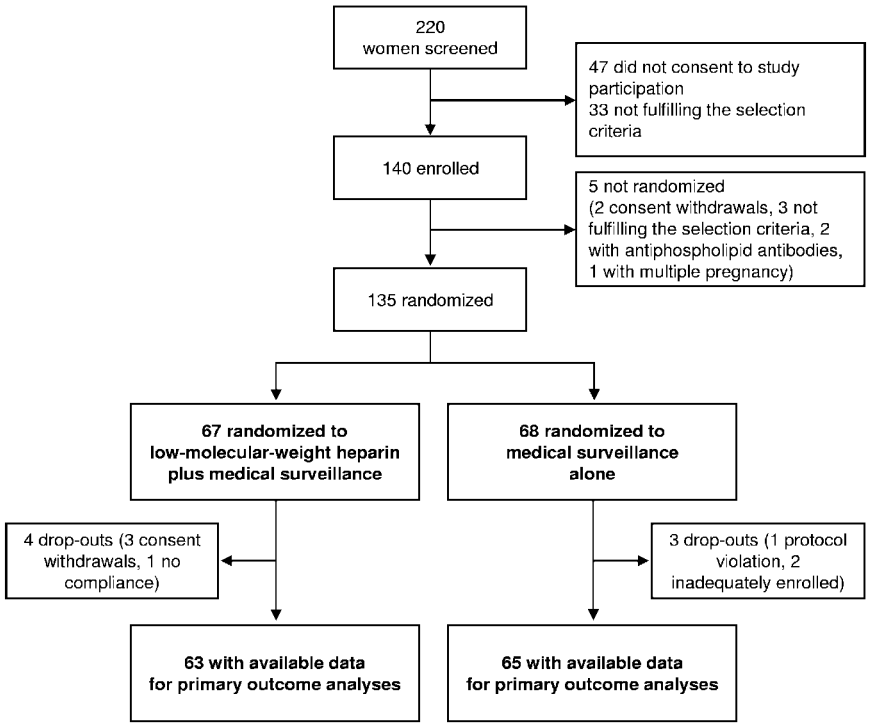

Figure 1. Study flow chart.

secondary outcomes, we also considered miscarriage (fetal loss below the 15th gestational week), preterm delivery (delivery between 25 and 36 weeks), preterm premature membrane rupture (between 25 and 36 weeks), and other pregnancy complications, such as gestational diabetes, cholestasis, and abnormal placental insertions. Mode of delivery (vaginal or cesarean) and neonatal APGAR scores were also recorded.

Statistical analysis

On the basis of data available when the protocol was designed,[14,15] we assumed a percentage of late pregnancy complications averaging 40% in controls. Considering as clinically relevant a 40% reduction in the percentage of events in women on active treatment with nadroparin compared with controls, we calculated that to provide the trial with an 80% power to detect at the 5% level of statistical significance a 40% reduction in the active treatment's event rate compared with the control arm (ie, from 40% to 24%), 133 women per study arm should be needed for primary outcome analyses. To verify these assumptions and to assess whether or not the study had to be prematurely concluded because of safety, efficacy, or futility, one interim analysis had been preplanned at the time when 50% of study participants had been randomized. The O'Brien and Fleming rule was used to determine the threshold for statistical significance at the time of interim evaluation.[16] This threshold was set at a P value of .0054 for the interim evaluation and .048 for the final analysis to keep the overall type I error at .05. All analyses were according to the intention-to-treat principle, with the exclusion of 7 patients with no information on the primary outcome. Primary and secondary outcomes were compared using χ^2 test, Fisher exact test, unpaired t test, or Wilcoxon rank-sum test as appropriate. For descriptive purposes, the Kaplan-Meier method was used to plot the probability of obstetric complications. The 95% CI around the difference in proportions was calculated using the Newcombe method. Analyses were carried out using SAS (Version 9.1) and Confidence Interval Analysis (Version 2.1.2). All P values were 2-sided.

Results

On April 4, 2010, 50% of planned study participants had been included. On the basis of prespecified protocol guidelines, on December 13, 2010, the Data and Safety Monitoring Board stopped the trial for futility reasons (see supplemental Appendix, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). The major statistical reason for futility was based on evidence that the absolute risk difference between nadroparin prophylaxis and surveillance alone (−16.0%) that had been hypothesized at the time of sample size estimation was not included in the 95% CI (ranging from −11.6% to +16.0%) of the absolute difference actually observed at interim analysis. An additional consideration of the Board was that a significant risk reduction with nadroparin at final analysis was extremely unlikely considering the trend to more events observed at interim analysis. Actually, to counterbalance this initial trend and achieve the 40% relative risk reduction expected in the whole study group, in the second half of patients to be included to achieve the planned sample size, nadroparin prophylaxis should have been associated with an 80% risk reduction. This was considered unrealistic by the Board.

The 25 women (12 in the nadroparin arm), who at the time of the decision of the Board were still pregnant, were maintained in their original treatment arm and were actively followed up to delivery or progression to an end point. At final analyses, of the 220 women who had been screened for study participation, 47 did not consent to inclusion (in most cases because of refusal to stop already ongoing heparin or aspirin therapy) and 33 did not fulfill the eligibility criteria. Of the remaining 135 women, 67 had been randomized to receive nadroparin in addition to medical surveillance and 68 to medical surveillance alone. Seven of randomized women prematurely withdrew from the study; thus, 63 and 65 women were finally available for primary outcome analyses in the nadroparin and control arm, respectively (Figure 1).

Baseline characteristics of study participants

Baseline characteristics, including the number of previous uncomplicated pregnancies and the distribution of previous late complications of pregnancy and hemostasis abnormalities identified at screening evaluation, were similar between treatment arms (Table

Table 1. Characteristics of study participants at randomization according to treatment arm

	Nadroparin and medical surveillance (N = 67)	Medical surveillance alone (N = 68)
Median age, y (range)	34 (23-42)	34 (19-45)
Body mass index, kg/m^2, mean (SD)	24 (4)	24 (5)
White ethnicity, n (%)	56 (84)	54 (79)
Previous uncomplicated pregnancies, n (%)	25 (37)	23 (34)
Previous pregnancy complication, n (%)*		
Preeclampsia	16 (24)	24 (35)
Mild	0	0
Severe	11 (16)	14 (21)
Unknown	5 (8)	10 (15)
Eclampsia	0	0
HELLP syndrome	9 (13)	3 (4)
Intrauterine fetal death	25 (37)	24 (35)
FGR	16 (24)	12 (18)
Placental abruption	1 (2)	4 (6)
Gestational week at randomization, mean (SD)‡	11 (2)	11 (2)
Current smokers (≥ 5 cigarettes per day), n (%)	5 (8)	3 (5)
Screened for thrombophilia, n (%)†	65 (97)	66 (97)
Antithrombin deficiency	2 (3)	3 (5)
Protein C deficiency	2 (3)	0
Protein S deficiency	37 (57)	39 (59)
Factor V Leiden	3 (5)	4 (6)
Prothrombin G20210A	1 (2)	1 (2)
Combined abnormalities	1 (2)‡	0

*Previous complications not available in 1 nontreated woman.
†Thrombophilia screening not available in 2 treated and 2 nontreated women.
‡Antithrombin deficiency and protein C deficiency.

1). Independent of treatment allocation, the most frequent previous pregnancy complications we re intrauterine fetal deaths and preeclampsia, reported in 49 (36%) and 40 (30%) of randomized women, respectively. As expected, the most frequent hemostasis abnormality was acquired protein S deficiency, known to develop physiologically during pregnancy, which was recognized in 76 (56%) of 131 women screened for thrombophilia. One or more additional hemostasis abnormalities were observed in 16 (12%) women (Table 1).

Main outcomes

Overall, 13 of 63 women (21%) randomized to active treatment compared with 12 of 65 randomized to surveillance alone (18%) had a combined end point. The percentage was similar: absolute (95% CI) event risk difference, 2.2 (−11.6 to 16.0; $P = .76$, between groups) as well as the distribution of single components of the composite end point (Table 2; Figure 2). Six women on nadroparin compared with 3 controls had preeclampsia or the HELLP syndrome.

Secondary outcomes

The incidence of serious adverse events, including pregnancy complications different from primary outcomes and treatment-related or unrelated maternal or fetal/neonatal events, was similar in the 2 treatment groups (Table 3). One woman in the control group was hospitalized because of a urethral bleeding that recovered spontaneously with no need for blood transfusion. No heparin-induced thrombocytopenia or other treatment related serious events were observed.

Overall, there were 156 and 146 nonserious adverse events in the active treatment and control arm, respectively. A major bleeding leading to the loss of approximately 3 L of blood complicated a cesarean section in a woman on medical surveillance alone. Minor bleeding episodes were reported in 3 women on nadroparin and in 8 controls. Skin reaction at the site of heparin injection was reported by 6 women. A miscarriage occurred in a woman in the control arm, and a mild fetal growth delay was observed in 3 women on active treatment and in 2 controls.

Other outcomes

Abnormal uterine artery velocimetry was observed in 14 heparin-treated women (4 at 20th, 7 at 28th, and 3 at 36th week of gestation) and in 12 controls (3 at 20th, 6 at 28th, and 3 at 36th weeks of gestation). Time to delivery and the number of cesarean sections did not differ between groups (Table 4). Independent of treatment allocation, the birth weight was below the 10th centile in 24.6% of

Table 2. Late pregnancy complications in study participants available for primary outcome analysis, according to treatment arm

	Nadroparin and medical surveillance (n = 63)	Medical surveillance alone (n = 65)	Absolute risk difference (95% CI)	*P*
Recurrent pregnancy complications, n (%)	13 (20.6)	12 (18.5)	2.2 (−11.6 to 16.0)	.76
Preeclampsia	5 (7.9)	3 (4.6)	3.3 (−5.9 to 13.1)	.44
Eclampsia	0	0	NA	NA
HELLP syndrome	1 (1.6)	0	1.6 (−4.2 to 8.5)	.49
Intrauterine fetal death	2 (3.2)	1 (1.5)	1.6 (−5.4 to 9.4)	.62
FGR	5 (7.9)	7 (10.8)	−2.8 (−13.6 to 8.0)	.58
Placental abruption	0	1 (1.5)	−1.5 (−8.2 to 4.3)	1.0

NA indicates not applicable.

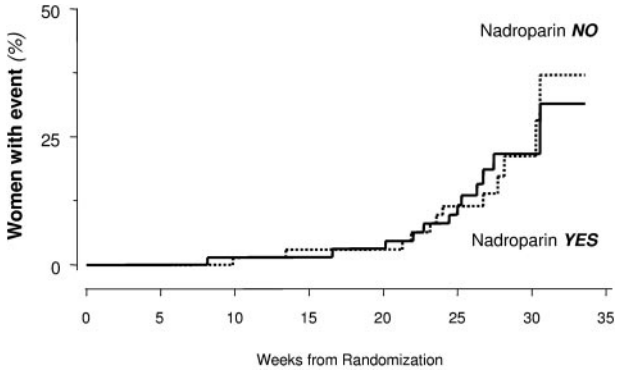

Figure 2. Women with primary composite outcomes during the observation period according to treatment arm.

newborns, ranged from the 10th to the 49th and from the 50th to the 89th centile in 48.4% and 19.7% of cases, respectively, and exceeded the 90th centile in the remaining 7.4%. Birth weight distribution in different centiles was similar ($P = .61$) for the 2 treatment groups. The APGAR score was less than 7 in 2 newborns in the active group and in 3 newborns in the control group. Occasional aspirin intake was never recorded in the study participants.

Main outcomes independent of treatment allocation

Late complications were observed in 12 of 50 women (24%) with previous predominantly maternal complications, such as preeclampsia or HELLP syndrome, compared with 12 of 73 women with previous fetal complications, such as intrauterine fetal death or FGR (16%, $P = .30$, Figure 3). Maternal complications were observed in 8 of those with previous maternal complications (16%) and in only one of those with previous fetal complications (1%, $P = .003$). Severe complications, such as HELLP syndrome, preeclampsia, and fetal death, were observed in 9 women with previous maternal complications (18%) compared with 3 with previous fetal complications (4%, $P = .01$). Of the 5 women with previous placental abruption, one had a recurrence of the same event, whereas the other 4 women had no events.

Discussion

Antithrombotic prophylaxis with low-molecular-weight heparin in addition to medical surveillance failed to decrease the number of late pregnancy complications compared with medical surveillance alone in 135 women with a previous history of preeclampsia, eclampsia, HELLP syndrome, intrauterine fetal death, FGR, or placental abruption. Baseline characteristics of study participants were similar in the 2 study arms, so that failure to detect any treatment effect is unlikely to be explained by a random clustering of risk factors for poorer outcomes in the heparin arm that might have offset the potential benefit of active intervention. Treatment allocation was balanced within each participating center, and medical surveillance was the same for all included women, which also reasonably excluded any appreciable source of bias that might have confounded data analysis and interpretation.

Our findings are in harmony with the results of a recent meta-analysis of 5 randomized clinical trials addressing the role of antenatal antithrombotic prophylaxis with low-molecular-weight heparins in 484 women at risk of late pregnancy complications.[9] None of the aforementioned studies detected a treatment effect on the primary outcomes that included perinatal mortality, preterm birth less than 34 weeks' gestation, or major neurodevelopmental delay at child follow-up. A few studies found a treatment effect of heparin on secondary outcomes, such as the development of preeclampsia,[15,17] eclampsia,[7] or infant birth weight below the 10th centile.[7,17-19] These findings, however, were heterogeneous among different studies, probably reflecting an effect of chance rather than a true treatment effect.

Our data differ from those of a recent study by Rey et al showing that dalteparin reduced the recurrence of late pregnancy complications in 116 women.[7] However, as acknowledged by the authors,[7] that study had methodologic limitations that flawed the findings, such as the concomitant use of aspirin that was unbalanced between treatment groups and started at different times in different women. Moreover, the study was prematurely stopped because of funding issues and slow recruitment rate, which might have led to exaggerated treatment effect.[20] Another single-center, pilot study found that enoxaparin treatment compared with observation alone reduced the incidence of late pregnancy complications in a highly selected population of women with previous placental abruption without fetal loss.[8] The present data show that these findings cannot be generalized to late pregnancy complications other than placental abruption.

An additional, novel finding of this study was that, independent of treatment allocation, complications with predominant maternal involvement, such as HELLP syndrome and preeclampsia, tended to cluster in women with previous maternal complications, whereas fetal complications, such as intrauterine fetal death and FGR, tended to be higher among women with previous fetal complications. Late complications were remarkably more frequent in women with previous maternal events than in those with previous

Table 3. Serious adverse events according to treatment arm

	Nadroparin and medical surveillance	Medical surveillance alone
Pregnancy complications other than end point		
Miscarriage*	1	0
Termination†	0	2
Gestational diabetes	0	2
Gestational hypertension	4	6
Cholestasis	3	1
Premature rupture of membranes	3	3
Oligohydramnios	4	3
Placenta previa	1	1
Risk of preterm delivery	4	2
Abnormal uterine artery velocimetry	14	12
Others‡	1	2
Other maternal adverse events		
Bleeding	1	2
Thrombocytopenia	0	0
Others§	5	0
Fetal/neonatal adverse events		
Chromosomal or congenital abnormalities‖	0	2
Abnormal cardiotocography	0	1
Others¶	1	1

*Miscarriage was defined as fetal loss occurring within the 15th gestational week.

†Terminations were at the 18th gestational week for chromosomal abnormality (trisomy 18) and at the 19th gestational week for fetal malformations (severe dextrocardia and diaphragmatic hernia).

‡Uterine contractions in 1 treated and 1 nontreated woman, and renal pelvic dilatation in 1 nontreated women.

§Headache in 3 women, epigastralgia in 1 woman, and dyspnea in 1 woman.

‖Described for terminations.

¶Cystic fibrosis in 1 treated woman and jaundice in 1 nontreated woman.

Table 4. Timing and modalities of delivery according to treatment arm

	Nadroparin and medical surveillance	Medical surveillance alone	*P*
Gestational week at delivery, mean (SD)	38 (3.5)	37 (4.6)	.69
Delivery after 38th week, n (%)	32 (52)	41 (64)	.16
Delivery at or before 38th week, n (%)	30 (48)	23 (36)	NA
Before 35th week, n (%)	7 (11)	10 (16)	.48
Before 31st week, n (%)	2 (3)	3 (5)	1.0
Caesarean section, n (%)	31 (50)	24 (38)	.16

Timing and modalities not available in 1 of the 63 treated and in 1 of the 65 nontreated women with data on pregnancy outcome.
NA indicates not applicable.

fetal events and the most severe ones, such as the HELLP syndrome, preeclampsia, and intrauterine fetal death, almost entirely clustered among women with previous predominant maternal complications. These women appear to be at highest risk of serious events during subsequent pregnancies and are therefore in most urgent need of effective preventive measures, whereas those with previous fetal complications appear to have relatively good outcomes independently of treatment.

The major limitation of our study was the open design and lack of a placebo arm. This limitation, however, is common to the majority of trials in this clinical setting[7,8,21] and is explained by difficulties in justifying to study participants the real need for repeated subcutaneous injections of ineffective medications, which might translate into suboptimal compliance to treatment guidelines and offset the potential advantages of a blinded design. Moreover, the main efficacy variable included hard end points that were allocated on the basis of predefined, objective and clear-cut diagnostic criteria, and data analyses were blinded to treatment allocation. Thus, the design was adequate to test the working hypothesis, and the results were very unlikely affected by the unmasked treatment allocation. The observed number of recurrent pregnancy complications in controls who had received medical surveillance alone was only half than that expected on the basis of the literature reports until 2006, when this study was designed. On the other hand, it is in line with event rates reported in more recent series[22-24] and might reflect closer patient monitoring and progressive improvements in supportive treatments. Another plausible explanation would be that women on heparin therapy for established thrombophilia were not included in the trial because of available evidence that antithrombotic prophylaxis may have a specific indication in this setting.[2] The finding that the prevalence of thrombophilia in our series, even after exclusion of cases with physiologic pregnancy-induced protein S deficiency, was 2-fold that observed in the general population, most probably explained by an association between hypercoagulability and increased susceptibility to late complications of pregnancy.[6] Uneven patient inclusion in different centers was not an issue because randomization was balanced by center and analyses were adjusted for the center effect.

The major strength of the trial was the multicenter, prospective, randomized, and controlled design, which compared interventions based on real-world clinical practice. Selection criteria allowed identifying a study population that closely reflected the average population of pregnant women exposed to antithrombotic treatments despite lack of proven efficacy. Both factors contribute to the wide generalizability of our findings to the majority of women at risk of unnecessary antithrombotic prophylaxis. Hence, even though this trial was stopped for futility and safety considerations, it does contribute valuable data toward evidence-based practice.

In conclusion, considering that nadroparin may share with other heparins and analogues a similar class effect and that the dose of nadroparin we used has a proven antithrombotic efficacy,[25] our present findings, combined with evidence from previous trials,[21,26] definitely challenge the role of routine antithrombotic prophylaxis with heparins in women considered at risk because of previous pregnancy-related complications. Better understanding of the mechanisms underlying placental vascular disease will hopefully

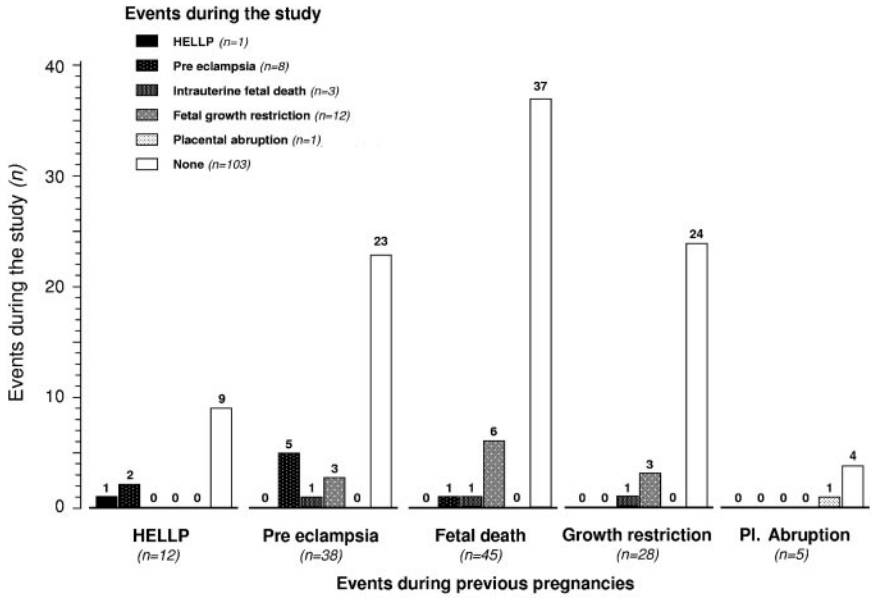

Figure 3. Distribution of events during the observation period in different subgroups of study participants categorized according to previous history of placenta-mediated complications and independent of treatment allocation. The numbers at the top of each column describe the number of events.

provide the background for more specific and effective interventions to prevent onset and ameliorate outcomes of late complications of pregnancy, in particular in women at highest risk of severe events because of previous HELLP syndrome or preeclampsia. In the meantime, antithrombotic prophylaxis should not be routinely administered to prevent recurrences of placenta-mediated pregnancy complications and should be restricted to women who have a proven benefit from this intervention, such as those with previous thromboembolic events[6] and perhaps those with previous placental abruption without fetal loss.[8]

Acknowledgments

The authors thank Serena M. Passamonti and Tullia Battaglioli at the Hemophilia and Thrombosis Center, Milano, Italy, for their help in coordinating the study; Nadia Rubis and Bogdan Ene-Iordache of the Clinical Research Center Aldo e Cele Daccò who supervised study monitoring and data handling; Ilaria Fojadelli, Ilaria Maffeis, Greta Carrara, and Giuseppe Stanzione who contributed to data analysis; all the doctors and nurses in charge of study participants; all the women who, with their participation, allowed the finalization of the study; and the pharmaceutical companies Italfarmaco (Milano, Italy) and GlaxoSmithKline (Verona, Italy), which supplied nadroparin according to the Good Manufacturing Practice without any kind of involvement in study design, conduction, and monitoring as well as in data handling, analysis, and reporting.

This work was supported by the Italian Drug Agency (Agenzia Italiana del Farmaco) of the Ministry of Health (grant for independent research; trial registration: EudraCT 2006-004205-26).

Authorship

Contribution: I.M., I.C., G.P., G.R., and P.M.M. designed the study and interpreted the results (G.P. died before the results were available); I.C., P.V., B.A., F.F., G.B.L.S., M.B., S.R., and L.M. identified and followed the patients; O.D. and G.G. designed the case record forms and monitored the study; S.C. designed the data base and contributed to data handling; A.P. performed the statistical analyses; I.M. and P.R. contributed to data analyses and interpretation and wrote the initial draft and the final version of the manuscript; G.R. and P.M.M. provided major intellectual contribution to the manuscript; and all authors had full access to data, critically revised the manuscript, and approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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