A Retrospective Analysis of Fondaparinux Versus Enoxaparin Treatment in Women with Infertility or Pregnancy Loss

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Keywords
Anticoagulant, antiphospholipid antibody syndrome, fondaparinux, heparin, immunotherapy

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Submitted March 25, 2009;
accepted July 15, 2009.

Citation
Winger EE, Reed JL. A retrospective analysis of fondaparinux versus enoxaparin treatment in women with infertility or pregnancy loss. Am J Reprod Immunol 2009; 62: 253–260

doi:10.1111/j.1600-0897.2009.00733.x

Problem
We compared the pregnancy success rates and safety parameters of fondaparinux versus enoxaparin, combined with immunotherapy, in patients with a history of miscarriage and/or infertility and coagulant defects.

Method of study
A total of 127 pregnancies in 110 patients with a history of miscarriage and/or infertility were retrospectively evaluated. Of these, 29 pregnancies used fondaparinux 2.5 mg daily and 98 pregnancies used enoxaparin 30 mg twice daily.

Results
The pregnancy success rate was 59% (17/29; 95% CI, 41–75%) for patients receiving fondaparinux and 58% (57/98; 95% CI, 48–68%) for patients receiving enoxaparin. No difference was detected in birth weight (2.7 ± 0.8 and 2.9 ± 0.6 kg, respectively) or gestational age at delivery (37.3 ± 2.2 and 37.7 ± 2.1 weeks, respectively). No birth defects, severe bleeding-related complications, or serious allergic reactions were observed.

Conclusion
In patients with a history of miscarriage, infertility, and coagulant defects receiving immunotherapy, fondaparinux resulted in successful pregnancy outcomes comparable with enoxaparin therapy. Although no difference in outcome was observed in our analysis, a much larger study is required to achieve statistical power.

Introduction

Unexplained miscarriage and infertility are an enigmatic problem affecting approximately 6% of couples trying to start a family. Contributing to these losses are immunologic disorders and the clotting disorders, also known as the thrombophilias.[1–3] Two major groups of thrombophilias have been described, the inherited and the acquired. Among the acquired thrombophilias, antiphospholipid antibody syndrome is the best recognized as a cause of miscarriage.[4] Among the inherited thrombophilias, a diverse group of inherited polymorphisms associated with the coagulation cascade such as factor V Leiden and prothrombin G20210A has also been implicated in pregnancy loss.[5–7] For many years, unfractionated heparin was considered the treatment of choice for thrombophilia in pregnancy.[6] Over the past decade, the use of low-molecular-weight heparin (LMWH) has become more prevalent based on studies that demonstrated safety and efficacy of LMWH during pregnancy. In a study performed by Sarto et al.,

30/35 (85%) of the pregnancies treated with antithrombotic therapy ended in live birth, while 16/105 (15%) of the pregnancies without the therapy ended in live birth ($P < 0.001$).[8] Brenner et al. studied 61 pregnancies treated with antithrombotic therapy (40 or 80 mg enoxaparin/day) in which only one thrombotic episode and one mild bleeding episode were observed.[9] In a later prospective, multi-center trial, Kutteh et al. tracked the complications of a pregnant group taking LMWH versus another group taking UFH. No major bleeding episodes were observed. In addition, no cases of deep venous thrombosis, thrombocytopenia, pre-eclampsia, gestational diabetes, or bone fractures were observed in that study.[10] Therefore, enoxaparin appears to be both safe and effective for use in pregnancy. However, LMWH has several drawbacks; it is often associated with bruising at the injection site and has a shorter half-life compared with newer anticoagulants.

Fondaparinux, an indirect factor Xa inhibitor, has been shown to be similar or superior to LMWH as prophylaxis after orthopedic or abdominal surgery in individuals at risk for thromboembolic complications, in the treatment of venous thromboembolism in conjunction with warfarin, and in the treatment of pulmonary embolism when administered with warfarin.[11–14] The use of fondaparinux in pregnancy appears to be well-tolerated.[15,16] In addition, its 17–21 hr half-life offers once-daily dosing, injections may be less painful, and rashes and allergic reactions are less frequent compared with that of the LMWH enoxaparin.[17,18] However, despite these potential advantages, there are no adequate and well-controlled studies in pregnant women, and the efficacy and safety of fondaparinux for pregnancy achievement and maintenance have not been established.

We report a retrospective evaluation of pregnancy success and safety of fondaparinux versus enoxaparin therapy, combined with immunotherapy, in women with a history of infertility or pregnancy loss and coagulant defects. The primary outcome was successful pregnancy with live birth; safety outcomes included bleeding, allergic reactions, and birth defects.

Materials and methods

Study Design

In this single-center, retrospective study, we evaluated live birth rates and safety of fondaparinux (Arixtra®; GlaxoSmithKline, Philadelphia, PA, USA) versus enoxaparin (Lovenox®; Sanofi-Aventis, Bridgewater, NJ, USA) therapy, combined with immunotherapy, in women with a history of immunologically related miscarriage and/or infertility. The patients were seen at the Alan E. Beer Center for Reproductive Immunology and Genetics in Los Gatos, CA, USA, which specializes in treating recurrent pregnancy loss and infertility (approximately 20–30 new patients per month, distributed worldwide), including testing for thrombophilias and providing immunomodulatory and antithrombotic therapy when appropriate.[8,9,19–23] Testing and treatment were performed using standard protocols that target immunologic and coagulation abnormalities. The study was approved by the Institutional Review Board (WIRB Study Number 1094182). Patient confidentiality was strictly maintained.

Patients

Study participants were identified by reviewing records of patients treated at the clinic between November 2005 and July 2007. Because enoxaparin was used substantially more frequently than fondaparinux during this period, we limited the sample size for the enoxaparin treatment group to approximately 100 randomly selected, eligible patients. However, because the number of fondaparinux patients was limited, all eligible fondaparinux patients were included in this study. Women were eligible if they were ≥28 years old with a history of recurrent (≥3) pregnancy failures (primary or secondary), and/or demonstrated a history of infertility with acquired or hereditary thrombophilia. All patients received obstetrical management in the US for natural pregnancy or *in-vitro* fertilization (IVF), and were administered fondaparinux 2.5 mg daily or enoxaparin 30 mg twice daily. Patients were excluded if they were >46 years of age or had a contraindication to the use of LMWH or fondaparinux.

A comprehensive database is maintained at the Alan E. Beer Center, and all enoxaparin-treated patients seen during the November 2005–July 2007 period were screened in a random order until a comparable number was identified for the enoxaparin group. In addition, all fondaparinux patients were screened to identify as many eligible patients for the fondaparinux group as possible. Patients who received treatment for different pregnancies on separate occasions may have been entered into a group, or across groups, more than once.

Pre-conception Testing

Patients underwent immunologic and genetic testing pre-conception. Immunologic testing was performed at the Rosalind Franklin Clinical Laboratory, Chicago, IL, USA. Natural killer cell (NK) cytotoxicity was assessed by flow cytometry, where labeled K562 target cells were incubated with isolated patient mononuclear cells and propidium iodide, which stains dead cells. Target cell killing was assessed by quantification of dually labeled cells. NK cytotoxicity was tested at an effector to target ratio of 50:1 and was regarded as 'elevated' when target cell killing was >15%. Patients were also tested for antiphospholipid antibody (six types: cardiolipin, serine, ethanolamine, glycerol, inositol, and phosphatiditic acid; three classes: IgM, IgG, or IgA); a titer of 1:50 for any antibody was considered 'positive'. Patients were tested for antinuclear antibody antibodies (ANA) and DNA histone antibodies, and a titer of 1:40 was considered 'positive'. Patients underwent evaluation for a variety of gene mutations and were considered 'positive' for inherited thrombophilia upon detection of any one of the following: heterozygous or homozygous factor V Leiden R506Q, prothrombin G20210A, or plasminogen activator inhibitor 4G/5G; homozygous methylene tetrahydrofolate reductase (MTHFR) C677T; or compound heterozygous MTHFR C677T/A1298C.

Treatment

Patients received 81 mg aspirin daily starting at day one of the cycle of conception through delivery. Fondaparinux (2.5 mg daily) or enoxaparin (30 mg twice daily) was started on cycle day 6 of the conception cycle and continued through at least 12 weeks of pregnancy. When pregnancy was attempted through assisted reproductive techniques, e.g., IVF, anticoagulant therapy was discontinued for 48 hr (enoxaparin) or 72 hr (fondaparinux) before egg retrieval and restarted 12 hr after the transfer procedure. The decision to prescribe fondaparinux or enoxaparin was determined primarily by the physician's personal preference or the patient's insurance coverage. Enoxaparin was more frequently prescribed because it had more literature supporting its safety in pregnancy, plus it was more frequently covered by insurance. Conception rates were comparable between the fondaparinux and enoxaparin treatment groups.

Patients also received one or more forms of immunotherapy, based on pre-conception testing. Intravenous immunoglobulin (IVIG), when used, was administered at 400 mg/kg body weight at least once during the cycle of conception and/or at least once after a positive pregnancy test with NK cytotoxicity (50:1 effector: target cell killing ratio) of >15% and/or $CD56^+$ >12%. Additional IVIG was given during later pregnancy, if these percentages remained elevated. Some patients were self-referred to a non-US clinic for lymphocyte immunization therapy (LIT),[24,25] administered within 6 months pre-conception. Tumor necrosis factor-alpha (TNF-α) therapy was administered in patients with an TNF-α:interleukin (IL)-10 ratio >30.6, interferon gamma:IL-10 ratio >20.5, or CD57 elevation via endometrial biopsy (defined as >4 CD57 cells per high power microscope field).[22,23,26–29] In such patients, adalimumab (40 mg by subcutaneous injection every 1–2 weeks) or etanercept (25 mg by subcutaneous injection every 84 h) was generally initiated 30 days before starting a cycle of conception and discontinued when a positive pregnancy test occurred or when embryonic cardiac activity was observed via ultrasound. Corticosteroids were administered in patients with positive antinuclear antibody and/or elevated (>12%) NK cell number (CD56) at pre-conception.[30,31] Either prednisone was given 5 mg twice daily, starting on day 6 of the cycle of conception and increased to 10 mg twice daily when a positive pregnancy test occurred, or dexamethasone 1 mg daily was started on day 6 of the cycle of conception and continued at that dose. Corticosteroids were usually tapered and stopped at the beginning of 10 weeks gestation.

Data Collection and Analyses

Patient baseline clinical and laboratory features, and outcome data were extracted from database medical records, independently audited before analyses. The primary outcome was a successful pregnancy with live birth. Miscarriage was defined as a pregnancy that failed after having achieved a beta-hCG of 25 or greater and/or demonstrated a visible sac using ultrasound. Ectopic pregnancies and elective terminations were not considered as miscarriages. Safety assessments included severe bleeding-related complications, vaginal bleeding, allergic reactions, and birth defects. Data were summarized for patients (counted separately at each pregnancy, if more than

1 pregnancy) grouped by anticoagulant treatment. Categorical data were reported using counts and percentages (and 95% confidence interval, CI, for the primary outcome) and compared between groups using Fisher's exact test. Continuous data were reported as mean ± S.D. and compared between groups using a Student's *t*-test. Significance was declared at $P < 0.05$. All statistical calculations were made using Graphpad Software Inc.®, La Jolla, CA, USA.

Results

Study Population

We evaluated 127 pregnancies in 110 patients with a history of miscarriage and/or infertility and who received injectable anticoagulant therapy with fondaparinux 2.5 mg daily (29 pregnancies) or enoxaparin 30 mg twice daily (98 pregnancies). The study population included one patient who received fondaparinux during two separate pregnancies; nine patients who received enoxaparin during separate pregnancies (six patients during two pregnancies, two patients during three pregnancies, and one patient during five pregnancies); and two patients who received enoxaparin during a pregnancy and fondaparinux during another, separate pregnancy.

The treatment groups were similar in terms of maternal age (37.1 ± 4.3 versus 36.1 ± 4.3 years), the number of previous miscarriages (2.8 ± 2.7 versus 2.5 ± 1.9 losses), and maternal immunologic and thrombophilic status (Table I). In each group, approximately one-half had elevated NK cytotoxicity or antiphospholipid antibody. Inherited thrombophilia was present in 24% (7/29) of patients administered fondaparinux and 43% (42/98) of patients administered enoxaparin ($P = 0.08$). The most common immunotherapies were IVIG (≥83%, each group) and corticosteroid (≥57%, each group).

Table I Baseline Characteristics

Feature	Fondaparinux 29 pregnancies	Enoxaparin 98 pregnancies	*P* value
Maternal age, mean ± S.D., year	37.1 ± 4.3	36.1 ± 4.3	0.24
Prior miscarriages, mean ± S.D., number	2.8 ± 2.7*	2.5 ± 1.9*	0.51
Pre-conception testing, % (*n*)			
Positive NK Assay 50:1	52 (15)	45 (44)	0.53
Positive NK CD56	28 (8)	20 (20)	0.45
Antiphospholipid antibody	62 (18)	52 (51)	0.40
Antinuclear antibody	17 (5)	21 (21)	0.79
Inherited thrombophilia	24 (7)	43 (42)	0.08
Immunotherapy, % (*n*)			
IVIG	90 (26)	83 (81)	0.56
LIT	34 (10)	40 (39)	0.67
Anti-TNF-α	28 (8)	23 (23)	0.63
Corticosteroid	62 (18)	57 (56)	0.67

*Median = 2, each group (range of 0–11 for fondaparinux group and 0–12 for enoxaparin group).

Efficacy

Table II summarizes the pregnancy outcomes. The successful pregnancy rate was 59% (17/29; 95% CI, 41–75%) for patients receiving fondaparinux and 58% (57/98; 95% CI, 48–68%) for patients receiving enoxaparin ($P = 1.0$). The gestational age at delivery was also comparable between groups (37.3 ± 2.2 and 37.7 ± 2.1 weeks, respectively). Of the 17 successful pregnancies with fondaparinux therapy, 76% (13) were singletons, 18% (three sets) twins, and 6% (one set) triplets. Among the 57 successful pregnancies with enoxaparin therapy, 86% (49) were singletons and 14% (eight sets) twins. No difference in infant birth weight was detected between the fondaparinux and enoxaparin groups (2.7 ± 0.8 and 2.9 ± 0.6 kg, respectively). In each group, one ectopic pregnancy occurred and was electively terminated. Miscarriage occurred in the remaining pregnancies, without a between-group difference in frequency [fondaparinux group: 38% (11/29); enoxaparin group: 41% (40/98), $P = 0.83$].

Among the patients administered anticoagulants during multiple, separate pregnancies, successful deliveries occurred in two of four (50%) pregnancies in the fondaparinux group and 11 of 25 (44%) in the enoxaparin group. These frequencies were not significantly different from each other or from those of the overall treatment groups ($P = 1.0$).

Safety

Table III summarizes the safety outcomes. No severe bleeding-related complications were observed in either group. Vaginal bleeding occurred in 28%

Table II Efficacy

Outcome	Fondaparinux, 29 pregnancies	Enoxaparin, 98 pregnancies	*P* value
Successful pregnancy with live birth, % (*n*)	59 (17)	58 (57)	1.00
Gestational age at delivery, mean ± S.D., week	37.3 ± 2.2	37.7 ± 2.1	0.37
Birth weight, mean ± S.D., g	2733 ± 753	2903 ± 580	0.29
Ectopic pregnancy, % (*n*)	3 (1)	1 (1)	0.40
Miscarriage, % (*n*)	38 (11)	41 (40)	0.83

(8/29) of fondaparinux-treated patients and 15% (15/98) of enoxaparin-treated patients ($P = 0.17$), typically between 7 and 9 weeks of gestation. For pregnancies in which vaginal bleeding did, versus did not, occur, delivery rates were 63% (5/8) versus 57% (12/21), in the fondaparinux group ($P = 1.0$), and 60% (9/15) versus 57% (48/83), in the enoxaparin group ($P = 1.0$). Thus, vaginal bleeding was not associated with delivery rates, or, correspondingly, miscarriage incidence.

There were no anaphylactic reactions. Rash was infrequently reported (<4% in each group) and typically treated using diphenhydramine (Benadryl®). The use of various immunotherapies in combination with anticoagulant therapy precluded causal attribution of these events.

No birth defects were observed in the babies born. One baby (enoxaparin group) had a genetic enzyme disorder, for which genetic counseling was advised to the family.

Discussion

We present the largest reported sampling (to our knowledge) of pregnant women administered fondaparinux therapy, and the first comparative study between fondaparinux and a LWMH for anticoagulation during pregnancy. In this retrospective study of women with a history of infertility or pregnancy loss, we investigated the effectiveness and safety of fondaparinux 2.5 mg once daily (29 pregnancies) versus enoxaparin 30 mg twice daily (98 pregnancies), combined with immunotherapy. The study population included 110 patients with immunologic abnormality and/or thrombophilias, and some 12 patients received therapy on multiple, separate pregnancies. The treatment groups were well-matched at baseline, and this supported the validity of comparisons between their outcomes.

The pregnancy success rates of 59% (17/29; 95% CI, 41–75%) for patients receiving fondaparinux and

Table III Safety

Outcome	Fondaparinux, 29 pregnancies	Enoxaparin, 98 pregnancies	*P* value
Severe bleeding-related complication, % (*n*)	0 (0)	0 (0)	1.0
Vaginal bleeding, % (*n*)	28 (8)	15 (15)	0.17
Gestational age at bleeding, mean ± S.D., week	8.5 ± 3.4	7.3 ± 3.8	0.46
Pregnancy Success rates: Vaginal bleeding versus no bleeding	63% (5/8) versus 57% (12/21)	60% (9/15) versus 57% (48/83)	1.0
Anaphylactic reaction, % (*n*)	0 (0)	0 (0)	1.0
Rash, % (*n*)	3 (1)	4 (4)	1.0

58% (57/98; 95% CI, 48–68%) for patients receiving enoxaparin, when combined with immunotherapy, suggest similar effectiveness of the two anticoagulants. Other efficacy measures, including birth weight and gestational age at delivery, were also comparable between the treatment groups. It should be noted that the pregnancy success rate observed at our clinic among a similar patient group taking immunotherapy but not anticoagulants is notably lower than the success rates observed within this study [45% (34/75) success rate observed without anticoagulants, compared with the 59%and 58% success rates observed in this study]. This suggests that the anticoagulant therapy indeed contributes additional therapeutic benefit to the immunotherapy treatments already prescribed. The patient history and treatment profile of this non-anticoagulated group are similar to those of the two groups in our study (mean age 37.7 ± 4.2 years, mean history 2.5 ± 2.3 prior miscarriages, with a treatment profile of 67% using IVIG, 21% using LIT, 19% using a TNF-α inhibitor, with 41% testing positive for inherited thrombophilia). Therefore, because of these observations, and because of data published in the literature,[6–9] we suggest that both the enoxaparin and the fondaparinux protocols are contributing real therapeutic benefit to these high-risk obstetric populations.

Our results are encouraging although somewhat surprising. Recent literature suggests a major role for complement activation in fetal demise.[32] Specifically, Girardi suggests that heparins and their low-molecular-weight forms prevent obstetric complications in women with antiphospholipid antibody syndrome through their anticomplementary activities and not their anticoagulant effects.[33] C5a, a powerful anaphylaxitoxin that binds to receptors on neutrophils and endothelial cells, results in the expression of tissue factor, initiating the coagulation cascade and increasing the production of reactive oxygen species, leading to inflammation, decidual injury, and fetal death. Used in sub-anticoagulant doses, heparin has been found to be effective in the treatment of this syndrome, suggesting that one major effect of heparin might be its inhibition of complement activation. Moreover, used in sub-anticoagulant doses, heparin has been shown to prevent programmed cell death in human trophoblast.[34] Fondaparinux, on the other hand, is a synthetic pentasaccharide and is a specific inhibitor of factor Xa, with no known anticomplementary activity. It is therefore of particular note that comparable pregnancy success rates occurred in patients treated by either enoxaparin (a LMWH) or fondaparinux. A possible explanation for the comparable efficacy of fondaparinux and enoxaparin observed may be the role of factor Xa in non-coagulation-related signaling pathways. Factor Xa exerts direct effects on a wide variety of cells through cleavage of protease-activated receptors, PAR-1 and PAR-2, directing tissue remodeling among other effects.[35] In addition, both fondaparinux and enoxaparin are known to block the generation of thrombin, a direct activator of C5, which is known to lead to the generation of C5a, a recognized contributor to the abortion process. This mechanism may shed some light on the interesting data observed.[36]

Anticoagulant therapy with each drug was well-tolerated (including upon repeated exposure), without severe bleeding complications or serious allergic reactions. Vaginal bleeding occurred in both groups; however, no between-group difference in frequency was detected and the delivery rates for patients with, versus without, vaginal bleeding were similar across groups. This should be reassuring to physicians contemplating the use of fondaparinux as an alternative to enoxaparin in immune-treated obstetric patients.

Limitations

A total of 12 patients received treatment during multiple, separate pregnancies, providing safety data relevant to drug re-exposure but may have biased efficacy results. The fact that pregnancy success rates were similar between patients who did, versus did not, have multiple treatments suggests no directional bias. Other limitations of the study include its retrospective nature, imbalanced group sizes owing to differences in availability of eligible patients, and possible effects of combining immunotherapies. The study sample size was based on feasibility and was not powered to detect pre-specified differences (or equivalencies) in outcome. Indeed, the confidence limits on the estimates of success rates were wide (See Results section), so the actual success rates could theoretically range from, for example, fondaparinux 41% and enoxaparin 68% to fondaparinux 75% versus enoxaparin 48%. This study comprised only 98 enoxaparin and 29 fondaparinux patients. Assuming that a 10% difference would be clinically significant, to detect that level of significance at $P < 0.05$ in 80% of trials would require approximately 305 patients in each treatment group.

In addition, we have limited data on outcome if patients in the study were given immunotherapy with baby aspirin without the anticoagulant. There is only a 10% difference when anticoagulants are used alone, immunotherapy could swamp out that difference, so the sample size required to show that the two anticoagulants are not different from each other when combined with immunotherapy is going to be much larger than 305 per group. The best one could do in an observational design is to suggest that more data are needed and that a registry for collection of data be established from multiple centers. It would be desirable to identify a cohort of patients in whom there was no added immunotherapy.

In conclusion, 'true' differences in efficacy and safety profile in pregnant women between fondaparinux and enoxaparin remain to be established. This may require a much larger, observational trial, possibly involving multiple clinics.

Conclusions

These retrospective data suggest that in women with miscarriage and/or infertility treated with a combination of immunotherapies and anticoagulants, fondaparinux is well-tolerated and enables successful pregnancy outcomes at a rate comparable with that of enoxaparin therapy. Because fondaparinux also offers more convenient once-daily dosing and, in previous studies, fewer negative side effects than enoxaparin, we propose that fondaparinux may someday offer an attractive therapeutic alternative to enoxaparin in immune-treated pregnancy. However, prospective studies are needed.

Acknowledgments

We thank Dr. Graham Turpie and Dr. Marcie Hursting for their helpful suggestions and their valuable assistance with the data analysis.

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