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ORIGINAL RESEARCH ARTICLE

The Fetal Safety of Enoxaparin Use During Pregnancy: A Population-Based Retrospective Cohort Study

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Abstract

Introduction Enoxaparin is widely used during pregnancy as pregnancy is a hypercoagulable state; however, its fetal safety has scarcely been investigated.

Objective Our study aimed to examine fetal safety following enoxaparin exposure during pregnancy.

Methods A population-based, retrospective cohort study was performed by linking computerized databases, including the drug dispensing registries of Clalit Health Services in Israel and maternal and infant hospital records, between 1998 and 2009. Multivariate logistic regression models were used to examine associations between first- and third-trimester exposure to enoxaparin, major malformations, and other adverse birth outcomes, adjusted for confounders.

Results From a total of 109,473 singleton pregnancies, 418 and 572 were exposed to enoxaparin during the first and third trimesters, respectively. Exposure to enoxaparin during the first trimester of pregnancy was not associated with an increased risk of major congenital malformations [adjusted odds ratio (aOR) 1.1, 95% confidence interval (CI) 0.8–1.6], while exposure during the third trimester was not associated with an increased risk of low birth weight (aOR 1.1, 95% CI 0.8–1.4), low Apgar score (aOR 0.9, 95% CI 0.4–1.8), or risk of perinatal mortality (aOR 0.6, 95% CI 0.1–2.9).

Conclusion Exposure to enoxaparin during pregnancy was not associated with an increased risk of major malformations in general or according to organ systems. Nonetheless, risk for specific malformations cannot be ruled out.

Key Points

First-trimester exposure to enoxaparin was not associated with an increased risk of major congenital malformations.

Third-trimester exposure to enoxaparin was not associated with an increased risk of fetal mortality, low birth weight, low Apgar scores, or neonatal bleeding.

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1 Introduction

As pregnancy is a hypercoagulable state, the risk for thromboembolic events rises. During pregnancy, the rise in levels of coagulation factors are accompanied by decreased fibrinolytic activity [1]. The combination of these two processes increases the overall risk for thromboembolic events four- to tenfold in pregnant women compared with non-pregnant women [1–3].

Thrombophilic women who become pregnant have higher associated risks for fetal loss and pregnancy complications, including pre-eclampsia, placental abruption, and intrauterine growth restriction (IUGR) [4, 5]; therefore, prophylactic anticoagulation therapy for pregnant women with thrombophilia is frequently recommended.

Among the main anticoagulation therapies available are the coumarins, acting as vitamin K antagonists; however, warfarin, a coumarin derivative, is teratogenic in humans exposed during the first trimester [6]. Widely used alternatives to warfarin, i.e. heparins, including the forms of low-molecular-weight heparin (LMWH), act by enhancing antithrombin activity and are considered to be a safer alternative to coumarins during pregnancy [7]. Enoxaparin is a widely used LMWH for anticoagulation therapy during pregnancy, but tinzaparin and dalteparin are nowadays considered as equivalent options [8].

Until recently, LMWHs, specifically enoxaparin, were used during pregnancy to prevent recurrent pregnancy loss and placental vascular complications [9, 10]. A clinical trial published in 2014 found antepartum prophylactic treatment with LMWHs inefficient in reducing the occurrence of these complications among pregnant women with thrombophilia [11]. Furthermore, treatment with LMWHs was found to increase the risk of minor bleeding.

Although enoxaparin does not appear to cross the human placenta, it may theoretically affect embryo and fetal development through interactions with the trophoblast and placental vasculature. In some clinical studies, increased bleeding propensity has been shown to be a possible risk to the fetus that warrants investigation. This is especially important as the conditions for which enoxaparin is administered can increase fetal risk themselves (bias by indication) and may confound the evaluation of enoxaparin safety, calling for large epidemiological studies.

The main aim of the current study was to evaluate the fetal safety of enoxaparin use during pregnancy.

2 Materials and Methods

2.1 Study Design

A population-based retrospective cohort study was conducted among residents of the Southern District of Israel. We included all women 15–45 years of age who were registered in the Clalit Health Services maintenance organization and who had singleton deliveries or pregnancy terminations for medical reasons at Soroka Medical Center between 1 January 1998 and 31 December 2009. Clalit Health Services is the main health provider in the Southern District, insuring 70% of all residents, while Soroka Medical Center is the regional district hospital where 98% of deliveries take place [12, 13].

Women who had been diagnosed with hereditary thrombophilia were excluded from the study, and, with almost all of them treated with enoxaparin, indication bias would be impossible to rule out. Women who were treated with other anticoagulants, women younger than 15 years or older than 45 years of age, births before the 27th gestational week, pregnancies exposed to folic acid antagonists, pregnancies with chromosomal defects, and pregnancies with multiple fetuses were also excluded from the study.

2.2 Data Sources

The cohort was created by linking four separate databases according to a unique identification number provided by the Israeli Ministry of Interior. The first database was the Clalit Health Services drug dispensation computerized database, which contained the records of dispensed drugs, including the date of dispensation, and the Anatomical Therapeutic Chemical (ATC) classification codes of the drugs (including the commercial and generic names). The second computerized database containing mothers' medical records is housed in the Division of Obstetrics and Gynecology at Soroka Medical Center. This database provided maternal demographic information, including ethnic group (Jewish or Bedouin Muslim), maternal age, parity, medical diagnosis during pregnancy and delivery, self-report of smoking during pregnancy, and delivery data. Adverse birth outcomes that were recorded included perinatal death, infant bleeding, low birth weight (<2500 g), very low birth weight (<1500 g), and low Apgar score at 1 and 5 min (<7). The diagnoses are reviewed routinely by a trained medical secretary before entry into the database. Data regarding major malformations, diagnosed in newborns or infants who were admitted until the age of 12 months, were collected from the Soroka Medical Center Hospitalization computerized database, which includes demographic information and medical diagnoses [coded by the International Classification of Diseases, Ninth Revision (ICD-9)] of patients admitted to Soroka Medical Center. All clinical information regarding women who underwent pregnancy termination due to medical reasons originated from a non-computerized database collected by the Committee for Termination of Pregnancies at Soroka Medical Center.

2.3 Data Extraction

Because enoxaparin could influence different organs in the different stages of pregnancy, two exposure groups were defined: pregnant women in whom enoxaparin was dispensed at least once from the first day of the last menstrual period until the 13th gestational week were counted as the first-trimester-exposure group, while women in whom enoxaparin was dispensed at least once from the 27th gestational week onwards were classified into the third-trimester-exposure group. The unexposed group in each trimester comprised of women who were not exposed to enoxaparin in the particular trimester.

We used the definitions of major congenital malformations developed by the Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control and Prevention [14] for both live births and pregnancy terminations due to major malformations. In subclass analyses of major malformations, the following specific defects were examined: central nervous system malformations (ICD-9 codes 740–743), cardiovascular malformations (ICD-9 codes 745–747), gastrointestinal malformations (ICD-9 codes 750–751), genitourinary malformations (ICD-9 codes 752–753), and musculoskeletal malformations (ICD-9 codes 754–756). All newborns at Soroka Medical Center are examined by board-certified neonatologists at the neonatology unit after delivery.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS statistics software, version 19 (IBM). Maternal characteristics were compared between the two exposure groups and unexposed pregnancies. The Chi-square test was used to compare categorical variables, and continuous variables were compared using Student's *t* test. Multivariate logistic regression models were constructed to assess the independent risk for adverse pregnancy outcomes following exposure to enoxaparin.

The multivariate models for major malformations were adjusted for mother's age, ethnicity (Bedouin vs. Jewish), parity, diabetes mellitus, repeated pregnancy loss (defined as three consecutive spontaneous abortions), ischemic cardiac disease, perinatal mortality in previous pregnancy, and the year of birth.

All other multivariate models were adjusted for lack of perinatal care, maternal age, parity, ethnicity (Jewish vs. Bedouin Muslim), gestational age, and year of birth/pregnancy termination. In addition, the risk for perinatal mortality was adjusted for maternal diabetes mellitus (gestational and pre-gestational), maternal smoking, major congenital malformations, birth weight, cesarean section, and mortality in previous pregnancies; the risk for low birth weight and very low birth weight was adjusted for major congenital malformations and intrauterine growth restriction; the risk for low Apgar scores was adjusted for major congenital malformations and birth weight; and the risk for maternal bleeding was adjusted for birth weight and maternal fever during labor.

Furthermore, we performed a dose-response analysis between defined daily dose (DDD) dispensed during the first trimester of pregnancy and the rate of major malformations using a multivariate logistic regression. The DDD for enoxaparin is 2 IU [15].

Because significant differences regarding maternal characteristics were found between exposed and unexposed pregnancies, a secondary analysis for total major malformations was performed using propensity score matching (R, the MatchIt package) [16] for both first- and third-trimester exposures. A total of 413 pregnancies exposed to enoxaparin during the first trimester of pregnancy were compared with 1235 matched unexposed pregnancies, and a total of 567 pregnancies exposed to enoxaparin during the third trimester of pregnancy were compared with 1697 matched unexposed pregnancies. The matching was performed such that the propensity for exposure to enoxaparin for every exposed pregnancy was as close as 0.1 standard deviations from the propensity of the matched unexposed pregnancies. The odds ratio (OR) and 95% confidence interval (CI) for total major malformations and perinatal mortality were calculated.

Because the results suggested a non-significantly decreased risk for perinatal mortality following third-trimester exposure to enoxaparin, a question of competing risks bias was raised, such that exposed women have undergone pregnancy termination in a higher proportion compared with delivered pregnancies, and that perinatal mortality may have been more frequent among this group of pregnancies. By excluding terminated pregnancies, a bias could occur, such that exposure is found to be protective against perinatal mortality. To address this question, we performed a sensitivity analysis by defining every terminated pregnancy as being exposed to enoxaparin during the third trimester of pregnancy, and every terminated pregnancy that was exposed to enoxaparin during the first trimester as ending with perinatal mortality.

The study was approved by the Institutional Ethics Committee of Soroka Medical Center.

3 Results

Enoxaparin use during the first trimester of pregnancy increased substantially during the study period, and the rate of exposure during the last year of the study was ninefold higher than during the first year (Fig. 1).

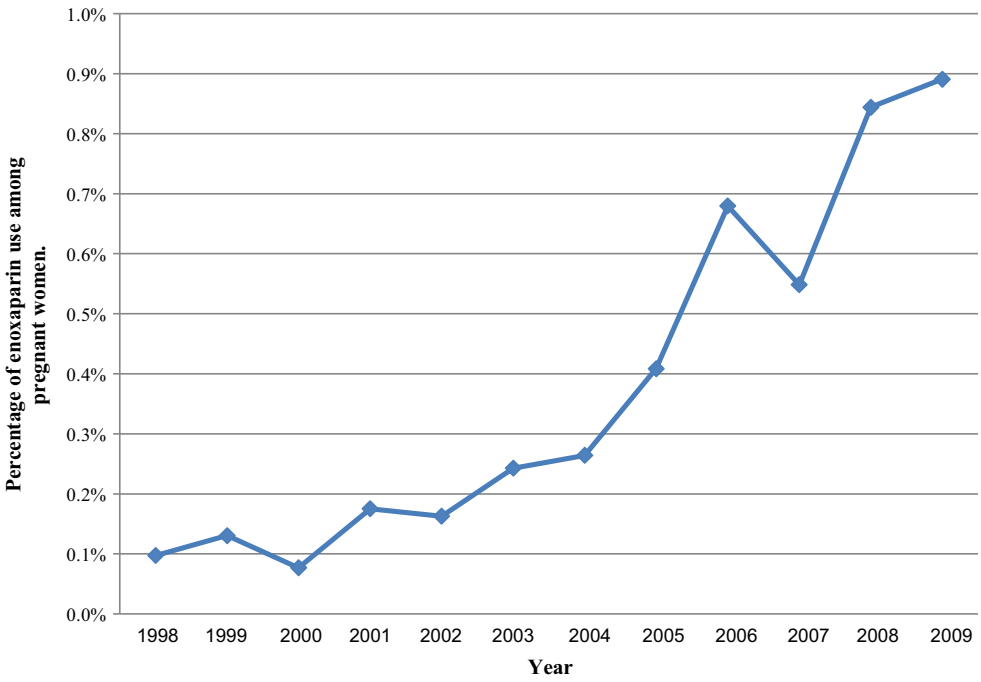

Fig. 1 Enoxaparin exposure rates of pregnant women given the drug during the first trimester of pregnancy, according to the birth year of their offspring or year of pregnancy termination

Among women insured by Clalit Health Services during the study period, there were a total of 114,957 pregnancies, of which 1237 were terminated due to medical reasons. We analyzed 109,473 pregnancies that met the inclusion criteria, of which 108,302 were singleton births and 1171 were pregnancy terminations.

The pattern of exposure to enoxaparin throughout the trimesters is presented in Fig. 2. A total of 418 women were characterized as being exposed to enoxaparin during the first trimester, compared with 109,055 unexposed women; 572 women were defined as being exposed to enoxaparin in the third trimester of pregnancy, compared with 107,342 unexposed women; and 317 women were exposed to enoxaparin during both the first and third trimesters.

The following pattern of exposure occurred among the following groups of pregnancies that were excluded from the study: maternal age older than 45 years or younger than 15 years [8/490 exposed excluded pregnancies (1.6%), compared with 857/114,465 non-excluded (0.7%), $p = 0.024$]; pregnancies that ended before the 27th gestational week [0/536 exposed excluded pregnancies (0%), compared with 865/113,029 non-excluded (0.76%), $p = 0.042$]; pregnancies exposed to other anticoagulation medicines [22/55 exposed excluded pregnancies (40%), compared with 843/114,904 non-excluded (0.73%), $p < 0.001$]; pregnancies exposed to folic acid antagonists [9/646 exposed excluded pregnancies (1.39%), compared with 856/114,313 non-excluded (0.74%), $p = 0.06$]; women diagnosed with inherited thrombophilia [243/360 exposed excluded pregnancies (67.5%), compared with 622/114,599 non-excluded (0.54%), $p < 0.001$]; pregnancies with multiple fetuses [42/4176 exposed excluded pregnancies (1%), compared with 823/110,783 non-excluded (0.74%), $p = 0.054$].

The group exposed to enoxaparin during the first trimester of pregnancy ($n = 418$) comprised 57.7% Jewish women, while the majority of the unexposed group were Bedouins (64.5%, $p < 0.001$). Exposed women were generally older (31.0 ± 5.1 vs. 28.6 ± 5.9 years, $p < 0.001$) and were characterized by slightly lower parity (mean 3.1 ± 1.8 vs. 3.7 ± 2.6, $p < 0.001$) than unexposed women. Furthermore, exposed women had higher rates of diabetes mellitus (2.4 vs. 1.0%, $p = 0.003$) and chronic hypertension (4.1 vs. 1.5%, $p < 0.001$) (Table 1). More than half of the women who were exposed to enoxaparin during the first trimester were diagnosed with recurrent pregnancy loss (52% compared with 5.5% of unexposed women, $p < 0.001$). Significant differences were also found in the rates of prior obstetrical complications, such as placental abruption (6.0 vs. 0.9%), pre-eclampsia (0.7 vs. 0.1%), and perinatal mortality (11.0 vs. 1.9%) (Table 2).

The characteristics of the 572 women exposed to enoxaparin during the third trimester of pregnancy were generally similar to those exposed during the first trimester; however, a smaller proportion of women exposed during the third trimester had a lack of perinatal care compared with the unexposed group (1.7 vs. 9.2%, $p < 0.001$). Overall, gestational age at birth for the exposure group (first and third trimesters) was shorter compared with that of the unexposed group (37.9 ± 2.2 vs. 39.2 ± 2.0 weeks).

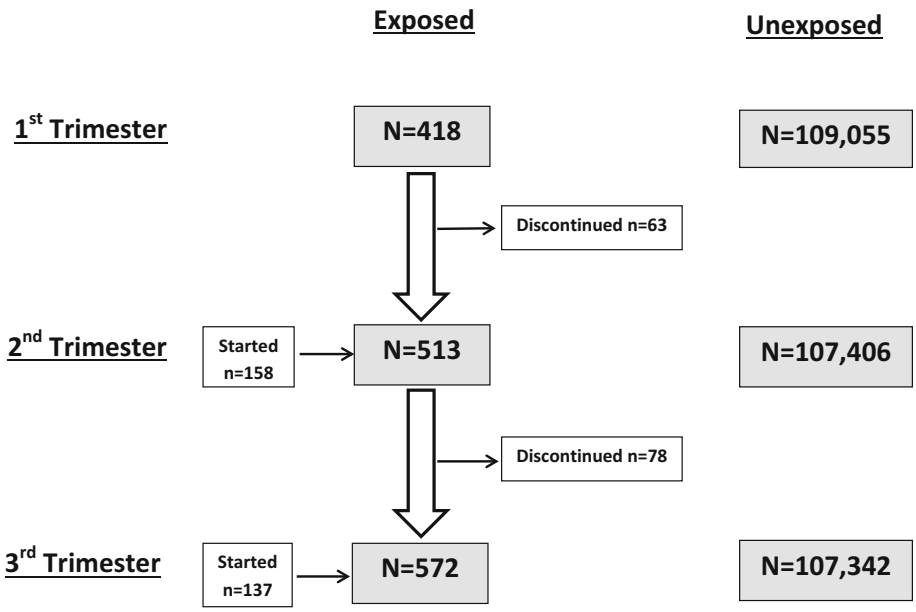

Fig. 2 Pattern of exposure to enoxaparin throughout the trimesters

Table 1 Comparison of maternal characteristics between pregnancies exposed and not exposed to enoxaparin during the first and third trimesters of pregnancy

Characteristics	First-trimester exposure to enoxaparin		*p* value	Third-trimester exposure to enoxaparin		*p* value
	Yes (*n* = 418)	No (*n* = 109,055)		Yes (*n* = 572)	No (*n* = 107,342)	
Maternal age, years (mean ± SD)	31.0 ± 5.1	28.6 ± 5.9	<0.001	31.0 ± 5.4	28.6 ± 5.9	<0.001
Ethnic group						
Jews	241 (57.7)	38,707 (35.5)	<0.001	262 (45.8)	37,723 (35.2)	<0.001
Bedouins	177 (42.3)	70,336 (64.5)		310 (54.2)	69,496 (64.8)	
Maternal smoking	10 (2.4)	2320 (2.1)	0.71	12 (2.1)	2287 (2.1)	0.954
Maternal diabetes mellitus	10 (2.4)	1056 (1.0)	0.003	69 (12.1)	6093 (5.7)	<0.001
Maternal chronic hypertension	17 (4.1)	1611 (1.5)	<0.001	35 (6.1)	1573 (1.5)	<0.001
Parity (mean ± SD)	3.1 ± 1.8	3.7 ± 2.6	<0.001	3.4 ± 2.2	3.7 ± 2.6	0.002
Pregnancy terminations	5 (1.2)	1166 (1.1)	0.808	NA	NA	
Maternal fever during labor	NA	NA	0.016	13 (2.3)	1133 (1.1)	0.011
Lack of perinatal care	8 (1.9)	9893 (9.2)	<0.001	10 (1.7)	9840 (9.2)	<0.001

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *NA* not applicable

A total of 6395 infants (5.8%) were classified with at least one major malformation. These included 906 (14.2%) with central nervous system malformations, 2715 (42.5%) with cardiovascular malformations, 343 (5.8%) with gastrointestinal malformations, 874 (14.7%) with genitourinary malformations, and 1593 (26.7%) with musculoskeletal malformations. The overall rate of major malformations was higher in the first-trimester-exposure group (8.1%) compared with the unexposed group (5.8%; crude OR 1.4, 95% CI 1.0–2.0). However, no significant association was found after adjustment for potential confounders [adjusted OR (aOR) 1.2, 95% CI 0.8–1.7]. Furthermore, no association was found between exposure to enoxaparin and other subclasses of major malformations (Table 3).

No dose response was found between the amount of defined daily doses (DDD) dispensed throughout the first trimester of pregnancy and major malformation (Table 4).

No increased risk was detected for low or very low birth weight (aOR 1.1, 95% CI 0.8–1.4, and aOR 0.8, 95% CI 0.4–2.0, respectively), low Apgar scores at the first and fifth minute (aOR 0.7, 95% CI 0.5–1.0, and aOR 0.9, 95% CI 0.4–1.8, respectively), or for infant bleeding (aOR 1.4, 95% CI 0.4–4.4). On the other hand, an apparent decreased

Table 2 Comparison of maternal medical conditions and indications for enoxaparin between pregnancies exposed and not exposed to enoxaparin during the first and third trimesters of pregnancy

Medical condition	First-trimester exposure to enoxaparin		*p* value	Third-trimester exposure to enoxaparin		*p* value
	Yes (*n* = 418)	No (*n* = 109,055)		Yes (*n* = 572)	No (*n* = 107,342)	
Repeated pregnancy loss	219 (52.5)	6009 (5.5)	<0.001	225 (39.3)	5830 (5.4)	<0.001
Acquired thrombophilia	97 (23.2)	66 (0.1)	<0.001	127 (22.2)	24 (0.02)	<0.001
History of thrombotic event	47 (11.2)	2034 (1.9)	<0.001	107 (18.7)	1961 (1.8)	<0.001
Perinatal mortality in previous gestations	46 (11.0)	2100 (1.9)	<0.001	66 (11.5)	1989 (1.9)	<0.001
Intrauterine growth restriction in previous gestations	25 (6.0)	2542 (2.3)	<0.001	51 (8.9)	2446 (2.3)	<0.001
Placental abruption in previous gestations	25 (6.0)	980 (0.9)	<0.001	38 (6.6)	936 (0.9)	<0.001
Pre-eclampsia in previous gestations	3 (0.7)	109 (0.1)	<0.001	3 (0.5)	108 (0.1)	0.002
Ischemic cardiac disease	8 (1.9)	513 (0.5)	<0.001	10 (1.7)	497 (0.5)	<0.001
Ischemic cerebrovascular disease	8 (1.9)	16 (0.015)	<0.001	15 (2.6)	8 (0.007)	<0.001

Data are expressed as *n* (%)

Table 3 Odds ratios (adjusted and unadjusted) for major congenital malformations following intrauterine exposure to enoxaparin during the first trimester of pregnancy

Congenital malformations	Exposure to enoxaparin		OR (95% CI)	
	Yes (*n* = 418) (%)	No (*n* = 109,055) (%)	Adjusted[a]	Unadjusted
Total major congenital malformations	34 (8.1)	6361 (5.8)	1.1 (0.8–1.6)	1.4 (1.0–2.0)
CNS	9 (2.2)	897 (0.8)	2.0 (0.9–4.0)	2.7 (1.4–5.2)
CVS	13 (3.1)	2704 (2.5)	1.0 (0.6–1.7)	1.3 (0.7–2.2)
Gastrointestinal	2 (0.5)	341 (0.3)	1.5 (0.4–6.2)	1.5 (0.4–6.2)
Genitourinary	3 (0.7)	871 (0.8)	0.8 (0.3–2.6)	0.9 (0.3–2.8)
Musculoskeletal	8 (1.9)	1585 (1.5)	1.2 (0.6–2.5)	1.3 (0.7–2.7)

OR odds ratio, *CI* confidence interval, *CNS* central nervous system, *CVS* cardiovascular

[a] The ORs for all outcomes were adjusted for maternal age, ethnicity, parity, pre-gestational diabetes, recurrent pregnancy loss, and year of birth/pregnancy termination. The ORs for CNS, CVS, and total major malformations were also adjusted for cardiac morbidity and a history of perinatal death. The ORs for CNS malformation were additionally adjusted for folic acid consumption

Table 4 Risk (adjusted ORs and 95% CIs) for major congenital malformations following exposure to enoxaparin according to levels of defined daily dose (results from a multivariate logistic regression model)

Total number of DDDs[a]	Major congenital malformations *n/N* (%)[c]	Adjusted OR[b] (95% CI)
None	6361/109,055 (5.8)	1 (reference category)
2–76	13/154 (8.4)	1.2 (0.7–2.2)
77–126	11/150 (7.3)	1.0 (0.5–1.9)
127 and more	5/109 (4.6)	0.7 (0.3–1.6)

OR odds ratio, *CI* confidence interval, *DDD* defined daily dose

[a] DDD is the assumed average maintenance dose per day for a drug when it is used in adults for its main indication

[b] ORs are adjusted for mother's age, ethnicity (Bedouin vs. Jewish), parity, diabetes mellitus, repeated pregnancy loss, ischemic cardiac disease, perinatal mortality in a previous pregnancy, year of birth

[c] The amount of DDD was missing for five pregnant women

Table 5 Odds ratios (adjusted and unadjusted) for adverse birth outcomes following intrauterine exposure to enoxaparin during the third trimester of pregnancy

Adverse birth outcomes	Exposure to enoxaparin		OR (95% CI)	
	Yes (n = 572) (%)	No (n = 107,342) (%)	Adjusted[a]	Unadjusted
Low birth weight (<2500 g)	106 (18.5)	8370 (7.8)	1.1 (0.8–1.4)	2.7 (2.2–3.3)
Very low birth weight (<1500 g)	14 (2.4)	978 (0.9)	0.8 (0.4–2.0)	2.7 (1.6–4.7)
Apgar first min ≤7	37 (6.5)	5808 (5.5)	0.7 (0.5–1.0)	1.2 (0.9–1.7)
Apgar fifth min ≤7	8 (1.4)	881 (0.8)	0.9 (0.4–1.8)	1.7 (0.8–3.4)
Infant bleeding	3 (0.5)	229 (0.2)	1.4 (0.4–4.4)	2.5 (0.8–7.7)
Perinatal mortality	6 (1.0)	1060 (1.0)	0.6 (0.1–2.9)	1.1 (0.5–2.9)

OR odds ratio, *CI* confidence interval

[a] All multivariate models were adjusted for lack of perinatal care, maternal age, parity, ethnicity (Jewish vs. Bedouin Muslim), gestational age, and year of birth/pregnancy termination. The risk for perinatal mortality was also adjusted for maternal diabetes mellitus (gestational and pre-gestational), maternal smoking, major congenital malformations, birth weight, cesarean section, maternal diabetes, and mortality in previous pregnancies. The risk for low birth weight and very low birth weight was also adjusted for major congenital malformations and intrauterine growth restriction. The risk for low Apgar scores was also adjusted for major congenital malformations and birth weight. In addition, the risk for infant bleeding was also adjusted for birth weight and maternal fever during labor

risk for perinatal death (aOR 0.6, 95% CI 0.1–2.9) was observed (Table 5).

No increased risk was found in a secondary analysis using propensity score matching for total major malformations following first-trimester exposure to enoxaparin (OR 0.99, 95% CI 0.64–1.49) (see electronic supplementary material 1). A non-significant decreased risk for perinatal mortality was found for mortality following third-trimester exposure to enoxaparin using propensity score matching (OR 0.40, 95% CI 0.12–1.04) (see electronic supplementary material 2).

In a sensitivity analyses, a non-significant protective association was found between third-trimester exposure to enoxaparin and perinatal mortality (OR 0.67, 95% CI 0.15–3.03, p = 0.61).

4 Discussion

Exposure to enoxaparin during pregnancy was not associated with an increased risk of major malformations. Furthermore, no association was found between third-trimester exposure and adverse birth outcomes.

Due to the size of its molecule, enoxaparin is not likely to cross the placenta to significantly affect the fetus, for example, through increased bleeding; however, enoxaparin does have important interactions at the level of the placenta. For example, in women with antiphospholipid antibodies-induced trophoblast damage, enoxaparin has been shown to reverse such pathologies. Although it is not expected that the drug would increase fetal damage through trophoblast interactions, it may affect bleeding propensity at the placental level [17].

Our cohort includes not only major malformations diagnosed in newborns after delivery by board-certified neonatologists, but also diagnoses performed during hospitalizations up to 12 months of age. In addition, the study contains diagnoses performed on fetuses from pregnancy terminations for medical reasons. This could explain the relatively high rate of malformations in this study compared with previous studies. Furthermore, previous studies reported higher rates of malformation among the Bedouin compared with Jewish newborns [18, 19], a finding that has been attributed to high rates of consanguinity among Bedouins.

The cohort databases contain data regarding alcohol abuse. Because a large portion of the Southern District's women population comprises religious Jewish or Bedouin-Muslim communities, and because women of childbearing age in these communities rarely consume alcohol, none of the women in our study was diagnosed with alcohol abuse.

Because significant differences were found regarding maternal characteristics between exposed and unexposed pregnancies, a secondary analysis using propensity score matching was performed for total major malformations and perinatal mortality. Similar results were found.

Furthermore, the non-significant decreased risk for perinatal mortality raised a question of competing risks bias, such that exposed women have undergone pregnancy termination in a higher proportion compared with delivered pregnancies, and that perinatal mortality may have been more frequent among this group of pregnancies. A sensitivity analysis, performed by defining an extreme situation in which every terminated pregnancy was classified as exposed to enoxaparin during the third trimester of pregnancy, and every terminated pregnancy that was exposed to

enoxaparin in the first trimester was defined as ending with perinatal mortality, demonstrated a similar non-significant protective association between third-trimester exposure and perinatal mortality.

To the best of our knowledge, to date only one population-based study focused on enoxaparin safety during pregnancy. Unfortunately, this was a descriptive report that lacked an analytical comparison with a control group [20]. Other small studies reported conflicting results. Badawy et al. did not find an association between enoxaparin exposure during pregnancy and congenital malformations, low Apgar scores, or lower birth weight [21]. Gris and colleagues studied pregnant women who had placental vascular complications in previous gestations and found reduced risks of low birth weight and Apgar scores in women treated with enoxaparin [9, 10]. In our population-based study, only a small proportion of exposed women had previous placental vascular complications, which can explain the diverging results.

Our finding of a potential association, although not significant, between enoxaparin exposure during the third trimester and the reduced risk for perinatal death was not shown in previous studies. Hereditary thrombophilias are relatively common in the general population but are often undiagnosed and untreated [22]. Some unexposed women might have had undiagnosed, and therefore untreated, thrombophilias, hence possibly raising the mortality rate among unexposed pregnancies compared with exposed pregnancies.

Our study used data on drugs dispensed for pregnant woman from the Clalit Health Services computerized database, but information regarding adherence to therapy were not available. However, previous studies using the same database found the rate of adherence to be higher than 90% for women with deep vein thrombosis and familial Mediterranean fever [23]. Furthermore, previous studies demonstrated high rates of concordance between computerized pharmacy records and medication use in general [24–26], specifically for pregnant women [27].

Information about smoking status was self-reported and may underestimate the actual rate of smoking during pregnancy. Since there is no reason to assume the women in the exposure groups differed in their willingness to truthfully report their smoking habits, this is an unlikely source of bias.

5 Conclusion

First-trimester exposure to enoxaparin was not associated with an increased risk of major malformations in general, or according to organ systems, but risk for specific malformations cannot be ruled out. Third-trimester exposure to enoxaparin was found to be safe.

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Compliance with Ethical Standards

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Conflict of interest Meital Shlomo, Rafael Gorodischer, Sharon Daniel, Arnon Wiznitzer, Ilan Matok, Boris Fishman, Gideon Koren, and Amalia Levy have no conflicts of interest to declare that are directly relevant to the content of this study.

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