

HIGH PRESCRIPTION OF LOW MOLECULAR WEIGHT HEPARINS DURING PREGNANCY IN A HOSPITAL IN TETOVO, THE REPUBLIC OF MACEDONIA

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Abstract

Background: This study sought to explore the increase of usage of low molecular weight heparins (LMWH), for venous thromboembolism (VTE) treatment and prophylaxis during the period of pregnancy. **Materials and methods:** A retrospective study was undertaken during 01 January – 31 June of 2013, in the Department of Gynecology and Obstetrics, at Clinical Hospital in Tetova. Data were collected for the following: patient demographics, week and month of pregnancy, number of pregnancies for each patient, diagnosis, drug details and the cost for the entire period of hospitalization. **Results:** Over six months, the total number of pregnant women was 1020, from that number, 366 (35.88 %) were prescribed LMWH. Majority of patients given LMWH were aged 25-30, 196 (53.55 %). Clexane 2000 UI and Fraxiparine 0.4UI, were the most prescribed anticoagulant, 98 (26.78 %), respectively 97 (26.50 %) of patients received this therapy. The most common diagnosis that was found in the study was nonpathological pregnancy associated with high levels of D-dimers 177 (48.36 %) patients. **Conclusions:** The results of this study indicate that there is an urgent need to improve the prescription of anticoagulants in the Department of Gynecology and Obstetrics, Clinical Hospital of Tetova, Republic of Macedonia.

Keywords: Pregnancy; Anticoagulants; Prescription; Low molecular weight heparin

Introduction

Anticoagulant treatment for deep-vein thrombosis aims to prevent pulmonary embolism and recurrent thrombosis and also to avoid excessive bleeding. In addition, both the effect of therapy on the patients' well-being and the cost of therapy are factors to be weighed in determining the optimal treatment. It is current practice to treat acute venous thrombosis with intravenous standard (unfractionated) heparin for at least five days in a dose adjusted to lengthen the activated partial-thromboplastin time into a desired range (Koopman M, et al, 1996). LMWHs are effective and indicated for the prevention of venous thromboembolism, for the treatment of venous thrombosis, for the treatment of patients with unstable angina (Jack H, et al, 2001), LMWH do not cross the placenta (Dimitrakakis C, et al, 2000)(Omri A, et al, 1989)(Robin F, et al 1999) and have several clinical advantages over un-fractionated heparin. Their bioavailability is better, with a half life two to four times longer than un-fractionated heparin. The biological monitoring is reduced, and LMWH are easier to use with one or two daily injections, a feature that is particularly attractive to physicians and patients (Philippe D, et al, 2007).

Women with a history of VTE (with or without thrombophilia) are believed to have a higher risk of recurrence in subsequent pregnancies (Ginsberg J, et al, 2001). Estimates of the rate of recurrent venous thrombosis during pregnancy in women with a history of VTE have varied between zero and 13% (De Swieet M, et al, 1987)(Tengborn L, et al 1989)(Ginsberg J, et al, 2001). Treatment of VTE with LMWH has come of age. A large body of data for several of these products has been provided by well-designed clinical trials that featured clinically relevant end points. Estimates of treatment effect are available with acceptable confidence intervals. Treatment effects appear generalize, i.e., they apply to large populations of patients with VTE (10Carman, et al, 1999). Although the prevalence of clinically significant maternal heart disease during pregnancy is low (probably less than 1 percent) (Siu SC, et al, 2001), its presence increases the risk of adverse maternal, fetal and neonatal outcomes (Siu SC, et al, 2002). The aim of this study was to describe the consumption of anticoagulants, respectively low molecular weight heparins along pregnancy, in the Department of Gynecology and Obstetrics, at Clinical Hospital in Tetova.

Material and Methods

Study design

We collected data on low molecular weight heparins prescription, from the Hospital Archive during the period of six months from 1st January to 31st June 2013. Data were collected retrospectively from medical record of eligible patients. The collection started in October and finished in December 2013.

Data collection procedure

Data were collected for the following: patient demographics, week and month of pregnancy, number of pregnancies for each patient, duration of hospital stay, clinical and laboratory investigations, diagnosis, drug details; which include the name of the drug, dosage form, dose frequency, total cost of the drug, the amount of each given ampoule application and the cost for the entire period of hospitalization.

Results

Patient's demographic characteristics

Among the total number of 1020 pregnant women, 366 (35.88%) were prescribed low molecular weight heparins. The age range of pregnant women who visited the Department of Gynecology and Obstetrics was between 18 and 49 and the group with the highest attendance was 25 – 35: 196 (53.55 %) patients. The risk of adverse fetal outcomes was also substantially greater among women older than 35 years of age or younger than 20 years of age than among women between these ages with similar risk factors. Indexes of risk derived from and validated in this population may be used in the counseling of women before conception (13Reimold Sh, et al 2003). 101 (27.60 %) of the patients were from Tetova and the urban places around and the biggest number, 265 (72.40 %) patients, came from rural parts (villages) around Tetova and Gostivar. Patients' characteristics are summarized in Table 1.

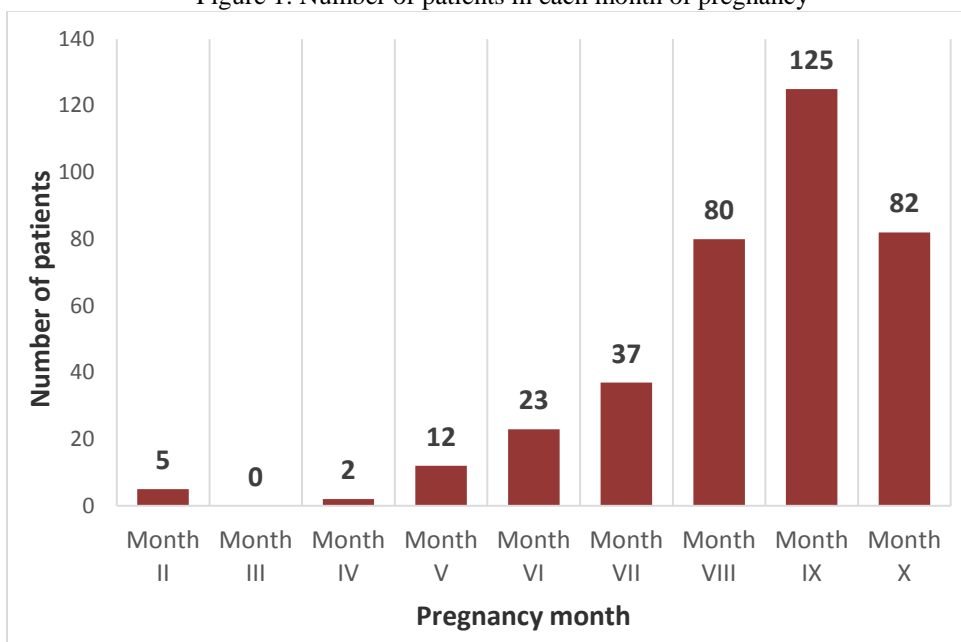
Table 1. Patient's demographic characteristics.

Age	Total frequency (N)	Percent (%)
18-20	2	0.55
21-24	46	12.57
25-30	196	53.55
31-35	79	21.58
>35	43	11.75
Living place	Total frequency (N)	Percent (%)
Urban	101	27.60
Rural	265	72.40

Ordinal number and the months of pregnancy

For 231 women (63.11 %) this was their first pregnancy, 68 (18.57 %) declared that this is their second, followed by 67 (18.31 %) for which this was their third, fourth or fifth pregnancy. The earliest stage of using LMWH was the second month of pregnancy, 5 (1.37 %) pregnant women received anticoagulant therapy over that month. The most common patients were women in the ninth month 125 (34.15 %), followed by them in the last month of pregnancy 82 (22.40 %). The detailed explanation about months of pregnancy is given in the Figure 1.

Figure 1. Number of patients in each month of pregnancy



Percentage share on usage of different classes of LMWH

The biggest percentage of patients, 26.78 % received Clexane (enoxaparin) 4000 IU anti-Factor XA in 0.4ml, followed by them with Fraxiparine (nadroparin calcium) 2850 IU anti-Factor XA in 0.3 ml, 26.50 %. 25.96 % of patients was prescribed Fraxiparine (nadroparin calcium) 3800 IU anti-Factor XA in 0.4 ml and Clexane (enoxaparin) 2000 IU anti-Factor XA in 0.2 ml received 20.22 %. Fragmine (dalteparin sodium) 5000 IU anti-Factor XA in 1 ml was the less anticoagulant prescribed, 0.54%.

Frequency of Diagnosis

The most common diagnosis that was found in the study was nonpathological pregnancy, associated with high levels of D-dimers 177 (48.36 %). 76 patients (20.76 %) were diagnosed hypercoagulable, 62 (16.93 %) had risky pregnancies and 9 (2.5 %) of them were carrying twins. 42

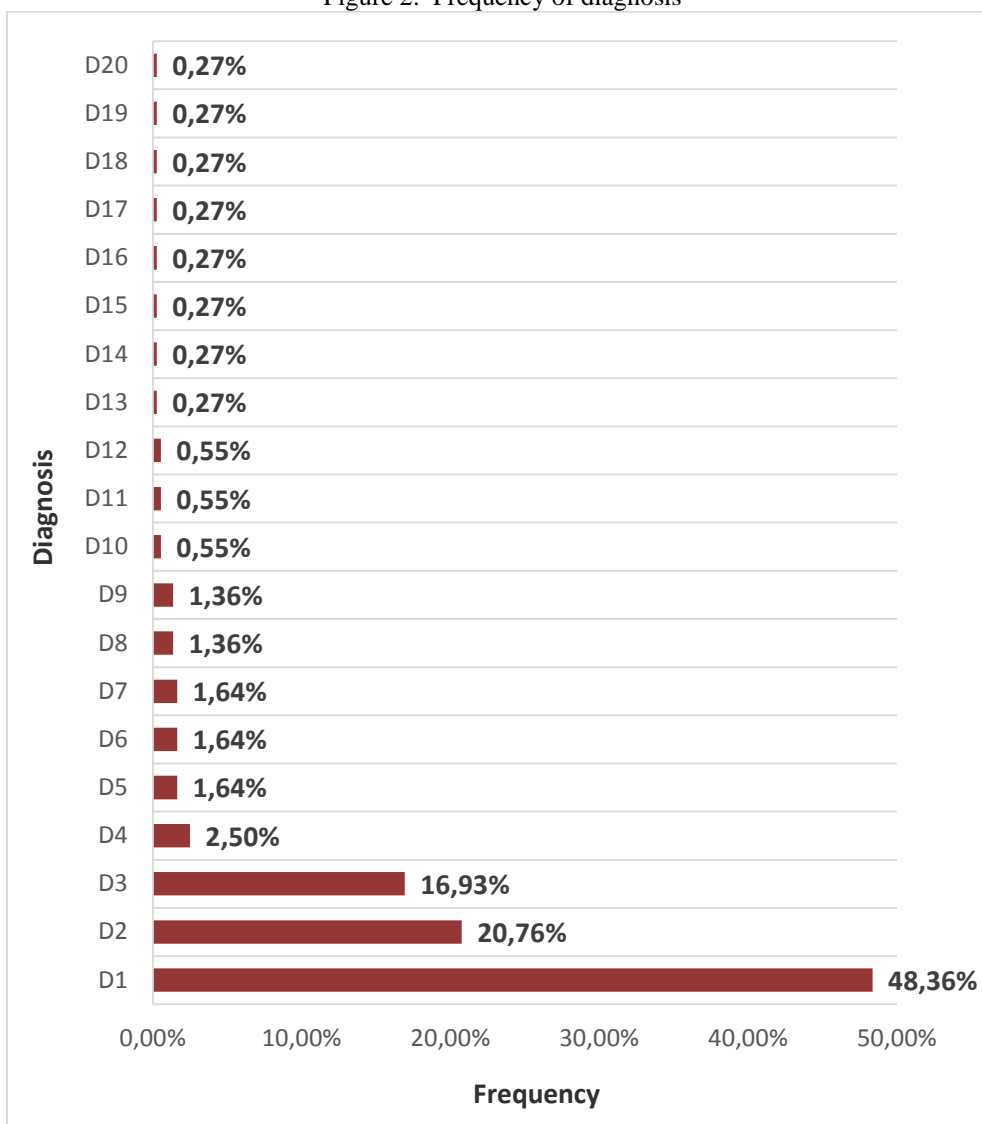
(11.45 %) patients had other diagnosis: pregnancy after IVF, pregnancy associated with diabetes mellitus, pregnancy associated with low levels of albumines and pregnancy after some miscarriages were among them (Table 2, Figure 2).

Table 2. Frequency of diagnosis

Diagnosis ID	Type of diagnosis	Total frequency (N)	Percent (%)
D1	Nonpathological pregnancy	177	48.36%
D2	Hyperthrombotical pregnancy	76	20.76%
D3	Risky pregnancies	62	16.93%
D4	Pregnancy with twins	9	2.5%
D5	Pregnancy afer some miscarriages	6	1.64%
D6	Gestosis pregnancy	6	1.64%
D7	Hypothrombotical pregnancy + hypoalbuminemia	6	1.64%
D8	Pregnancy afer IVF	5	1.36%
D9	EPH gestosis pregnancy	5	1.36%
D10	Pregnancy associated with hypoalbuminemia	2	0.55%
D11	Varices cruris pregnancy (Pregnant women with varicose veins)	2	0.55%
D12	Eph gestosis pregnancy + hypoalbuminemia	2	0.55%
D13	Pregnancy after FM In utero	1	0.27%
D14	SGA Pregnancy (small for gestational age)	1	0.27%
D15	Varices Valvulae pregnancy	1	0.27%
D16	Hyperthrombotical pregnancy + hypotensio	1	0.27%
D17	Risky pregnancy + Diabetes Mellitus	1	0.27%
D18	Hyperthrombotical + E gestosis pregnancy	1	0.27%
D19	Pregnancy after abruption of placenta	1	0.27%
D20	Pregnancy + fracturae tibia	1	0.27%

Compared with a year earlier, the number of patients with heparin treated with low molecular mass (low molecular weight heparin) is growing. From 1 January to 31 December 2012, the total number of pregnancy, 1447, 298 (20.60 %) of them were treated with anticoagulants.

Figure 2. Frequency of diagnosis



Discussion

To our knowledge, this is one of the first studies to investigate the prescription of anticoagulants in this hospital. Compared with a year earlier, the number of patients treated with low molecular weight heparins is growing. From 1 January to 31 December 2012 the total number of pregnancy, 1447, 298 (20.60 %) of them were treated with anticoagulants. In the period of 1 January to 30 June 2013, this number marks the doubling of cases. While for the entire year 2012, the number of patients treated was 298, only for the first six months of 2013, the number of patients was 366 (35.88 % respectively of the total number of pregnancy, which was in 1020)

For as much as they are safe for the baby, because they do not allow passing placental barrier, this therapy is being used increasingly. However, in our hospital, this number is too high, compared with other countries, thing which requires a detailed study about prescribing these medicines.

In pregnancy, however, long-term administration of heparin or LMWH is preferred to prevent systemic embolism in women with medical mechanical heart valves, and to prevent fetal loss in women with antiphospholipid antibodies. In all these instances the long-term use of heparin or LMWH carries a risk of osteoporosis (Griffith Sh, et al, 1965)(Monreal M, et al, 1994)(Jack H, et al 2001).

Significant reductions in bone density have been reported in about 30 % of patients, and symptomatic vertebral fractures occur in 2 to 3 % of patients receiving heparin for 1 month or more (Dahlman TC.1993)(Jack H, et al 2001).

The current American College of Chest Physicians guidelines recommend testing of women with adverse pregnancy outcomes (recurrent pregnancy loss, prior sever or recurrent preeclampsia, abruptions, or otherwise unexplained intrauterine death) for congenital thrombophilias and antiphospholipid antibodies, and offering treatment to such women, if thrombophilic with low-dose aspirin plus prophylactic heparin (unfractionated or LMWH) (Bates SM, et al 2004).

Limitations

Even though our study was not prospective and randomized, we have made control of all documents included in the medical chart for each patient individually. However there are cases when patients repeated, e.g. a pregnant woman receives therapy from the beginning of pregnancy until the end of it. And in our analysis, identified as a different patient, each time it is presented to the hospital to receive anticoagulants.

Despite this limitation this study has identified significant increase of prescribing these drugs, resulting in an irrational use of anticoagulants during pregnancy in Tetova, the Republic of Macedonia.

Conclusion

Indeed the benefits from the use of LMWH cross the undesirable side effects. Even though the prices are quite high used during the period of pregnancy. Careful management, however, is necessary for women treated with heparins. The results of this study indicate there is an urgent need to improve the prescription of anticoagulants in the Department of Gynecology and Obstetrics, Clinical Hospital of Tetova, Republic of Macedonia.

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