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## Venous Thromboembolism Risk and Adequacy of Prophylaxis in High Risk Pregnancy in the Arabian Gulf



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**Abstract: Objectives:** To estimate the prevalence of venous thromboembolism (VTE) risk factors in pregnancy and the proportion of pregnancies at risk of VTE that received the recommended prophylaxis according to the American College of Chest Physicians (ACCP) 2012 published guidelines in antenatal clinics in the Arabian Gulf.

**Methods:** The evaluation of venous thromboembolism (EVE)-Risk project was a non-interventional, cross-sectional, multi-centre, multi-national study of all eligible pregnant women ( $\geq 17$  years) screened during antenatal clinics from 7 centres in the Arabian Gulf countries (United Arab Emirates, Kuwait, Bahrain, Qatar and Oman). Pregnant women were recruited during a 3-month period between September and December 2012.

**Results:** Of 4,131 screened pregnant women, 32% ( $n=1,337$ ) had  $\geq 1$  risk factors for VTE. Common VTE risk factors included obesity (76%), multiparity (33%), recurrent miscarriages (9.1%), varicose veins (6.9%), thrombophilia (2.6%), immobilization (2.0%), sickle cell disease (2.8%) and previous VTE (1.6%). Only 8.3% ( $n=111$ ) of the high risk patients were on the recommended VTE prophylaxis. Enoxaparin was used in 80% ( $n=89$ ) of the cases followed by tinzaparin (4%;  $n=4$ ). Antiplatelet agents were prescribed in 11% ( $n=149$ ) of pregnant women. Of those on anticoagulants ( $n=111$ ), 59% ( $n=66$ ) were also co-prescribed antiplatelet agents. Side effects (mainly local bruising at the injection site) were reported in 12% ( $n=13$ ) of the cases.

**Conclusion:** A large proportion of pregnant women in the Arabian Gulf countries have  $\geq 1$  VTE risk factor with even a smaller fraction on prophylaxis. VTE risk assessment must be adopted to identify those at risk who would need VTE prophylaxis.

**Keywords:** Venous thromboembolism, deep vein thrombosis, antiplatelet, anticoagulation, pregnancy, Middle East.

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### INTRODUCTION

Venous thromboembolism (VTE) is one of the leading causes of mortality and morbidity during pregnancy and postpartum period [1]. It has been estimated that VTE occurs in 1 in 1,000 to 1 in 2,000 pregnancies, representing a 10-fold increase in the risk of VTE in pregnant women compared with non-pregnant women of the same childbearing age [2]. Deep venous thrombosis (DVT) constitutes 85% of all pregnancy-related symptomatic events, with roughly two thirds of all DVT cases occurring in the ante-partum period while half of these events occur before the third trimester [3]. In contrast, pulmonary embolism (PE) is relatively less

frequent during pregnancy but may be more frequent than DVT in the postpartum period [4].

High risk pregnant women include those with the following risk factors: past history of VTE, hereditary thrombophilia, antiphospholipid syndrome, prolonged immobilization, recurrent foetal loss and surgical intervention [3, 5]. Morbid obesity, the use of oestrogens in pregnancy and increased parity have also been recognized as potential risk factors for VTE in pregnancy [6, 7].

In pregnancy, the use of the anticoagulant, warfarin to prevent DVTs, can be associated with potential side effects to the mother and the foetus as it crosses the placenta and can cause bleeding and embryopathy [8]. Therefore, warfarin should generally be avoided during pregnancy. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) do not cross the placenta and thus appear to be safe to the foetus; however, side effects like bleeding, thrombocy-

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topenia and osteoporosis have been reported [9, 10]. The bleeding potential in the mother treated with UFH or LMWH is low and does not appear to be different from that reported in non-pregnant subjects [10]. LMWH probably causes less osteoporosis and thrombocytopenia than UFH [11, 12]. UFH, LMWH and warfarin are safe for the breast-fed infant when administered to the nursing mother [13].

Lessons learned from the global ENDORSE study on inadequate prophylaxis of medical and surgical patients, who were at risk of VTE in acute care centres, have raised questions concerning the level of awareness among health care professionals on issues related to VTE risk assessment and proper utilization of prophylactic measures during every day medical practice [14]. In pregnancy, similar studies are scarce. Hence, the primary objectives of this study were to estimate the prevalence of pregnant women with VTE risk factors in every day practice in antenatal clinics, as well as, to determine the proportion of these high risk women who received the recommended VTE prophylaxis according to the American College of Chest Physicians (ACCP) 2012 guidelines [15] in antenatal clinics in the Arabian Gulf countries. The secondary objectives of the study were to determine the types of anticoagulants in daily use and their side effects.

## METHODS

The evaluation of venous thromboembolism (EVE-Risk study) was a multi-national, multi-centre, non-interventional, observational, and cross sectional study in the Arabian Gulf. The selected maternity centres were located in the following countries: United Arab Emirates (UAE) (3 centres), Kuwait (1 centre), Bahrain (1 centre), Qatar (1 centre) and Oman (1 centre). Data was captured using data collection forms. The patients were evaluated at a single visit during a pre-defined study enrolment period of approximately 3 months duration (from 23 September 2012 to December 20, 2012). The information on VTE risk factors and prophylaxis with anticoagulants including related bleeding complications was recorded retrospectively. Follow up data collection was beyond the scope of this study.

The study included data of pregnant women who were  $\geq 17$  years of age with  $\geq 1$  of the following risk factors for VTE: past history of VTE, hereditary thrombophilia, antiphospholipid syndrome, recurrent foetal loss, immobilization, surgical intervention during pregnancy, morbid obesity (defined as documentation of morbid obesity in the patient hospital information system or of body mass index of  $>30$  kg/m<sup>2</sup> if weight and height were available), oestrogen use, multiparity ( $\geq 2$  pregnancies) and others (as justified by the treating obstetrician). The exclusion criteria included pregnant women who did not provide informed written consent as well as those with recent (*i.e.* pre-pregnancy) VTE or arterial occlusion and on full dose of anticoagulant therapy. Patient files with missing or incomplete data were also excluded. The case record form (CRF) included demographic data, obstetric risk factors for VTE, type of VTE prophylaxis and dosage, antiplatelet agent (aspirin) use, and types of bleeding complications that were attributed to VTE prophylaxis and antiplatelet agents. Patients data especially name, social number, telephone number and file number were kept

strictly confidential. Each CRF was identified with a unique number, which was referred to, for case identification. Data entry of the EVE-Risk registry was made by a research assistant with data verification (random 5%) performed by the biostatistician for the registry.

The study was conducted in accordance with the Declaration of Helsinki. The appropriate Research and Ethics committee in each of the participating centres approved the study. Informed written consents were also obtained from all patients enrolled in the study.

## STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analysed using Pearson's  $\chi^2$  or Fishers exact tests, as appropriate. For continuous variables, mean and standard deviation (SD) were used to present the data while analysis was performed using univariate ordinary least squares (OLS) regression. An *a priori* two-tailed level of significance was set at 0.05. Statistical analyses were performed using STATA version 13.1 (STATA Corporation, College Station, TX, USA).

## RESULTS

Of 4,131 screened pregnant women, a total of 32% (n=1,337) had  $\geq 1$  VTE risk factors. This included 608 (45%) from the UAE, 194 (15%) from Bahrain, 220 (16%) from Kuwait, 115 (9%) from Oman and 200 (15%) from Qatar. Demographic and clinical characteristics are shown in Table 1. The overall mean age of the cohort was  $33 \pm 6$  years, ranging from 17 - 50 years with significant differences between the countries ( $P < 0.001$ ). The overall mean gestational age was  $30 \pm 8$  weeks with significant differences among the participating countries ( $P < 0.001$ ).

Risk profile characteristics are summarized in Table 1. The overall prevalence of obesity in the study population was 76%, highest in Qatar and Kuwait (86%) and lowest in Oman (23%) ( $P < 0.001$ ). There were also significant differences in the prevalence of multiparity among participating countries ( $P < 0.001$ ); highest in Oman (60%) and lowest in Kuwait (17%). Recurrent miscarriages (9.1%) was the third most prevalent risk factor; highest in Oman (17%) and lowest in the UAE (3.1%) ( $P < 0.001$ ). Approximately 32% of the study population had  $\geq 1$  risk factor for VTE.

Anticoagulants were prescribed in 8.3% (n=111) of the pregnant women with  $\geq 1$  VTE risk factor (see second paragraph of Introduction for list of risk factors). Enoxaparin was the most commonly prescribed anticoagulant (80%). There were significant differences in enoxaparin use among the countries with the highest use in Oman (21%) and lowest in Qatar (3%) ( $P < 0.001$ ). Other anticoagulants were prescribed less frequently (Table 2). Table 3 summarizes antiplatelet and anticoagulant use in high risk pregnancies. Antiplatelet agents were administered in 11% (n=149) of the subjects; with the highest rate in Oman (27%; n=31) and lowest in Qatar (2.5%; n=5) ( $P < 0.001$ ). Of those on anticoagulants (n=111), 59% (n=66) were also co-prescribed antiplatelet agents. The combination of anticoagulants and antiplatelet agents was mostly prescribed for those pregnant women with

**Table 1. Demographic and risk profile characteristics of the evaluation of the study cohort country-wise.**

Characteristic	All (n=1,337)	UAE (n=608)	Bahrain (n=194)	Kuwait (n=220)	Oman (n=115)	Qatar (n=200)	P-value
Age, mean $\pm$ SD, years	33 $\pm$ 6	33 $\pm$ 6	33 $\pm$ 6	32 $\pm$ 6	34 $\pm$ 6	32 $\pm$ 6	<0.001
Risk, n (%)							
Obesity	1,014 (76%)	493 (81%)	133 (69%)	190 (86%)	27 (23%)	171 (86%)	<0.001
Multiparity	441 (33%)	230 (38%)	53 (27%)	38 (17%)	69 (60%)	51 (26%)	<0.001
Miscarriage	121 (9.1%)	19 (3.1%)	42 (22%)	17 (7.7%)	20 (17%)	23 (12%)	<0.001
Varicose veins	92 (6.9%)	31 (5.1%)	4 (2.1%)	14 (6.4%)	2 (1.7%)	41 (21%)	<0.001
Thrombophilia	34 (2.6%)	10 (1.6%)	8 (4.1%)	3 (1.4%)	11 (9.6%)	2 (1.0%)	<0.001
Immobilization	26 (2.0%)	7 (1.2%)	12 (6.2%)	1 (0.5%)	3 (2.6%)	3 (1.5%)	<0.001
VTE	21 (1.6%)	7 (1.2%)	3 (1.6%)	2 (0.9%)	7 (6.1%)	2 (1.0%)	0.004
SCD	37 (2.8%)	0	26 (13%)	0	11 (10%)	0	<0.001
Risk factors, n (%)							
1	908 (68%)	416 (68%)	113 (58%)	171 (78%)	84 (73%)	124 (62%)	<0.001
2	382 (29%)	184 (30%)	69 (36%)	43 (20%)	26 (23%)	60 (30%)	0.002
$\geq 3$	47 (3%)	8 (1.3%)	12 (6.2%)	6 (2.7%)	5 (4.4%)	16 (8.0%)	<0.001

Abbreviations: *SD* standard deviation, *VTE* venous thromboembolism, *SCD* sickle-cell disease, *UAE* United Arab Emirates.

Obesity was defined as documentation of obesity in the patient hospital information system or of body mass index of  $>30$  kg/m<sup>2</sup> if weight and height were available. Multiparity =  $\geq 2$  pregnancies.

Analyses were performed using univariate ordinary least squares (OLS) regression, Pearson's  $\chi^2$  test, and Fisher's exact test, wherever appropriate.

**Table 2. Prophylactic anticoagulant use of the study cohort country-wise.**

Anticoagulant	All (n=1,337)	UAE (n=608)	Bahrain (n=194)	Kuwait (n=220)	Oman (n=115)	Qatar (n=200)	P-value
LMWH							
Enoxaparin	89 (6.7%)	24 (4.0%)	16 (8.3%)	19 (8.6%)	24 (21%)	6 (3.0%)	<0.001
Tinzaparin	4 (0.3%)	4 (0.7%)	0	0	0	0	0.653
Vitamin K antagonist	2 (0.2%)	1 (0.2%)	0	0	1 (0.9%)	0	0.375
Not defined	16 (1.2%)	2 (0.3%)	4 (2.1%)	3 (1.4%)	5 (4.4%)	2 (1.0%)	0.005
Total	111 (8.3%)	31 (5.1%)	20 (10%)	22 (10%)	30 (26%)	8 (4.0%)	<0.001

Abbreviations: *LMWH* low molecular-weight heparin, *UAE* United Arab Emirates.

Analyses were performed using Pearson's  $\chi^2$  test or Fisher's exact test, wherever appropriate.

**Table 3.** Use of antiplatelet, anticoagulant or both, in pregnant women with various VTE risk factors (n=194).

Characteristic	Antiplatelet Alone (n=83)	Anticoagulation Alone (n=45)	Anticoagulation Plus Antiplatelet Use (n=66)	P-value
Obesity	61 (73%)	26 (58%)	31 (47%)	0.004
Multiparity	24 (29%)	16 (36%)	11 (17%)	0.066
Miscarriage	22 (27%)	7 (16%)	37 (56%)	<0.001
Varicose veins	2 (2.4%)	3 (6.7%)	3 (4.6%)	0.468
Thrombophilia	2 (2.4%)	8 (18%)	16 (24%)	<0.001
Immobilization	1 (1.2%)	4 (9%)	9 (14%)	0.007
VTE	2 (2.4%)	9 (20%)	3 (4.6%)	0.001
SCD	4 (4.8%)	3 (6.7%)	3 (4.6%)	0.840

Abbreviations: VTE venous thromboembolism, SCD sickle-cell disease.

Obesity = Defined as documentation of obesity in the patient hospital information system or of body mass index >30 kg/m<sup>2</sup> if weight and height were available. Multiparity = ≥2 pregnancies.

Analyses were performed using Pearson's  $\chi^2$  test or Fisher's exact test, wherever appropriate.

a history of miscarriage, obesity and thrombophilia, while the use of antiplatelet agents was mostly noted in obese patients.

The side effects profile of anticoagulants and antiplatelet agents is summarized in Table 4. The most reported side effect was local bruising at the site of injection, which was mainly associated with the concurrent administration of anticoagulants and antiplatelet agents.

## DISCUSSION

To our knowledge, the EVE-Risk project was the first study to assess the prevalence of pregnant women with VTE risk factors not only in the Arabian Gulf but the World at large, as well as the proportion of those at risk who received the recommended VTE prophylaxis in accordance with the ACCP 2012 guidelines [15]. The proportion of pregnancies with ≥1 risk factors associated with a higher risk of VTE was high in the Arabian Gulf, at 32%. Alarmingly, even a smaller proportion of these high risk pregnant women (only 8.3%) received the recommended VTE prophylaxis.

The increased rate of high risk pregnancies in the EVE-Risk study can be attributed to the high rate of obesity in the pregnant population (except for Oman (Table 1)). This is a reflection of the obesity epidemic in the populations of the Arabian Gulf states which has been explored in previous studies [16, 17]. Multiparity was variable between the different countries but more common in Oman where it constituted 60% of high risk pregnancies. Other risk factors that have been strongly associated with VTE in the literature [3, 5] like recurrent miscarriages, past history of VTE, hereditary thrombophilia, antiphospholipid syndrome and immobilization were also reported in our study and represent a significant number of those who were on prophylaxis. Pregnant sickle cell anaemia patients were reported in 2.8% of our high risk population, reflecting high prevalence of this disorder in the region.

The most frequently used prophylactic anticoagulants were LMWHs (Table 2), indicating the acceptance of this category of anticoagulants by the treating obstetricians, as well as their good safety profile in pregnancy. Indeed, only 14 patients reported bleeding episodes in relation to LMWH use. All of these episodes were either minor bleeds or local bruising (Table 4); 12 of which were on both anticoagulants and antiplatelets. This finding is supported by prior research that demonstrated the safety of LMWH in pregnancy, as well as the associated increased risk of bleeding with concomitant use of both anticoagulants and aspirin [18, 19].

It is interesting to observe in the EVE-Risk study that pregnant women with obesity were more likely to be on an antiplatelet agent, anticoagulant or both (73, 58 and 47%, respectively) (Table 3). This finding suggests that besides being a common health problem in the Arabian Gulf states, obesity is a common denominator with other conditions that require proper prophylaxis in pregnancy, thus adding to the risks of VTE in these situations. Obesity alone has been recognized as a risk factor for VTE in pregnancy [6], but it is not an absolute indication for using VTE prophylaxis unless associated with other risk factors. Unfortunately, there are no definitive studies in the literature that specifically evaluated the benefits of routine prophylaxis in morbidly obese pregnant women.

Recurrent miscarriage is another condition where routine use of prophylactic anticoagulants (with or without antiplatelet agents) is common practice [20]. It is also a risk factor for VTE in pregnancy and postpartum period [14, 21]. In our study, out of 121 pregnant women with miscarriages, 66 (55%) were on anticoagulants, antiplatelet agents or both (Tables 1 and 3). The reason why <50% of these pregnant women were not on any type of prophylaxis is not clear. It is possible that some of these cases were attending a clinic for the first time, hence they were not yet on prophylactic therapy. Other conditions that have been associated with VTE in pregnancy are thrombophilia and history of VTE. Of 34

**Table 4. Side effect profile of pregnant women who received prophylactic anticoagulant and/or antiplatelet medication (n=194).**

Side effect	All (n=194)	Anticoagulation Alone (n=45)	Anticoagulation PLUS Antiplatelet Use (n=66)	Antiplatelet Alone (n=83)
Minor nose bleed	1 (0.5%)	0	0	1 (1.2%)
Minor vaginal bleed	1 (0.5%)	0	1 (1.5%)	0
Local bruising	12 (6.2%)	1 (2.2%)	11 (17%)	0
None	180 (93%)	44 (98%)	54 (82%)	82 (98%)

cases with documented thrombophilia and 21 with past history of VTE, 26 (76%) and 14 (67%) were on a prophylactic measure, respectively.

Immobilization is another recognized VTE risk factor in all groups of patients, including pregnancy [14, 22]. We demonstrated in a previous study in the Arabian Gulf states that immobilization was the commonest risk factor for VTE in medical, surgical and postpartum state [23]. In this study, of 26 pregnant women who were reported to be immobile, 14 (54%) women were on prophylaxis. It is possible that some of these women were experiencing vaginal bleeding or threatened abortion, hence, they were not prescribed VTE prophylaxis. Pregnant women with sickle cell disease were considered at risk of VTE in our study; sickle cell disease has been recognized to be associated with venous thrombosis [24]. Of 37 pregnancies with sickle cell disease, 10 (27%) were on prophylaxis. Again, it is possible that some of these pregnancies were seen for the first time in the treating centre and thus, were not evaluated as a high risk for VTE, which explains their low rate of prophylaxis (Tables 1 and 3).

Despite the presence of guidelines and recommendations in support of wider adoption of VTE prophylaxis in groups that are at high risk, VTE prophylaxis continues to be underutilized in clinical practice [14, 23, 25]. The only study that assessed VTE risk and adequacy of prophylaxis in the Arabian Gulf states (Kuwait, Saudi Arabia, and the UAE) emerged from the global ENDORSE study [23]. However, this study was mainly based on selected surgical and medical patients rather than pregnant women. It was concluded that patients at VTE risk were almost 50% of medical and surgical patients. However, only 40% of at risk patients received the ACCP-recommended VTE prophylaxis.

Conclusions from the ENDORSE study [14] concerning the underutilization of VTE prophylaxis in high risk hospitalized patients cannot be extrapolated to a pregnant women population in general and to the EVE-Risk population in particular for many reasons. Among these reasons is that the ENDORSE study [14] included sick hospitalized medical and surgical patients. In contrast, the EVE-Risk study recruited mostly healthy mobile pregnant women attending routine antenatal care clinic visits.

Several factors might influence the decision of obstetricians before the initiation of VTE prophylaxis during pregnancy. Among them are the possible side effects of long-

term use of heparin or LMWH prophylaxis [26]. In addition, there is paucity of risk stratification models and international guidelines that would define the groups of pregnant women who need VTE prophylaxis as well as its duration; thus the decision of starting VTE prophylaxis in pregnancy depends mostly on the assessment of the treating obstetrician. Furthermore, the incidence of VTE in pregnancy is 1 in 1000 to 1 in 2000 pregnancies, which is low compared to hospitalized medical and surgical patients, an issue that contributes significantly to less usage of VTE prophylaxis in pregnancy [2, 27]. This notion is supported by a recent study that followed up 1,787 pregnant women in Italy with different risk factors and reported only 1 episode of superficial thrombophlebitis [28].

This study has limitations. Its cross-sectional design limits its ability to assess causal relationships. Furthermore, the study enlisted only a single hospital in each of the participating countries (except the UAE), which might not fully represent the demography in a country or the practice patterns of the whole Arabian Gulf region. Additionally, other risk factors, which have also been implicated in the pathogenesis of VTE, were not captured as part of the EVE-Risk registry. These include diabetes mellitus, metabolic syndrome and rheumatoid arthritis [29-31].

## CONCLUSION

A large proportion of pregnant women in the Arabian Gulf states have  $\geq 1$  VTE risk factors during routine visits to antenatal clinics. Obesity stands out as the commonest risk factor in our study. A small proportion of EVE-Risk population with risk factors of VTE received recommended VTE prophylaxis. LMWH was safe and well tolerated, however, concomitant use with an antiplatelet agent was associated with slight increase in minor bleeding. The EVE-Risk investigators suggest that more pregnant women in this study with  $\geq 1$  VTE risk factor should have been carefully assessed for VTE prophylaxis. However, to recognize these high risk patients, there is a need to establish a risk stratification model based on the recognized VTE risk factors.

## CONFLICT OF INTEREST

Ibrahim Al-Zakwani received an honorarium for his statistical analysis work-up of the EVE-Risk Disease registry. The other author(s) declare no conflicts of interest, financial or otherwise, with respect to the authorship and/or publication of this article.

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## REFERENCES

- [1] Chang J, Elam-Evans LD, Berg CJ, *et al.* Pregnancy-related mortality surveillance--United States, 1991-1999. *MMWR Surveill Summ* 2003; 52(2): 1-8.
- [2] Jacobsen AF, Skjeldstad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium--a register-based case-control study. *Am J Obstet Gynecol* 2008; 198(2): 233.e1-7.
- [3] Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. *Obstet Gynecol Surv* 1999; 54(4): 265-71.
- [4] Gherman RB, Goodwin TM, Leung B, *et al.* Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. *Obstet Gynecol* 1999; 94(5 Pt 1): 730-4.
- [5] Ray JG, Langman LJ, Vermeulen MJ, Evrovski J, Yeo EL, Cole DE. Genetics University of Toronto Thrombophilia Study in Women (GUTTSI): genetic and other risk factors for venous thromboembolism in women. *Curr Control Trials Cardiovasc Med* 2001; 2(3): 141-9.
- [6] Eichinger S, Hron G, Bialonczyk C, *et al.* Overweight, obesity, and the risk of recurrent venous thromboembolism. *Arch Intern Med* 2008; 168(15): 1678-83.
- [7] Cushman M, Kuller LH, Prentice R, *et al.* Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004; 292(13): 1573-80.
- [8] Shannon MS, Edwards MB, Long F, Taylor KM, Bagger JP, De Swiet M. Anticoagulant management of pregnancy following heart valve replacement in the United Kingdom, 1986-2002. *J Heart Valve Dis* 2008; 17(5): 526-32.
- [9] Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J, American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(6 Suppl): 844S-86S.
- [10] Clark NP, Delate T, Witt DM, Parker S, McDuffie R. A descriptive evaluation of unfractionated heparin use during pregnancy. *J Thromb Thrombolysis* 2009; 27(3): 267-73.
- [11] Deruelle P, Coulon C. The use of low-molecular-weight heparins in pregnancy--how safe are they? *Curr Opin Obstet Gynecol* 2007; 19(6): 573-7.
- [12] Le Templier G, Rodger MA. Heparin-induced osteoporosis and pregnancy. *Curr Opin Pulm Med* 2008; 14(5): 403-7.
- [13] Clark SL, Porter TF, West FG. Coumarin derivatives and breastfeeding. *Obstet Gynecol* 2000; 95(6 Pt 1): 938-40.
- [14] Cohen AT, Tapson VF, Bergmann JF, *et al.* Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. *Lancet* 2008; 371(9610): 387-94.
- [15] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuneman HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl): 7S-47S.
- [16] Sweileh WM, Zyoud SH, Al-Jabi SW, Sawalha AF. Quantity and quality of obesity-related research in Arab countries: assessment and comparative analysis. *Health Res Policy Syst* 2014; 12: 33.
- [17] Ng M, Fleming T, Robinson M, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384(9945): 766-81.
- [18] Romualdi E, Dentali F, Rancan E, *et al.* Anticoagulant therapy for venous thromboembolism during pregnancy: a systematic review and a meta-analysis of the literature. *J Thromb Haemost* 2013; 11(2): 270-81.
- [19] Klinkhardt U, Breddin HK, Esslinger HU, Haas S, Kalatzis A, Harder S. Interaction between the LMWH rivaroxan and aspirin in healthy volunteers. *Br J Clin Pharmacol* 2000; 49(4): 337-41.
- [20] De Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. *Cochrane database Syst Rev* 2014; 7: CD004734.
- [21] Martínez-Zamora MÁ, Cervera R, Balasch J. Thromboembolism risk following recurrent miscarriage. *Expert Rev Cardiovasc Ther* 2013; 11(3): 1503-13.
- [22] Bates SM, Greer I, Middeldorp S, *et al.* VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(2 Suppl): e691S-736S.
- [23] Al Sayegh F, Almahmeed W, Al Humood S, *et al.* Global Risk Profile Verification in Patients with Venous Thromboembolism (GRIP VTE) in 5 Gulf countries. *Clin Appl Thromb Hemost* 2009; 15(3): 289-96.
- [24] Naik RP, Streiff MB, Haywood C Jr, Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. *Am J Med* 2013; 126(5): 443-9.
- [25] Anderson FA, Goldhaber SZ, Tapson VF, *et al.* Improving Practices in US Hospitals to Prevent Venous Thromboembolism: lessons from ENDORSE. *Am J Med* 2010; 123(12): 1099-106.e8.
- [26] James AH. Venous thromboembolism: mechanisms, treatment and public awareness. *Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol* 2009; 29(3): 326-31.
- [27] Togli MR, Weg JG. Venous thromboembolism during pregnancy. *N Engl J Med* 1996; 335(2): 108-14.
- [28] Testa S, Passamonti SM, Paoletti O, *et al.* The "Pregnancy Healthcare Program" for the prevention of venous thromboembolism in pregnancy. *Intern Emerg Med* 2015; 10(2): 129-34.
- [29] Yang Z, Liu H, Xie X, Tan Z, Qin T, Kang P. The influence of diabetes mellitus on the post-operative outcome of elective primary total knee replacement: a systematic review and meta-analysis. *Bone Joint J* 2014; 96-B(12): 1637-43.
- [30] Dentali F, Squizzato A, Ageno W. The metabolic syndrome as a risk factor for venous and arterial thrombosis. *Semin Thromb Hemost* 2009; 35(5): 451-7.
- [31] Ungprasert P, Srivali N, Spanuchart I, Thongprayoon C, Knight EL. Risk of venous thromboembolism in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol* 2014; 33(3): 297-304.