



**ICT 2023**

28th International  
Congress on Thrombosis

# Preganancy and need for anticoagultion

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## Declaration of Conflict Of Interest

- I have no potential conflict of interest to report

# Case Presentation

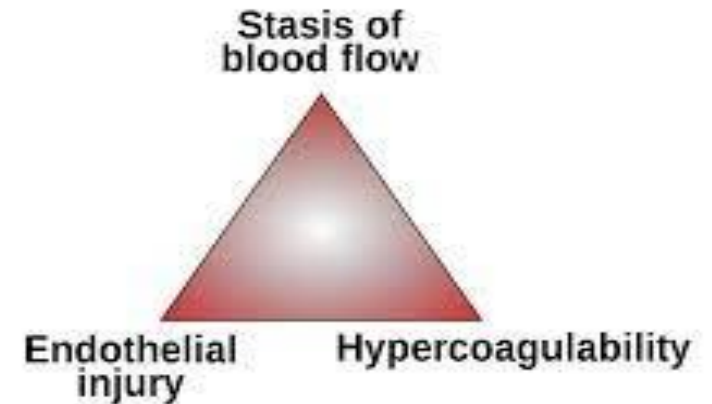
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- Maha is a 24 years old young lady came to my clinic for second opinion with history of full-term pregnancy , at time of delivery she born dead baby , complicated with Left leg DVT two week after delivery .
- This was her first pregnancy .
- No previous miscarriages.
- Baby dies at birth .
- Pregnancy induced VTE .
- **What is the best treatment/preventive approached for this lady for next pregnancy ?**

# Pregnancy is risk Factor

Increased venous thromboembolism risks are due to physiological changes in pregnancy contributing to all three components of **Virchow's triad**:

1. Hypercoagulability,
2. Stasis of Blood flow
3. Endothelial damage.



## Preganancy is risk Factor

- .Pregnant women and women in the post-partum period have a 4–5-times risk .
- .VTE complicates ~1.2 of every 1000 deliveries .
- .Women with a previous VTE have higher risks (2–10%) of recurrent venous thromboembolism in pregnancy and post partum than do other women.
- .Pregnancy-associated VTE is a leading cause of maternal morbidity and mortality

Int J Gynaecol Obstet . 2016 Jan;132(1):4-10.  
Birth Defects Res C Embryo Today .2015 Sep;105(3):167-84  
the MEGA study *J Thromb Haemost.* 2008; 6: 632-637

# Preganancy and need for anticoagultion

1. Why we need Anticoagultion ?
2. Who need it ?
3. Which types of anticoagultion ?
4. What is the dose ?
5. Is anticoagultion safe for fetus ?
6. What is the bleeding risk /HIT ?



# 1. Why we need Anticoagulation ?

1. Protection.

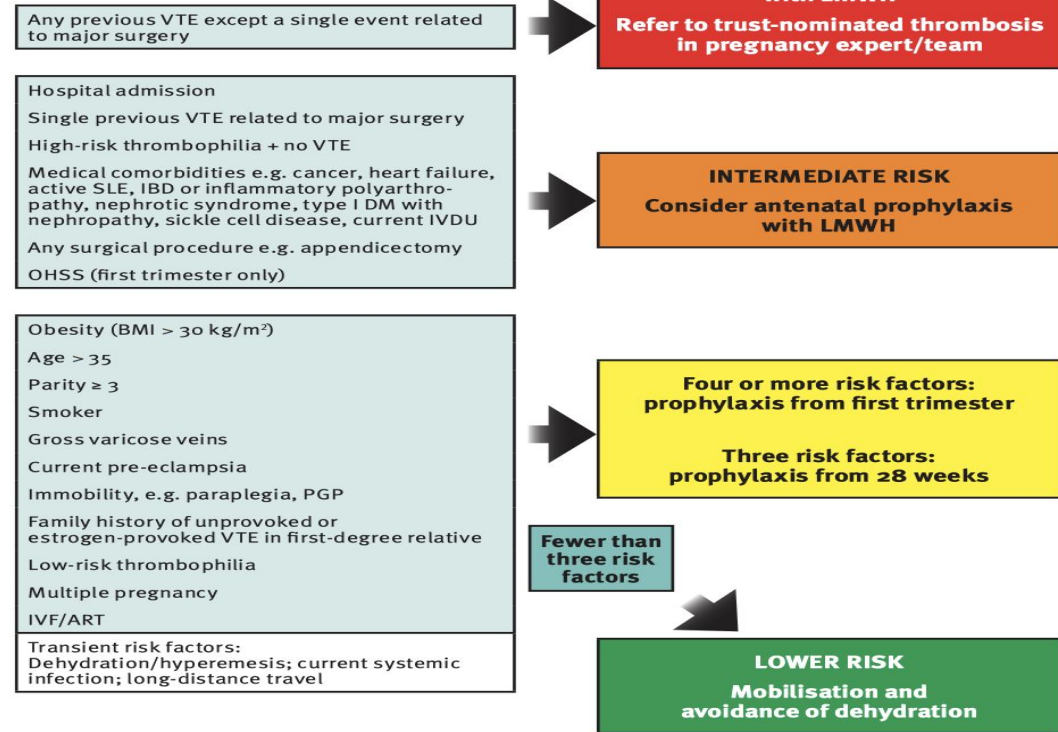
2. Treatment.



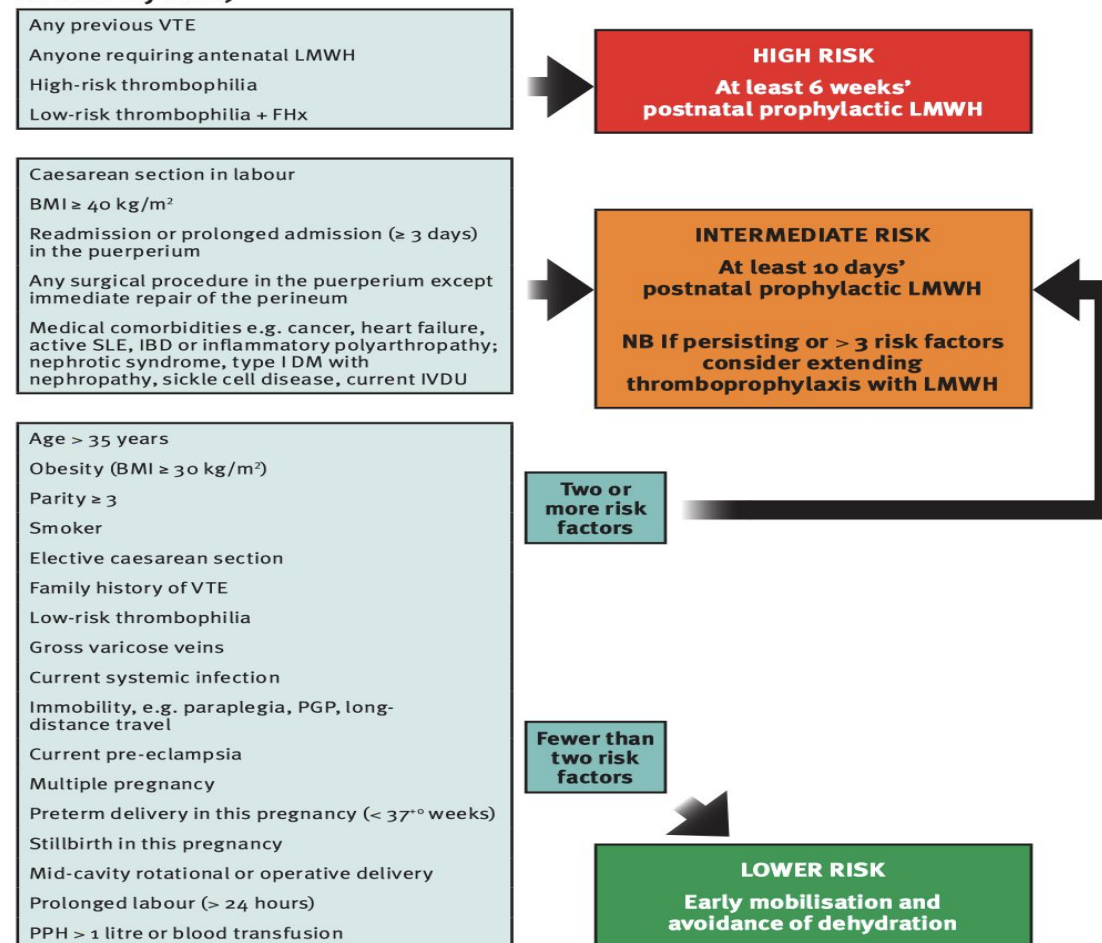
# VTE risk assessment in pregnancy

## Appendix I: Obstetric thromboprophylaxis risk assessment and management

### Antenatal assessment and management (to be assessed at booking and repeated if admitted)



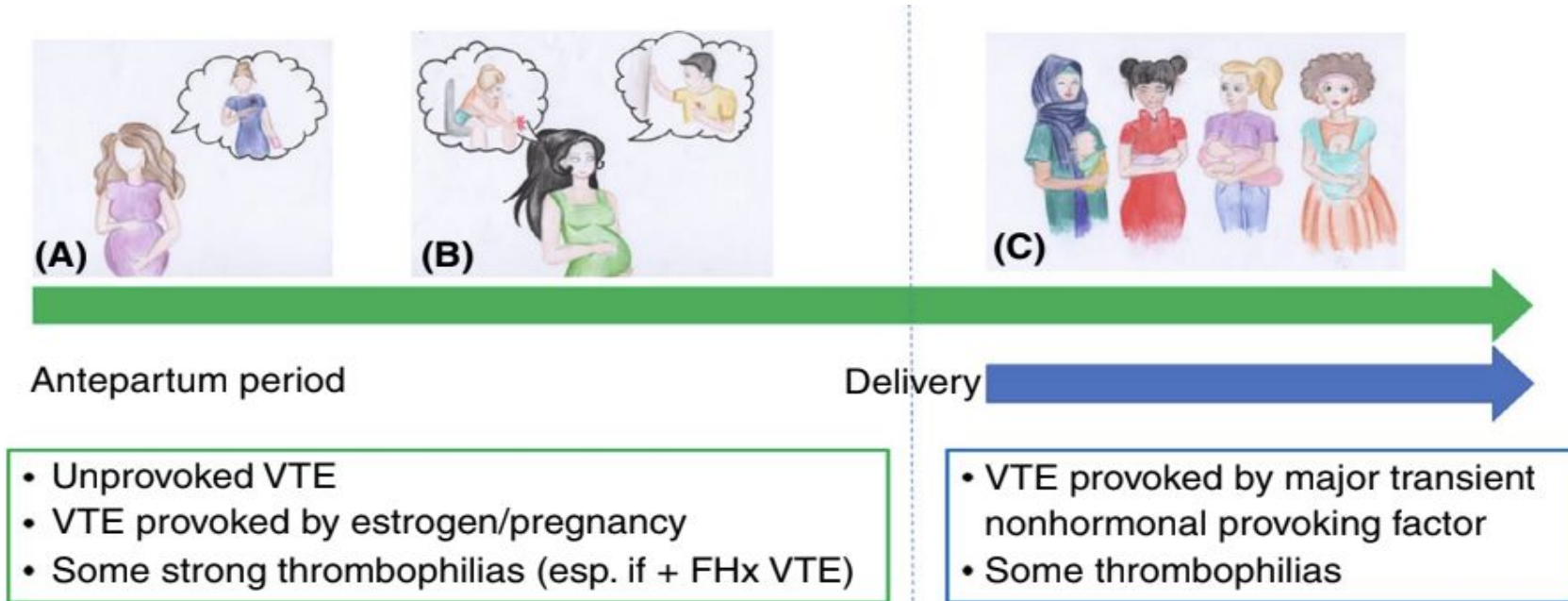
### Postnatal assessment and management (to be assessed on delivery suite)



#### Antenatal and postnatal prophylactic dose of LMWH

Weight < 50 kg = 20 mg enoxaparin/2500 units dalteparin/3500 units tinzaparin daily  
 Weight 50–90 kg = 40 mg enoxaparin/5000 units dalteparin/4500 units tinzaparin daily  
 Weight 91–130 kg = 60 mg enoxaparin/7500 units dalteparin/7000 units tinzaparin daily  
 Weight 131–170 kg = 80 mg enoxaparin/10 000 units dalteparin/9000 units tinzaparin daily  
 Weight > 170 kg = 0.6 mg/kg/day enoxaparin/ 75 u/kg/day dalteparin/ 75 u/kg/day tinzaparin

# American College of Chest Physicians / ASH guidelines



Bates .Blood Adv. 2018;2(22):3317–59.  
Bates SM . Chest. 2012;141(2 Suppl):e691S–736S  
Karl Ewins .Res Pract Thromb Haemost. 2020;4:183–192.

## 2. Who Need it ?

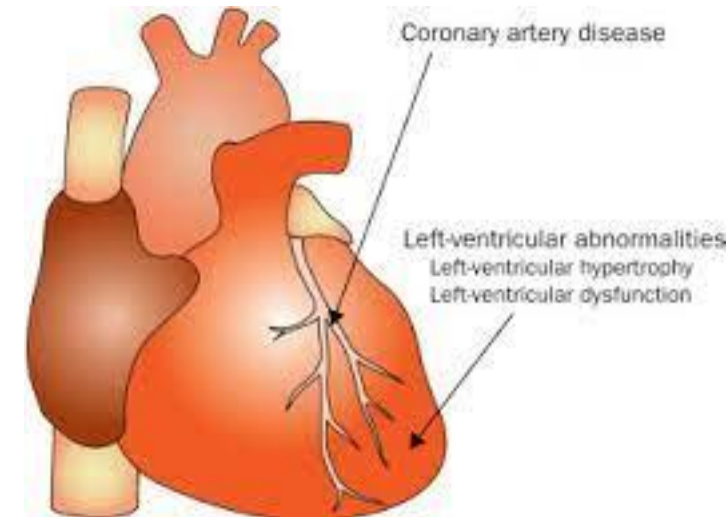
### Indications for antithrombotic agents

Prosthetic heart  
valves diseases

Thrombosis  
Prevention /Treatment  
Inherited  
thrombophilia

Atrial fibrillation/  
Left Ventricular  
dysfunction

fetal risk versus  
maternal  
thromboembolism



## Inherited thrombophilia

Inherited thrombophilia with VTE vs No VTE

Inherited thrombophilia with recurrent fetal loss

## high-risk thrombophilias

High absolute risk of pregnancy-associated VTE.

The risk was independent of a positive family history of thrombosis .

- Antithrombin (AT) deficiency
- Factor V Leiden homozygote
- Heterozygosity for both FVL and prothrombin G20210A

Blood. 2016 Sep

## Low-risk inherited thrombophilias

No personal or family history of VTE  
low absolute risk of VTE

- FVL heterozygote
- Prothrombin G20210A heterozygote
- Protein C deficiency
- Protein S deficiency

- In a prospective study of patients with low-risk pregnancies and no history of thromboembolism, 0 of the 134 those heterozygous for FVL had a VTE during pregnancy or up to six weeks postpartum
- In a prospective study of 1707 nulliparous Australian patients with no prior history of adverse pregnancy outcome or personal or family history of VTE.  
0 of 92 pregnant patients heterozygous for FVL and 0 of 41 pregnant patients heterozygous for prothrombin G20210A developed VTE.

Dizon-Townson *Obstet Gynecol.* 2005;106(3):517.

**ALIFE 2 trial** : open-label, randomized, controlled trial , 326 women , randomly assigned 1:1 to subcutaneous LMWH once daily or standard pregnancy care .

**Table 3 Inclusion and exclusion criteria**

Inclusion criteria	<ul style="list-style-type: none"> <li>• Women with recurrent miscarriage and/or intra-uterine fetal deaths (that is <math>\geq</math> two miscarriages of intra-uterine fetal deaths, irrespective of gestational age)</li> <li>• Confirmed inherited thrombophilia<sup>a</sup> <ul style="list-style-type: none"> <li>◦ factor V Leiden mutation</li> <li>◦ prothrombin gene mutation (G20210A)</li> <li>◦ protein S deficiency</li> <li>◦ protein C deficiency</li> <li>◦ antithrombin deficiency</li> </ul> </li> <li>• Pregnancy confirmed by urine pregnancy test</li> <li>• Age 18 to 42 years at randomization</li> <li>• Willing and able to give informed consent</li> </ul>
Exclusion criteria	<ul style="list-style-type: none"> <li>• Duration of current pregnancy <math>\geq</math> 7 weeks, based on first day of last menstruation</li> <li>• Indication for anticoagulant treatment during pregnancy (e.g., prosthetic heart valves, a history of venous thromboembolism or antiphospholipid syndrome)</li> <li>• Contraindications to LMWH (previous heparin-induced thrombocytopenia, active bleeding or renal insufficiency with creatinine clearance of <math>&lt;</math> 30 ml/minute)</li> <li>• Known allergy to at least three different LMWH preparations</li> <li>• Previous inclusion in the ALIFE2 study (for another pregnancy)</li> </ul>

<sup>a</sup>Protein S, protein C and antithrombin deficiencies need to be confirmed by two tests, performed on two separate occasions and not during anticoagulant therapy. Protein S tests should not be performed during pregnancy or in the 6-week post-partum period since spuriously low levels may then be observed.

Type of thrombophilia		
Factor V Leiden mutation; heterozygous	95 (58%)	89 (55%)
Factor V Leiden mutation; homozygous	5 (3%)	0 (0%)
Prothrombin G20210A mutation; heterozygous	39 (24%)	44 (27%)
Prothrombin G20210A mutation; homozygous	0	2 (1%)
Antithrombin deficiency	2 (1%)	5 (3%)
Protein C deficiency	5 (3%)	8 (5%)
Protein S deficiency	23 (14%)	21 (13%)
Combined thrombophilia <sup>‡</sup>	5 (3%)	7 (4%)

(Table 1 continues in next column)

Quenby .Lancet .May 31, 2023

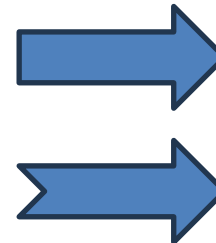
# ALIFE 2 trial

The live birth rates 71.6 % in the LMWH group Vs 70.9 %in the standard surveillance group .

	LMWH (n=162)	Standard care (n=158)	Unadjusted analysis*	Adjusted analysis†	Absolute risk difference
Livebirth	116 (72%)	112 (71%)	1.04 (0.64 to 1.68); p=0.99	1.08 (0.65 to 1.78); p=0.77	0.7% (95% CI -9.2% to 10.6%)
Pregnancy loss	46 (28%)	46‡ (29%)	..	..	..

Data are n (%) unless stated otherwise. LMWH=low-molecular-weight heparin. \*Odds ratio (95% CI) and  $\chi^2$  test p value with continuity correction. †Odds ratio (95% CI) and p value logistic regression adjusted for maternal age (<36 years,  $\geq 36$  years), number of miscarriages (2,  $\geq 3$ ), tertiary or non-tertiary centre, and randomising country (UK, Netherlands), with the standard surveillance group as the reference group. ‡One set of triplets in the standard care group was counted as a livebirth as two of the three fetuses were livebirths; the other was terminated at 8 + 3 weeks' gestation. This termination has not been counted in this table.

**Table 2: Pregnancy outcome (livebirth rates)**



	LMWH	Standard care
Type of early pregnancy loss		
Biochemical loss	7/162 (4%)	6/158 (4%)
Ectopic pregnancy	3/162 (2%)	1/158 (1%)
Intrauterine pregnancy identified on ultrasound scan		
Miscarriage <12 weeks	34/152* (22%)	34/151* (23%)
Termination of pregnancy	1/152 (1%)	2/151 (1%)
Reached second trimester		
Miscarriage 12–24 weeks	1/117 (1%)	3/115 (3%)
Reached third trimester (livebirth)		
Stillbirth	0/116	0/112
Total number of pregnancy losses	46/162 (28%)	46/158 (29%)
Obstetric complications in third trimester	n=116	n=112
Pre-eclampsia or HELLP syndrome	4/114 (4%)	3/109 (3%)
Small for gestational age†	12/111 (11%)‡	15/104 (14%)
Placental abruption	1/114 (1%)	1/109 (1%)
Premature birth <37 weeks' gestation	15/116 (13%)	15/112 (13%)
Congenital anomalies	3/104 (3%)§	2/103 (2%)¶
Other complications during entire pregnancy	n=164	n=162
Confirmed deep vein thrombosis or pulmonary embolism	1/154 (1%)	0/144 (0%)
Easy bruising	73/164 (45%)	16/162 (10%)
Adverse events during entire pregnancy	n=164	n=162
Post-partum bleeding >500 mL	7 events	12 events
Major bleeding >100 mL	3 events	3 events
Clinically relevant non-major bleeding	9 events	14 events
Minor bleeding	35 events	27 events
Heparin-induced thrombocytopenia	0 events	0 events
Skin reactions at injection site	3 events	1 events
Total number of adverse events	57	57
Total number of participants reporting an adverse event	39/164 (24%)	37/162 (23%)

IUGR=intrauterine growth restriction. LMWH=low-molecular-weight heparin. \*A set of twins was miscarried (counted as one pregnancy); this happened once in both arms. †Small for gestational age was calculated using the customised GROW chart, less than the tenth centile. ‡One participant had twins who both had IUGR; this has been counted as one event. §One baby had respiratory distress, stenosis anus with fistula, and anorectal malfunction surgery to correct imperforate anus. One baby had an extra toe on the right foot. One baby had an undescended right testis. ¶One baby had oesophageal atresia and one baby had Down syndrome. ||Took LMWH although randomised to standard care.

**Table 3: Pregnancy loss and secondary outcome measures**

# ALIFE 2 trial

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## The conclusion :

# The use of LMWH did not improve the live birth rate among women with recurrent miscarriage and inherited thrombophilia.

#Do not test for inherited thrombophilia in women with recurrent miscarriage, as there are no therapeutic consequences

Quenby. Lancet .May 31, 2023

# Preganancy and need for anticoagultion

1. Why we need Anticoagultion ?

2. Who need it ?

**3. Which types of anticoagultion ?**

4. What is the dose ?

5. Is safe for fetus ?

6. What is the bleeding risk/HIT ?



### 3. Which types of anticoagulation ?

#### Challenging due to

1. The potential teratogenic effects
2. Management of anticoagulation around the time of labor , unpredictable onset of labor and the use of neuraxial anesthesia for management of labor pain.

#### Heparins :

Do not cross the placenta and do not result in fetal anticoagulation.  
Not been associated with increase in risk of congenital anomalies .

- A. Low molecular weight (LMW) heparins .**
- B. Unfractionated heparin.**

Clin Obstet Gynaecol. 1986;13(2):349. ,  
Clin Perinatol. 1986;13(4):719  
Arch Intern Med. 1989;149(10):2233

### 3. Which types of anticoagulation ?

#### Fondaparinux, Argatroban , Danaparoid

There is less information on the fetal effects of these agents, but available evidence suggests they are reasonable options can be used if Pregnancies complicated by HIT

**Danaparoid** does not cross the placenta. Lacking High-quality data regarding use during pregnancy.

**Argatroban** is likely to cross the placenta due to its small size, although this has not been well studied ( case report)

Chest. 2012;141(2 Suppl):e691S.  
Thromb Haemost. 2005;93(1):63.  
J Obstet Gynaecol Res. 2012 Apr;38(4):749-52.  
Pharmacotherapy. 2008;28(12):1531.

### 3. Which types of anticoagulation ?

#### A. Avoidance of Warfrain

-1) Crosses the placenta, 2)A teratogen, 3) causes fetal anticoagulation.

Exposure during early pregnancy can result in embryopathy.

Exposure later in pregnancy can cause fetal bleeding, including intracranial hemorrhage.

#### B. Avoidance of direct oral anticoagulants

[Dabigatran](#), [rivaroxaban](#), [apixaban](#), and [edoxaban](#) are not used during pregnancy because information on efficacy and fetal safety is lacking and Breast feeding .

# Preganancy and need for anticoagultion

1. Why we need Anticoagultion ?

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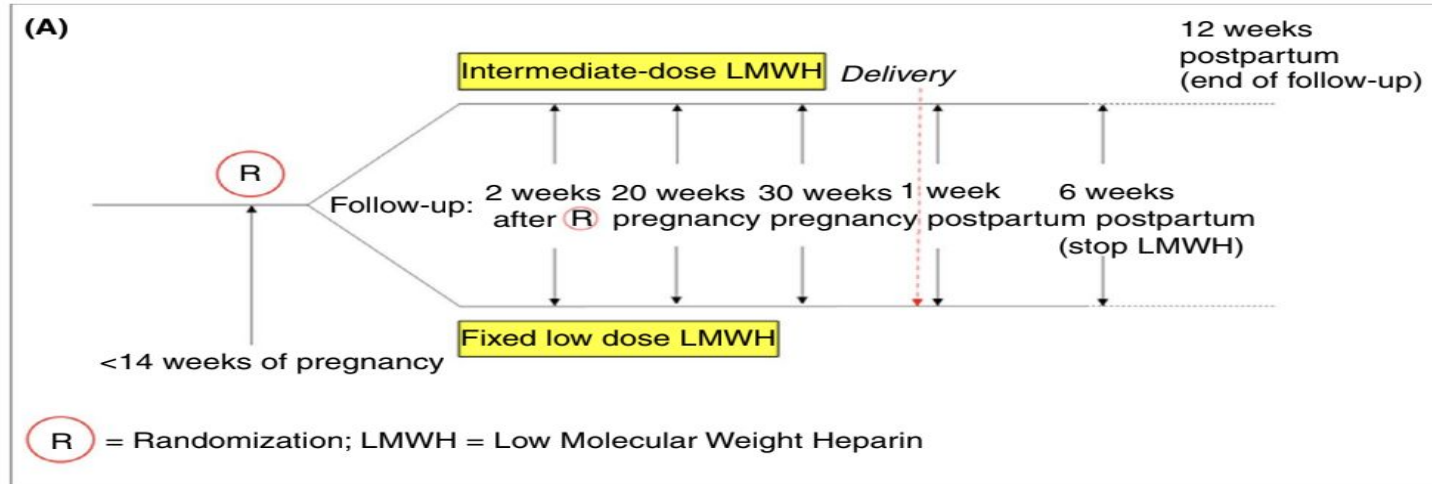
3. Which types of anticoagultion ?

**4. What is the dose ?**

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6. What is the bleeding risk /HIT?

Intermediate-dose versus low-dose LMWH in pregnant and post-partum women  
 a history of VTE open-label, multicenter, randomized, controlled trial  
 nine countries



[www.highlowstudy.org](http://www.highlowstudy.org)

NCT01828697  
 (clinicaltrials.gov)

**Eligibility criteria:**

- Age  $\geq 18$  years
- <14 weeks pregnant
- Previous objectively confirmed VTE:
  - Unprovoked
  - Provoked by hormones
  - VTE in pregnancy
  - VTE postpartum (PP)
  - Minor provoking factor

(B)

**Primary efficacy outcome:**

- Symptomatic recurrent VTE up to 6 weeks PP

**Primary safety outcomes:**

- Major bleeding
- Composite: major & clinically relevant non-major bleeding
- Early & late PP haemorrhage
- PP blood transfusion
- Mortality

(C)

**FIGURE 3** Overview of the Highlow study ([www.highlowstudy.org](http://www.highlowstudy.org); NCT01828697, [clinicaltrials.gov](http://clinicaltrials.gov)). (A) Study flowchart from randomization to follow up; (B and C) Eligibility criteria, primary efficacy outcome, and primary safety outcomes

## Highlow study :

### Efficacy outcome.:

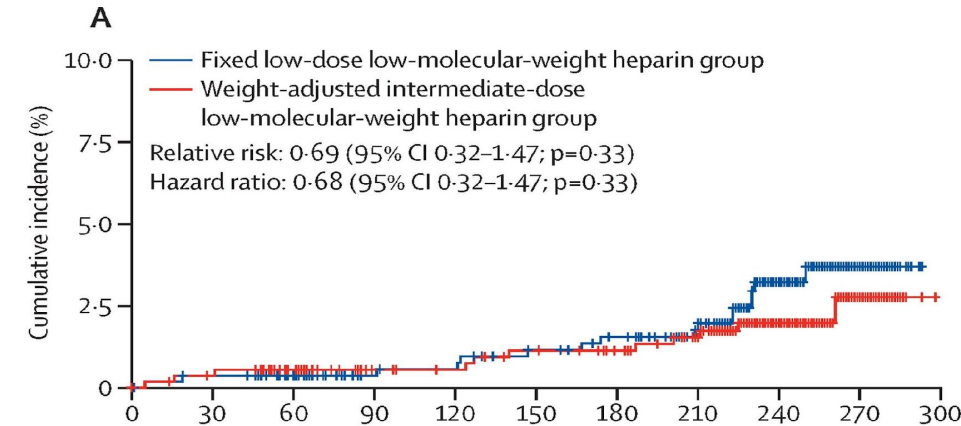
VTE 2% of the weight-adjusted intermediate-dose LMWH group vs. 3% of the fixed low-dose LMWH group ( $p = 0.33$ ).

### The primary safety outcome :

major bleeding 4% of the weight-adjusted intermediate-dose LMWH group vs. 4% of the fixed low-dose LMWH group ( $p =$  not significant).

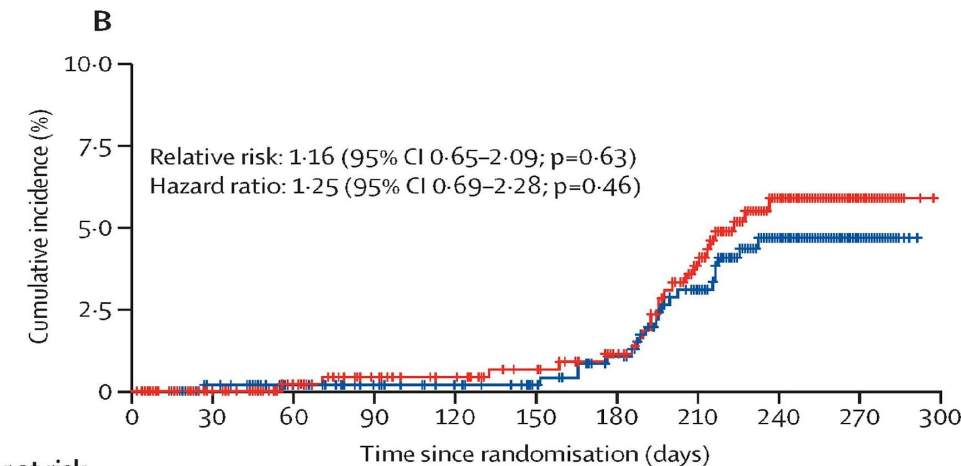
Interpretation:  
weight-adjusted intermediate-dose LMWH was not superior to fixed low-dose LMWH. not associated with a reduction in recurrent venous thromboembolism.

IM Bistervels *Lancet*. 2022 Nov 19;400(10365):1777-1787



**Number at risk**

Fixed low-dose low-molecular-weight heparin group	555	549	532	510	508	501	494	471	294	68	0
Weight-adjusted intermediate-dose low-molecular-weight heparin group	555	550	535	515	511	506	500	489	281	70	0

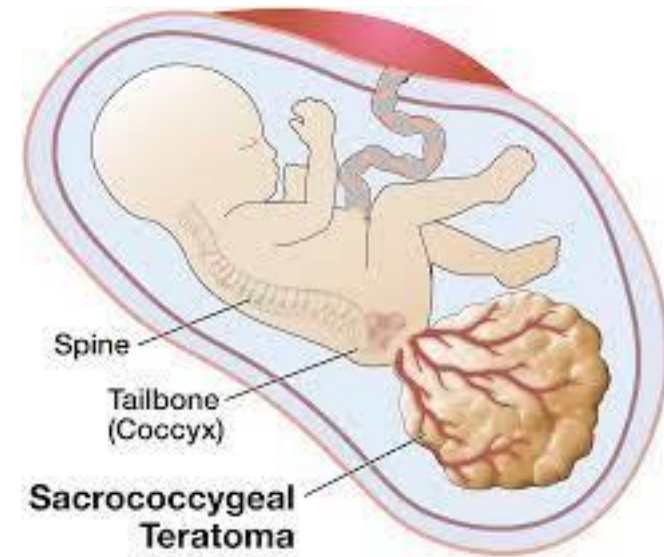


**Number at risk**

Fixed low-dose low-molecular-weight heparin group	525	513	497	481	473	462	449	411	242	52	0
Weight-adjusted intermediate-dose low-molecular-weight heparin group	520	494	464	446	438	427	413	380	210	56	0

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## Fetal and neonatal outcome of exposure to anticoagulants during pregnancy

Small for gestational age

warfarin embryopathy such as nasal hypoplasia.

subependymal intraventricular hemorrhage shown on neonatal ultrasonography.

V Wang . Am J Med Genet . 1993 Jan 1;45(1):17-21.

# Preganancy and need for anticoagultion

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# Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy .

A systematic review that aimed to assess the safety and efficacy of LMWH during pregnancy reported **a 2.0% (95% CI, 1.50%-2.61%)** overall risk of “significant maternal bleeding” for women receiving LMWH for thromboprophylaxis, adverse pregnancy outcome, or unspecified indications.

Greer .Blood 2005 Jul 15;106(2):401-7

Table 3. Complications reported with LMWH use in pregnancy for different indications and different LMWHs

Indication and LMWH used	Total, no.	DVT, no. (%)	PE, no. (%)	Other or unspecified VTE, no. (%)	Arterial thrombosis, no. (%)	Severe antenatal bleeding, no. (%)	PPH exceeding 500 mL, no. (%)	Wound hematoma, no. (%)	Allergy, no. (%)	Low platelet count, no. (%)	Osteoporosis, no. (%)
<b>Treatment</b>											
Enoxaparin	105	1 (0.95)	0 (0)	0 (0)	0 (0)	1 (0.95)	1 (0.95)	0 (0)	2 (1.90)	1 (0.95)	0 (0)
Dalteparin	49	1 (2.04)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.04)	0 (0)	0 (0)	0 (0)	0 (0)
Nadroparin	20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal	174	2 (1.15)	0 (0)	0 (0)	0 (0)	1 (0.57)	2 (1.15)	0 (0)	2 (1.15)	1 (0.57)	0 (0)
<b>Thromboprophylaxis</b>											
Enoxaparin	855	7 (0.8)	3* (0.35)	0 (0)	9 (1.05)	4 (0.47)	10 (1.17)	0 (0)	1 (0.12)	2 (0.24)	0 (0)
Dalteparin	385	1† (0.26)	0 (0)	2 (0.52)	4 (1.04)	2 (0.52)	14‡ (3.6)	0 (0)	14 (3.63)	0 (0)	1 (0.26)
Nadroparin	33	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Certoparin	108	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified	55	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Thromboprophylaxis for RPL</b>											
Enoxaparin	235	0 (0)	0 (0)	1 (0.43)	1 (0.43)	1 (0.43)	0 (0)	0 (0)	3 (1.30)	0 (0)	0 (0)
Dalteparin	110	2 (1.82)	1 (0.91)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	99	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
<b>Unspecified</b>											
Dalteparin	245	4 (1.63)	1 (0.41)	0 (0)	0 (0)	4 (1.63)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nadroparin	420	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	18 (4.29)	0 (0)	0 (0)
Other/unspecified	55	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	17§ (30.9)	12 (21.8)	0 (0)	0 (0)
Subtotal	2603	14 (0.54)	5 (0.19)	3 (0.12)	14 (0.54)	11 (0.42)	24 (0.92)	17 (0.65)	48¶ (1.84)	2 (0.08)	1 (0.04)
Total	2777	16 (0.58)	5 (0.18)	3 (0.11)	14 (0.50)	12 (0.43)	26 (0.94)	17 (0.61)	50 (1.80)	3 (0.11)	1 (0.04)

No patients reported HIT.

\*One PE occurred in a patient receiving a 20-mg/kg dose of enoxaparin.

†In a patient receiving a 2500-IU dose of dalteparin.

‡Nine had dextran.

§All less than 2 hours before cesarean.

¶Three patients had a general allergic reaction.

# The Relationship between Use of Low Molecular Weight Heparin during Pregnancy and Risk of Peripartum Adverse Events: A Meta-Analysis

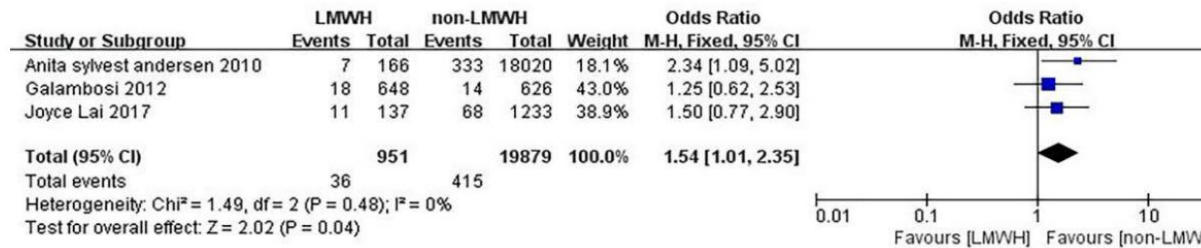


Figure 6: Fetal growth restriction incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

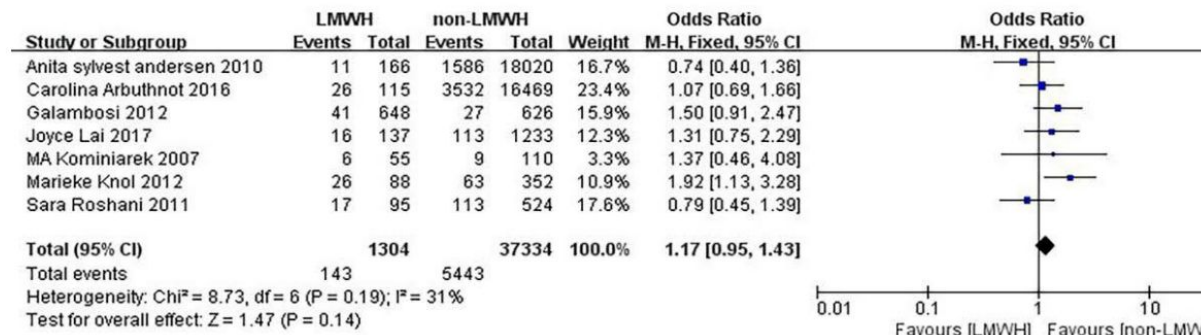


Figure 7: Postpartum hemorrhage incidences in pregnant women treated with LMWH and pregnant women without anticoagulant therapy.

## Conclusion:

no statistically significant differences in the risk of abortion, preterm birth, stillbirth, preeclampsia, or postpartum hemorrhage between pregnant women who used LMWH as anticoagulant and those who did not use LMWH.

Using LMWH in pregnant women does not increase pregnancy related maternal and fetal complications

Xiaorong Y, A Meta-Analysis. Ann Hematol Oncol. 2021; 8(11): 1372

# Heparin-induced thrombocytopenia (HIT)

HIT can occur in any patient receiving any amount of heparin

The incidence in pregnancy is very low.

This was illustrated in a meta-analysis of 2777 pregnancies during which LMW heparin was administered; no instances of HIT were reported

LMW heparin appears less likely to precipitate HIT compared with UFH.

Greer A. Blood 2005 Jul 15;106(2):401-7.

## Case Presentation

Maha is a 24 year old lady came to my clinic for second opinion with history of full term pregnancy ended with born dead baby complicated with Left leg DVT two week after delivery .

This is her first pregnancy :  
No previous miscarriages  
Baby died at birth  
Pregnancy induced VTE

**What is the best treatment approached for this lady for next pregnancy ?**

VTE prophylaxis during and 6 weeks postpartum .  
She had 2 babies 3yrs old and 1 year .

# Take home message :

- Assessment of VTE risk factors in pregnancy/postpartum.
- LMWH is the preferred over UFH .
- weight-adjusted intermediate-dose LMWH was not superior to fixed low-dose LMWH.
- Heparin-induced thrombocytopenia in pregnant women is extremely rare.
- The use of LMWH did not improve the live birth rate among women with recurrent miscarriage and inherited thrombophilia.
- Do not test for inherited thrombophilia in women with recurrent miscarriage.
- Recommend against the use of oral Xa inhibitors and oral direct thrombin inhibitors for the treatment of VTE in pregnancy.

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# ICT 2023

28th International  
Congress on Thrombosis



# Thank you

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