PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement 2013
Guidelines According to Scientific Evidence

Developed under the auspices of the:

Cardiovascular Disease Educational and Research Trust (UK)
European Venous Forum
North American Thrombosis Forum
International Union of Angiology and
Union Internationale du Phlebologie

Gynecology & Obstetrics

Chapter 5

Risk of VTE in Gynecologic Surgery Patients

- **Thromboembolic complications after gynecologic surgery occur with the same frequency as in general surgery**
- **PE is a leading cause of death following gynecologic cancer surgery**
  - ~ 20% of perioperative hysterectomy deaths[1,2]
- **Patients ≥40 years of age undergoing major gynecologic surgery have a significant risk of postoperative VTE**
  - Risk is increased by age, obesity, malignancy, history of VTE, immobility, thrombophilia[3,4]

1. Greer IA. Baillieres Clin Obstet Gynaecol 1997; 11:403-30.
2. Report of the National Confidential Enquiry into perioperative Deaths. 1991/92. 1993.
3. Kakkar VV, et al. Am J Surg 1970; 120:527-30.
4. Clayton JK, et al. Br Med J 1976; 2:910-2.

Incidence of DVT * in the Absence of Prophylaxis
Gynecologic Surgery - Benign

Study	Patients (n)	DVT Incidence	95% CI
Ballard et al, 1973[1]	55	16	
Bonnar & Walsh, 1972[2]	140	15	
Taberner et al, 1978[3]	48	11	
Walsh et al, 1974[4]	217	21	
Total	**460**	**63 (14%)**	**11% to 17%**

*Diagnosed by surveillance with objective methods: phlebography, FUT or DUS

1. Ballard RM, et al. J Obstet Gynaecol Br Commonw 1973; 80:469-72.
2. Bonnar J, Walsh J. J Lancet 1972; 1:614-6.
3. Taberner DA, et al. Br Med J 1978; 1:272-4.
4. Walsh JJ, et al. J Obstet Gynaecol Br Commonw 1974; 81:311-6.

Incidence of DVT in the Absence of Prophylaxis
Gynecologic Surgery - Malignancy

Study	Patients (n)	DVT Incidence	95% CI
Ballard et al, 1973[1]	55	15	
Walsh et al, 1974[2]	45	16	
Taberner et al, 1978[3]	48	11	
Clarke-Pearson et al, 1983[4]	97	12	
Clarke-Pearson et al, 1983[5]	52	17	
Clarke-Pearson et al, 1983[6]	103	19	
Total	**400**	**90 (22.5%)**	**19% to 27%**

1. Ballard RM, et al. J Obstet Gynaecol Br Commonw 1973; 80:469-72.
2. Walsh JJ, et al. J Obstet Gynaecol Br Commonw 1974; 81:311-6.
3. Taberner DA, et al. Br Med J 1978; 1:272-4.
4. Clarke-Pearson DL, et al. Am J Obstet Gynecol 1983; 145:606-13.
5. Clarke-Pearson DL, et al. Gynecol Oncol 1984; 18:226-32.
6. Clarke-Pearson DL, et al. Obstet Gynecol 1990; 75:684-9.

Risk Categories for Gynecologic Surgical Patients

High Risk Category
Major surgery, age >60
Major surgery, age 40-60 & cancer or history of DVT/PE or other risk factors including thrombophilia
Moderate Risk Category
Major surgery, age 40-60 without other risk factors
Minor surgery, age <40 on estrogen therapy
Minor surgery, age >60
Low Risk Category
Major surgery, age <40 without any other risk factors*
Minor surgery, age 40-60 without any other risk factors*

[a] The risk is increased by sepsis, presence of varicose veins, general immobility

Minor surgery: Operations other than abdominal lasting less than 45 minutes
Major surgery: Any intra-abdominal operation and all other operations lasting more than 45 minutes.

Additional Risk Factors in Gynecologic Surgery[1-5]

- **Nature and duration of the operation**
- **Type of anesthesia**
- **Dehydration**
- **Sepsis**
- **Varicose veins**
- **Hormone therapy**

1. Kakkar VV, et al. Am J Surg 1970; 120:527-30.
2. Clayton JK, et al. Br Med J 1976; 2:910-2.
3. Havig O. Acta Chir Scand Suppl 1977; 478:1-120.
4. Lowe GD, et al. Lancet 1982; 1:1474.
5. Sue-Ling HM, et al. Lancet 1986; 1:1173-6.

Estrogen Use and VTE Risk

- **Oral contraceptives with estrogen are associated with increased risk for VTE[1]**
- **However, the increase in absolute risk is low**
  - Risk increases from 5 to 15-30 per 100,000 women-years[2]
  - Postoperative risk increases from 0.5% to 1%[3]
  - The absolute excess risk in COC users has to be balanced against the risk of stopping the pill 4-6 weeks before surgery which includes unwanted pregnancy, the effects of surgery and anesthesia on a pregnancy, and the risks of subsequent termination. Each case should be assessed in relation to additional risk factors.
- **Progestogen-only oral contraceptives do not require discontinuation even when immobilization is expected[4]**

1. Rosendaal FR, et al. Thromb Haemost 2001; 86:112-23.
2. Jick H, et al. Lancet 1995; 346:1589-93.
3. Vessey MP, et al. Br Med J 1970; 3:123-6.
4. Conard J, et al. Contraception 2004; 70:437-41.

Hormone Replacement Therapy and VTE Risk

- **Hormone replacement therapy (HRT) is a VTE risk factor in surgical patients[1]**
  - HRT does not need to be stopped prior to surgery if appropriate thromboprophylaxis is used[2]
  - Transdermal HRT has less effect on blood coagulation and a substantially lower VTE risk than oral HRT[3]
  - In women with ovarian hyperstimulation syndrome, thromboprophylaxis with pregnancy dosage of LMWH is advised[4]

1. Grady D, et al. Ann Intern Med 2000; 132:689-96.
2. Greer IA, Walker ID. Royal College of Obstetricians and Gynaecologists, guideline no 19. London, 2004.
3. Scarabin PY, et al. Lancet 2003; 362:428-32.
4. Nelson SM. Thromb Res 2009; 123 Suppl 3:S8-S15.

General Considerations
Low-Risk Patients - Gynecology

- **A RCT involving 196 women undergoing major gynecological surgery demonstrated a lower DVT rate with use of GEC compared with no GEC (0 vs 4%; P < 0.05)[1]**
- **Thromboprophylaxis with GEC stockings should be used in addition to early ambulation and adequate hydration**

1. Turner GM, et al. Br J Obstet Gynaecol 1984; 91:588-91.

General Considerations
Moderate-Risk Patients - Gynecology

- **Two RCT involving 207 patients having surgery for benign gynecologic disease demonstrated that LDUH (5,000 IU, 12 h) reduced DVT[1,2]**
  - LDUH reduced asymptomatic DVT from 25% to 4.8% (RR 0.19; 95% CI 0.07 to 0.48)
- **LMWH is effective for preventing DVT[3,4]**
- **Complex laparoscopic surgery poses similar VTE risk as open procedures[5]**

1. Ballard RM, et al. J Obstet Gynaecol Br Commonw 1973; 80:469-72.
2. Taberner DA, et al. Br Med J 1978; 1:272-4.
3. Borstad E, et al. Acta Obstet Gynecol Scand 1988; 67:99-103.
4. Maxwell GL, et al. Obstet Gynecol 2001; 98:989-95.
5. Clarke-Pearson DL, Abaid LN. Obstet Gynecol 2012; 119:155-67.

General Considerations
High-Risk Patients - Gynecology

- **In patients having gynecologic surgery for malignancy, LDUH administered 8-hourly was effective in reducing VTE risk[1,2]**
  - LDUH administered 12-hourly was not effective[1,2]
  - LDUH administered 8-hourly reduced asymptomatic DVT from 18.4% to 8.7% (RR 0.47; 95% CI 0.22 to 0.98)
- **Subsequent RCTs have shown equivalent efficacy for LMWH and LDUH administered 8-hourly and no difference in the risk of bleeding[3-6]**

1. Clarke-Pearson DL, et al. Am J Obstet Gynecol 1983; 145:606-13.
2. Clark-Pearson DL, et al. Obstet Gynecol 1990; 75:684-9.
3. ENOXACAN. Br J Surg 1997; 84:1099-103.
4. Baykal C, et al. Eur J Gynaecol Oncol 2001; 22:127-30.
5. Fricker JP, et al. Eur J Clin Invest 1988; 18:561-7.
6. Heilmann L, et al. Geburtshilfe Frauenheilkd 1989; 49:803-7.

General Considerations
High-Risk Patients - Gynecology

- **IPC has been shown to be as effective as LDUH or LMWH for preventing DVT when used continuously for 5 days, without any bleeding complications[1-3]**
  - RCT: 208 patients undergoing gynecologic surgery for malignancy; LDUH and IPC provided a similar reduction in the incidence of postoperative DVT, but LDUH was associated with a higher frequency of bleeding complications[3]
  - RCT: 332 patients undergoing surgery for abdominal and pelvic malignancy of which 8% were gynecologic operations; 4 weeks of prophylaxis with LMWH reduced venographic DVT from 12.0% in the 1 week prophylaxis group to 4.8% in the 4 week prophylaxis group (RR 0.40; 95% CI 0.18 to 0.88)[4]

1. Clarke-Pearson DL, et al. Obstet Gynecol 1984; 63:92-8.
2. Clark-Pearson DL, et al. Gynecol Oncol 1984; 18:226-32.
3. Clarke-Pearson DL, et al. Am J Obstet Gynecol 1993; 168:1146-53; discussion 1153-4.
4. Bergqvist D, et al. N Engl J Med 2002; 346:975-80.

VTE Prophylaxis Recommendations
Gynecology

- **Low-risk patients should receive thromboprophylaxis with GEC in addition to early ambulation and adequate hydration**
  - Level of evidence: Moderate
- **Moderate-risk patients: LDUH (5,000 IU, 12 h), LMWH (initiated and dosed according to labeling) or IPC are recommended**
  - Level of evidence: High
- **LMWH is the preferred method because it has the advantage of once daily injection and is less likely to cause HIT. IPC is the method of choice in patients with a high risk of bleeding**
  - Level of evidence: High

VTE Prophylaxis Recommendations
Gynecology

High-risk patients:

- **LMWH (initiated and dosed according to labeling) is recommended**
  - Level of evidence: High
- **Fondaparinux is recommended**
  - Level of evidence: Low
- **LDUH (5,000 IU 8 h) is recommended**
  - Level of evidence: High
- **IPC (throughout hospital stay) is recommended**
  - Level of evidence: Moderate

VTE Prophylaxis Recommendations
Gynecology

High-risk patients:

- **LMWH or LDUH combined with IPC or GEC stockings provide optimal prophylaxis**
  - Level of evidence: Moderate
- **Consideration should be given to continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days especially in patients with cancer**
  - Level of evidence: Low
- **Patients undergoing complex laparoscopic surgery should be provided with prophylaxis in accord with risk category**
  - Level of evidence: Low

Risk of VTE in Obstetrics

- **Pregnancy produces a five-fold increase in VTE risk**
- **Puerperium is the time of greatest risk, with a twenty-fold increase[1]**
- **The recent report "Saving Mothers' Lives" showed a sharp fall in deaths from VTE**
  - Attributed to better recognition of high risk women and use of thromboprophylaxis[2,3]

1. Heit JA, et al. Ann Intern Med 2005; 143:697-706.
2. Why mothers die 2000-2002. 6th report, RCOG Press. London, 2004.
3. Saving Mother's Lives. Br J Obs Gynaecol 2011; 118:1-203.

Risk Factors in Obstetrics

- **Pregnancy, history of thrombosis, thrombophilia, immobility, obesity and postpartum hemorrhage[1-3]**
- **Other risk factors include:[4,5]**
  - Age over 35 years
  - Caesarean section, especially emergency
  - Coexisting medical conditions
  - Surgical procedures during pregnancy and the puerperium
- **Risk assessment is recommended early during pregnancy and prior to Caesarean section[6]**

1. James AH, et al. Am J Obstet Gynecol 2006; 194:1311-5.
2. De Stefano V, et al. Br J Haematol 2006; 135:386-91.
3. Pabinger I, et al. J Thromb Haemost 2005; 3:949-54.
4. Jacobsen AF, et al. J Thromb Haemost 2008; 6:905-12.
5. Bonnar J. In Dalen J.E., ed. Venous Thromboembolism. New York: Marcel Dekker, 2003. pp. 217-33.
6. Why mothers die 2000-2002. 6th report, RCOG Press. London, 2004.

Management Strategies for Obstetrics

Clinical Situation	Recommended Management
Single previous VTE (not pregnancy or 'pill' related) associated with a transient risk factor and no additional current risk factors, such as obesity	**Antenatal:** surveillance or prophylactic doses of LMWH ± CEG stockings Discuss decision regarding antenatal LMWH with the woman **Postpartum:** anticoagulant therapy for at least 6 weeks ± GEC stockings
Single previous **idiopathic** VTE or pregnancy or COC related previous VTE or VTE with underlying thrombophilia and not on long-term anticoagulant therapy, or single previous VTE and additional current risk factor(s) (eg morbid obesity, nephrotic syndrome)	**Antenatal:** prophylactic doses of LMWH ± GEC stockings. NB: there is a strong case for more intense LMWH therapy in antithrombin deficiency **Postpartum:** anticoagulant therapy for at least 6 weeks ± GEC stockings
More than one previous episode of VTE, with no thrombophilia and not on long-term anticoagulant therapy	**Antenatal:** prophylactic doses of LMWH + GEC stockings **Postpartum:** anticoagulant therapy for at least 6 weeks + GEC stockings
Previous episode(s) of VTE in women receiving long-term anticoagulants (eg with underlying thrombophilia)	**Antenatal:** switch from oral anticoagulants to LMWH therapy + GEC stockings before 6th week of gestation **Postpartum:** resume long-term anticoagulants with LMWH overlap until INR is in therapeutic range + GEC stockings

Management Strategies for Obstetrics [continued]

Clinical Situation	Recommended Management
Thrombophilia (confirmed laboratory abnormality) but no prior VTE	**Antenatal:** surveillance or prophylactic LMWH ± GEC stockings. The indication for LMWH in the antenatal period is stronger in AT deficient women than in the presence of other thrombophilias, in symptomatic kindred compared to asymptomatic kindred and also where additional risk factors are present. **Postpartum:** anticoagulant therapy for at least 6 weeks ± GEC stockings
Following Caesarean section	Carry out risk assessment for VTE. If an additional risk factor such as emergency section in labour, age over 35 years, high BMI etc is present, provide thromboprophylaxis at least until discharge from hospital [a]
Following vaginal delivery	Carry out risk assessment for VTE. If two or more additional risk factors such as age over 35 years, high BMI etc are present consider thromboprophylaxis ± GEC stockings at least until discharge from hospital [a]

[a] NB where multiple risk factors are present consider extended prophylaxis after discharge

Suggested Thromboprophylactic Doses[1]
Antenatal and Postnatal LMWH

Weight (kg)	Enoxaparin	Dalteparin	Tinzaparin (75u/kg/day)
<50	20 mg daily	2500 units daily	3500 units daily
50-90	40 mg daily	5000 units daily	4500 units daily
91-130	60mg daily [a]	7500 units daily [a]	7000 units daily [a]
131-170	80 mg daily [a]	10,000 units daily [a]	9000 units daily [a]
>170	0.6 mg/kg/day [a]	75 units/kg/day [a]	75 units/kg/day [a]
High prophylactic intermediate dose for women 50-90kg	40 mg 12-hourly	5000 units 12-hourly	4500 units 12-hourly
Treatment dose	1 mg/kg/12 hourly antenatal; 1.5 mg/kg/d postnatal	100 u/kg/12 hourly Or 200 u/kg/d postnatal	175 u/kg/d antenatal and postnatal

[a] May be given in two divided doses

1. Empson M, et al. Cochrane Database Syst Rev 2005:CD002859.

VTE Prophylaxis Recommendations
Obstetrics

- **Previous VTE or a strong family history of VTE, particularly familial VTE at a young age (< 50 years) should be screened for inherited and acquired thrombophilia before pregnancy**
  - Level of evidence: Low
- **All should undergo VTE risk assessment in early pregnancy and repeated if admitted to a hospital with complications (hyperemesis, pre-eclampsia)**
  - Level of evidence: Low
- **LMWH is prophylaxis of choice compared with LDUH in view of efficacy and safety**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Obstetrics

- **Previous VTE with a temporary risk factor that is no longer present and no known thrombophilia or additional risk factors should be offered ante-partum and/or post-partum thromboprophylaxis with LMWH**
  - Level of evidence: Low
- **Previous VTE that was estrogen-related or presence of additional risk factors: LMWH should be started as early as possible in pregnancy and continued for 6 weeks following delivery**
  - Level of evidence: Low
- **GEC stockings during pregnancy should be considered in addition to postpartum prophylaxis**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Obstetrics

- **Patients with previous VTE and thrombophilias should be offered thromboprophylaxis with LMWH antenatally and throughout the 6 weeks postpartum**
  - Level of evidence: Moderate
- **Women on vitamin K antagonists should be switched to LMWH because of the risk of embryopathy between the 6th and 12th week of pregnancy. LMWH dosage should be similar to that used for the treatment of VTE**
  - Level of evidence: Moderate

VTE Prophylaxis Recommendations
Obstetrics

- **Patients with previous VTE and thrombophilia are at moderately increased risk of VTE and should receive LMWH (e.g. enoxaparin 40 mg daily, dalteparin 5,000 U daily or tinzaparin 4,500 U daily in women of normal body weight) from early pregnancy**
  - Level of evidence: Low
- **Women with no history of VTE but with a thrombophilic defect may require thromboprophylaxis, depending on the type of thrombophilia, family history, and the presence of additional risk factors. The risk of thrombosis should be discussed with the patient antenatally and GEC stockings should be considered**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Obstetrics

- **Women with antiphospholipid syndrome and previous VTE or adverse pregnancy outcome should receive thromboprophylaxis with LMWH or LDUH and low dose ASA (75mg/d) from the time pregnancy is diagnosed**
  - Level of evidence: High
- **In women with antiphospholipid syndrome and previous VTE, postpartum prophylaxis should be continued for 6 weeks**
  - Level of evidence: Low

VTE Prophylaxis Recommendations
Obstetrics

- **Postpartum thromboprophylaxis is recommended in women with previous VTE, known thrombophilias and other thrombotic risk factors. The first postpartum daily dose of s.c. LMWH should be given 3-4 h after delivery and should be continued for a minimum of 6 weeks**
  - Level of evidence: Moderate
- **In patients not at high-risk, prophylaxis should continue for 5-7 days, and the need for prophylaxis should be reviewed if the hospital stay continues beyond 7 days**
  - Level of evidence: Moderate

VTE Prophylaxis Recommendations
Obstetrics

- **Where anticoagulants are contraindicated, GEC stockings should be worn for at least 6 weeks following delivery**
  - Level of evidence: Low
- **Breast feeding is not contraindicated with either LMWH, LDUH or warfarin**
  - Level of evidence: Low