Venous thromboembolism in pregnancy - diagnosis, management, and treatment

BJA Education, 21(3): 117e123 (2021)
doi: 10.1016/j.bjae.2020.10.003
Advance Access Publication Date: 6 January 2021

Dr R . J .Elton May 2021

FIGURE 1 *Why Mothers Die*. Reproduced from Why Mothers Die Report, The Sixth Report of the Confidential Enquiries into Maternal Deaths in the UK, published in 2004. With the permission of the Confidential Enquiry into Maternal and Child Health

TABLE 1 Maternal deaths notified to the Confidential Enquiry.

	1991–93	1994–96 (+linkage)	1997–99 (+ linkage)	2000–02 CEMACH
Direct	129	134	106	106
Indirect	100	134	136	155
TOTAL	**229**	**268**	**242**	**261**

TABLE 2 Direct deaths reported to the Confidential Enquiry.

	1994–96	1997–99	2000–02
Thromboembolism	48	35	30
Hypertensive disease	20	15	14
Haemorrhage	12	7	17
Amniotic fluid embolism	17	8	5
Early pregnancy	15	17	15
Sepsis	14	14	11
Other Direct	7	7	8
Anaesthesia	1	3	6
TOTAL	134	106	106

Learning objectives

Learning objectives

By reading this article you should be able to:

- Identify women at high risk of venous thromboembolism in pregnancy.
- Discuss the management of venous thromboembolic events.
- Detail the management of women taking anticoagulant drugs in the peripartum period.

Key points

- Venous thromboembolism is the leading cause of direct maternal death in the UK.
- Pregnancy itself is an independent risk factor for venous thromboembolism and can increase the risk by four to five times.
- Signs and symptoms may be non-specific and often mimic normal symptoms of pregnancy.
- Risk assessment tools are useful in the prevention of venous thromboembolism, and risk must be reassessed at each admission.
- Anticoagulation with low molecular weight heparin is the treatment of choice, although caution must be exercised around its timing and delivery.

Venous thromboembolism

- Leading cause of mortality in pregnancy.
- NO real improvement in mortality in the last 12 years despite guidance
- Most clots happen either in six weeks post partum in the first and second trimester
- Virchows triad - venous stasis, vascular damage and hypercoagualibility

Risk Factors for VTE in Pregnancy

- Maternal specific
- Obstetric
- New onset/ transient risk

- Prevention depends on repeated assessment using the RCOG risk stratification tool for risk and need for anticoagulation

Maternal Morbidity

Women are identified for the Confidential Enquiries into Maternal Morbidity in different ways according to the topic. The women with pulmonary embolism were identified from an existing UKOSS study of pulmonary embolism in pregnancy and immediately postpartum, which identified women fulfilling the criteria in Box 1.1 between March 2015 and September 2016 (Goodacre et al. 2019).

All surviving women notified nationally were used as the sampling frame. A geographically representative sample of 40 women was drawn at random from this group. A full set of medical records was requested from each hospital and general practice concerned. The anonymised records then underwent expert assessment in exactly the same way as the records of the women who died. Consent was requested from women in Northern Ireland to participate, since legislation does not exist to allow inclusion of their data without consent. Hospitals provided only 34 of 40 requested sets of records; the care of these 34 women is described in Chapter 4.

Box 1.1: Case definition used in the UKOSS pulmonary embolism (PE) study

Any pregnant or postpartum woman meeting one of the following criteria:

EITHER: PE confirmed using suitable imaging (angiography, computed tomography, echocardiography, magnetic resonance imaging or ventilation-perfusion scan) showing a high probability of PE

OR: PE is confirmed at surgery or post-mortem

OR: A clinician has made a diagnosis of PE with signs and symptoms consistent with PE present AND the patient has received a course of anticoagulation therapy (>1 week)

2.4 Morbidity Enquiry - women with pulmonary embolism

A national cohort study was undertaken through the UK Obstetric Surveillance System between March 2015 and September 2016, identifying all pregnant and postpartum women diagnosed with pulmonary embolism (Goodacre et al. 2019). As described in section 1.4, a sample of 34 of these women who survived were included in the morbidity Confidential Enquiry. The characteristics of the women who survived and were selected for inclusion in the Confidential Enquiry into Maternal Morbidity are shown in Table 2.20. It is worth noting that, in contrast to the women who died overall, these women were on average younger, more likely to be having their second or subsequent pregnancy, to be white European and employed, and less likely to be overweight or obese with a small proportion who smoked. Around half (53%) had a pre-existing medical or mental health problem compared with 73% (159/217) of women who died.

Table 2.20: Characteristics of women who survived after pulmonary embolism

Characteristics	Total (n=34) Frequency (%)
Age (years)	
<25	7 (21)
25-34	19 (56)
≥35	8 (24)
Parity	
0	8 (24)
≥1	26 (76)
Ethnicity	
White European	30 (88)
Other	4 (12)
Socioeconomic status (Occupational classification)	
Employed (Either woman or partner)	28 (82)
Unemployed (Both)	5 (15)
Missing	1 (3)
Body mass index (BMI)	
18-24	20 (59)
25-29	11 (32)
≥30	3 (9)
Smoking status	
Yes	6 (18)
No	28 (82)
Any pre-existing medical or mental health problem (excluding obesity)	
Yes	18 (53)
No	16 (47)

Clinical VTE

- Presentation – commonly confusing
- Investigation – treat if suspicious , then investigate.
- Don’t measure D Dimer
- PE = CXR and ECG +/_ VQ/CTPA
- DVT – Duplex ultrasound, if legs features
- Uncertain PE = CTPA
- Normal imaging – treat and plan to repeat

Differential Diagnosis DVT

- Erythema, warmth swelling and Pain in lower limb, flank , lower abdomen, buttock or back
- Superfial thrombophlebitis,
- Baker's cyst,
- Lymphoedema,
- Cellulitis,
- popliteal aneurysms,
- Haematoma
- Muscle trauma
- Looks like Normal symptoms of pregnancy

Differential diagnosis of PE

- Mild dyspnoea through to shock

Heart failure

Pneumothorax

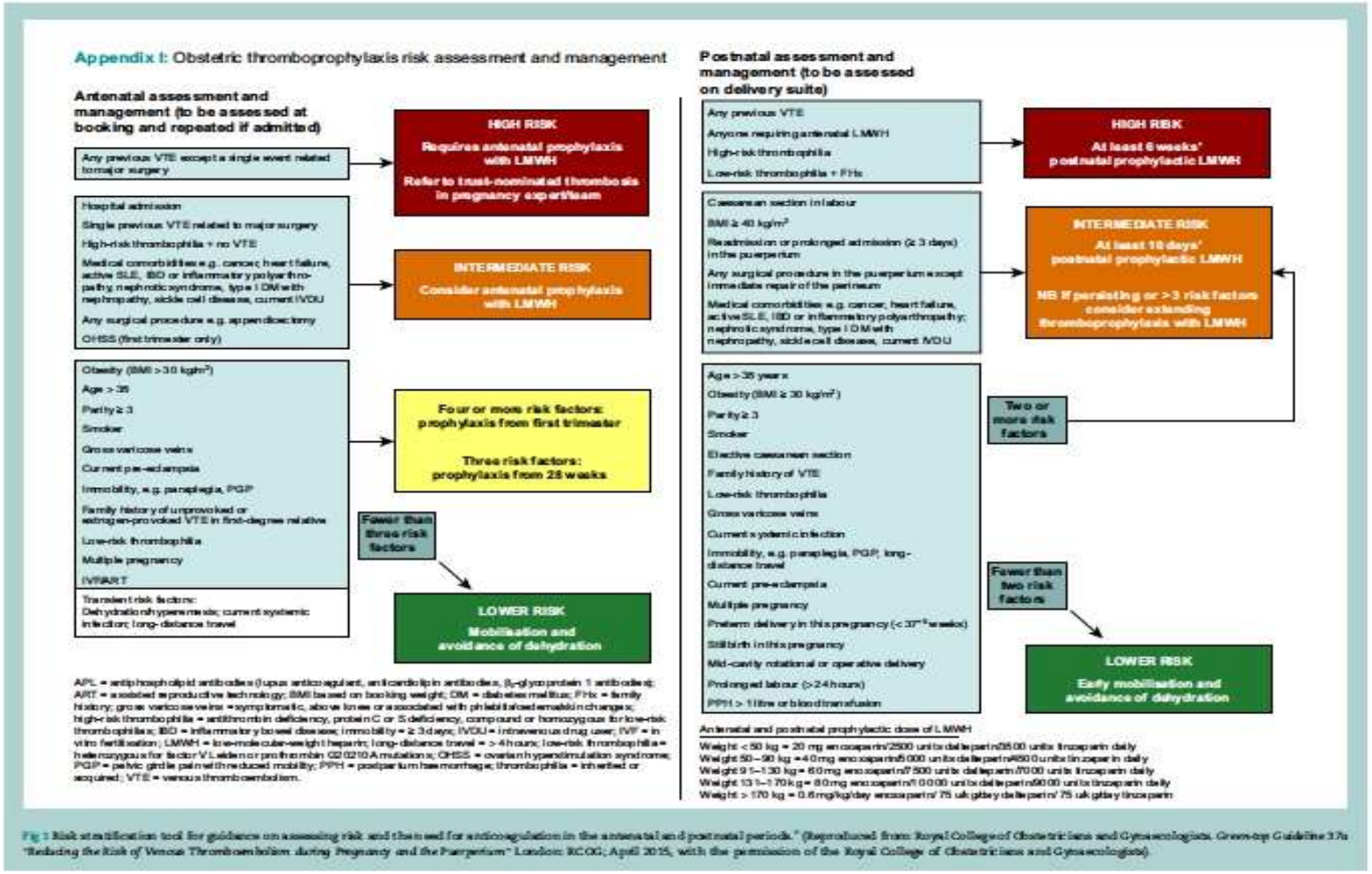
Peripartum cardiomyopathy

Aortic Dissection

Pneumonia

May accompany other disorders

How to use the Chart



Appendix I: Obstetric thromboprophylaxis risk assessment and management

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

Any previous VTE except a single event related to major surgery → **HIGH RISK** — Requires antenatal prophylaxis with LMWH — Refer to trust-nominated thrombosis in pregnancy expert/team

- Hospital admission
- Single previous VTE related to major surgery
- High-risk thrombophilia + no VTE
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU
- Any surgical procedure e.g. appendicectomy
- OHSS (first trimester only)

→ **INTERMEDIATE RISK** — Consider antenatal prophylaxis with LMWH

- Obesity (BMI >30 kg/m²)
- Age >35
- Parity ≥ 3
- Smoker
- Gross varicose veins
- Current pre-eclampsia
- Immobility, e.g. paraplegia, PGP
- Family history of unprovoked or oestrogen-provoked VTE in first-degree relative
- Low-risk thrombophilia
- Multiple pregnancy
- IVF/ART

→ **Four or more risk factors:** prophylaxis from first trimester; **Three risk factors:** prophylaxis from 28 weeks

Transient risk factors: Dehydration/hyperemesis; current systemic infection; long-distance travel

Fewer than three risk factors → **LOWER RISK** — Mobilisation and avoidance of dehydration

APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β2-glycoprotein 1 antibodies); ART = assisted reproductive technology; BMI based on booking weight; DM = diabetes mellitus; FHx = family history; gross varicose veins = symptomatic, above knee or associated with phlebitis/oedema/skin changes; high-risk thrombophilia = antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD = inflammatory bowel disease; immobility = ≥ 3 days; IVDU = intravenous drug user; IVF = in vitro fertilisation; LMWH = low-molecular-weight heparin; long-distance travel = > 4 hours; low-risk thrombophilia = heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS = ovarian hyperstimulation syndrome; PGP = pelvic girdle pain with reduced mobility; PPH = postpartum haemorrhage; thrombophilia = inherited or acquired; VTE = venous thromboembolism.

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

- Any previous VTE
- Anyone requiring antenatal LMWH
- High-risk thrombophilia
- Low-risk thrombophilia + FHx

→ **HIGH RISK** — At least 6 weeks' postnatal prophylactic LMWH

- Caesarean section in labour
- BMI ≥ 40 kg/m²
- Readmission or prolonged admission (≥ 3 days) in the puerperium
- Any surgical procedure in the puerperium except immediate repair of the perineum
- Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy; nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU

→ **INTERMEDIATE RISK** — At least 10 days' postnatal prophylactic LMWH — NB If persisting or > 3 risk factors consider extending thromboprophylaxis with LMWH

- Age >35 years
- Obesity (BMI ≥ 30 kg/m²)
- Parity ≥ 3
- Smoker
- Elective caesarean section
- Family history of VTE
- Low-risk thrombophilia
- Gross varicose veins
- Current systemic infection
- Immobility, e.g. paraplegia, PGP, long-distance travel
- Current pre-eclampsia
- Multiple pregnancy
- Preterm delivery in this pregnancy (< 37 [+6] weeks)
- Stillbirth in this pregnancy
- Mid-cavity rotational or operative delivery
- Prolonged labour (>24 hours)
- PPH > 1 litre or blood transfusion

Two or more risk factors → (INTERMEDIATE RISK)

Fewer than two risk factors → **LOWER RISK** — Early mobilisation and avoidance of dehydration

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

Fig 1 Risk stratification tool for guidance on assessing risk and the need for anticoagulation in the antenatal and postnatal periods.* (Reproduced from: Royal College of Obstetricians and Gynaecologists. Green-top Guideline 37a "Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium" London: RCOG; April 2015, with the permission of the Royal College of Obstetricians and Gynaecologists).

“She might have a VTE”

- GIVE Heparin – LMWH unless about to deliver soon or is acutely ill, UFH infusion
- Blood tests –FBC LIVER KIDNEY COAG
- Senior Clinician

Drug therapy

- Does the drug cross the Placenta
- Use LMWH
- Warfarin - only in late pregnancy
- DOAC – rivaroxaban etc – not used

- Beware contraindications – bleeding risk= rel platelets, clotting factors, stroke, liver disease, severe hypertension and obstetric haemorrhage
- Dosage based on booking weight and kidney fucntion

Monitoring and Maintenance of treatment

- No testing required for LMWH
- Testing required for UFH
- Multidisciplinary management
- Post partum - consider Warfarin – consider DOAC if not breast feeding

Prevention of thromboembolic events

- Mobilise
- Stay hydrated
- Compression stockings
- Preconceptual counselling for those at high risk and MDT management.
- Different lengths of treatment depending on risk factor score

Anaesthesia and Anticoagulation

- Vertebral Canal Haematoma – 150K (NAP3)
- NO direct evidence from pregnant women
- OAA rule is 12 or 24 hours depending on prophylactic or treatment dose.
- REALITY check – induction of labour solves nearly all concerns.
- Alternative analgesia will be opioids
- Alternative anaesthesia will be General anaesthesia

Neurology and Anticoagulation

- Observe motor function in labour
- Check motor function after delivery
- Use straight leg raising as the test at four hours
- Escalation policy required

Prevention and treatment of thromboembolism

There is clear evidence that doctors and midwives find existing risk scoring systems difficult to apply consistently in practice. There is a need for development of a tool to make the current risk assessment system simpler and more reproducible [Saving Lives, Improving Mothers' Care 2018] **ACTION: NHSE/I and equivalents in the devolved nations and Ireland.**

Audits should be conducted not only to assess whether thromboembolism risk assessment was performed, but also whether the calculated risk score was correct [Saving Lives, Improving Mothers' Care 2018] **ACTION: All Health Professionals, Service Managers.**

Reassessment of VTE risk after miscarriage or ectopic pregnancy to consider whether thromboprophylaxis is required is as important as reassessment of risk after giving birth [RCOG Green-top guideline 37a] **ACTION: All Health Professionals.**

Thrombolysis or surgical embolectomy should be considered for pregnant women with high-risk PE [ESC Guidelines for the diagnosis and management of acute pulmonary embolism 2019] **ACTION: All Health Professionals.**

Women should be offered a choice of LMWH or oral anticoagulant for postnatal therapy after discussion about the need for regular blood tests for monitoring of warfarin, particularly during the first 10 days of treatment [RCOG Green-top guideline 37b] **ACTION: All Health Professionals.**

Women should be advised that neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding [RCOG Green-top guideline 37b] **ACTION: All Health Professionals.**

Postnatal review for women who develop VTE during pregnancy or the puerperium should, whenever possible, be at an obstetric medicine clinic or a joint obstetric haematology clinic [RCOG Green-top guideline 37b] **ACTION: All Health Professionals.**

5.4 Overview of care and lessons to be learned

There were many instances in which the anaesthetic care was exemplary, and the anaesthetist initiated prompt and vital care in women with previously unrecognised critical illness. This emphasises that good maternity care depends on the anaesthetist being fully involved as part of the multidisciplinary team and why a senior anaesthetist should be involved in all serious incident reviews in maternity care.

There were, however, some instances in which the reviews of care by the anaesthetic assessors highlighted opportunities where care could have been improved.

Thromboprophylaxis

There were several occasions where there was an opportunity for the anaesthetist to review a woman's risk of venous thromboembolism (VTE) and to prescribe thromboprophylaxis in accordance with national guidelines. The review of the care of women who survived a pulmonary embolism, described in Chapter 6 of this report, highlighted a number of instances when there were gaps in women's thromboprophylaxis around the time of giving birth and highlighted a need to ensure that women on prophylactic or treatment dose anticoagulation have a structured management plan to guide clinicians during the antenatal, intrapartum and postpartum. While prescription of low molecular weight heparin (LMWH) should not be expected to be the sole responsibility of the anaesthetist, there may be opportunities for anaesthetists to ensure that management plans are followed.

Ensure that women on prophylactic and treatment dose anticoagulation have a structured management plan to guide practitioners during the antenatal, intrapartum and postpartum period.

Identify clear lines of responsibility to facilitate prescribing of thromboprophylaxis when indicated in the plan. **N**

Management of Massive life threatening thrombosis in pregnancy

- Collapse , shock , cardiac arrest.
- Team - Obs , Haem, Anaes
- Therapy- IV UFH of Thrombolysis or surgical thrombectomy. Depends on condition of patient
- Rsik of bleeding is 2-3%.

Key messages
from the report 2020

MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

In 2016-18, **217 women died** during or up to six weeks after pregnancy, from causes associated with their pregnancy, among 2,235,159 women giving birth in the UK.
9.7 women per 100,000 died during pregnancy or up to six weeks after childbirth or the end of pregnancy.

We need to talk about SUDEP

Act on:

Night-time seizures

Uncontrolled seizures

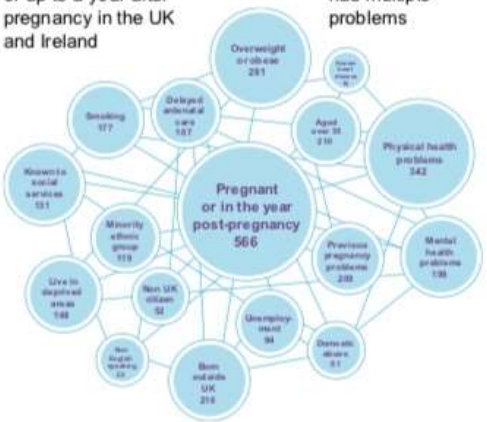
Ineffective treatment

to prevent **Sudden Unexpected Death in EPilepsy**

A constellation of biases

566 women died during or up to a year after pregnancy in the UK and Ireland

510 women (90%) had multiple problems



Systemic Biases due to pregnancy, health and other issues prevent women with complex and multiple problems receiving the care they need

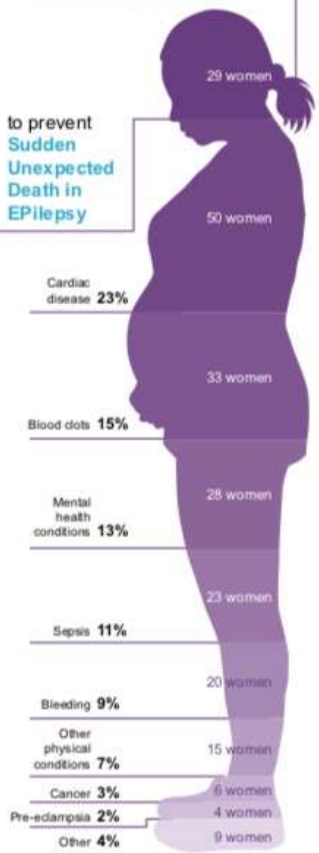
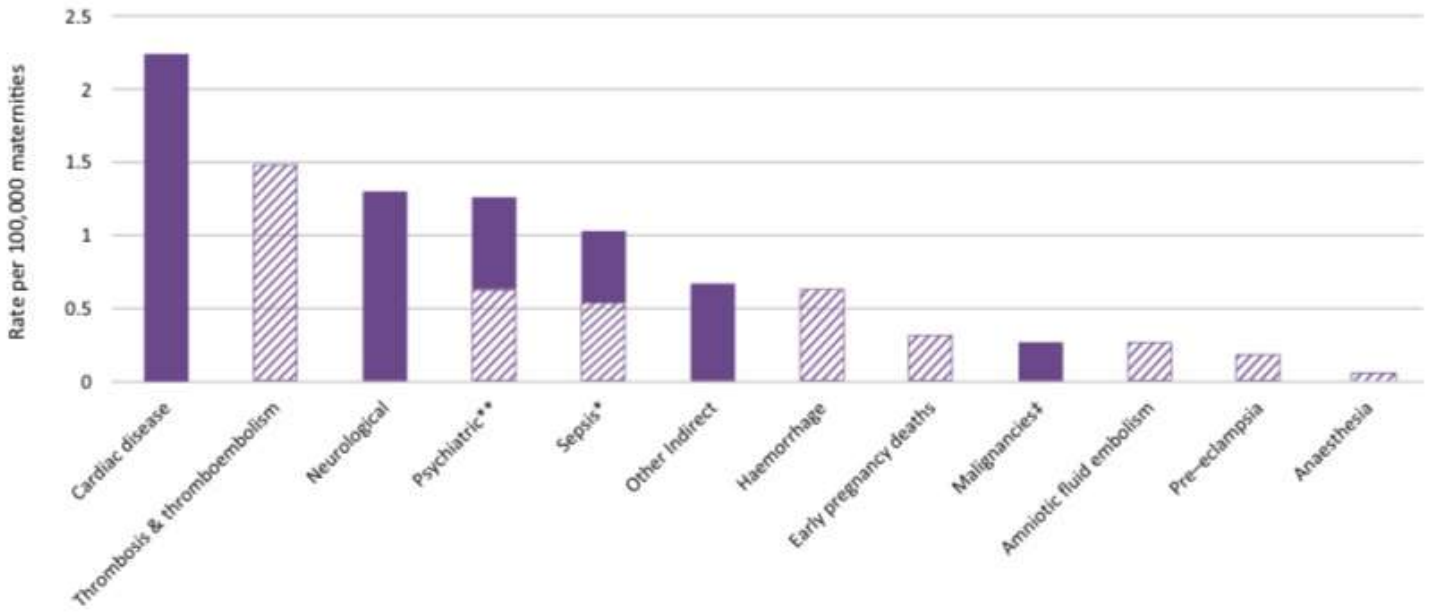


Figure 2.3: Maternal mortality by cause 2016-18



Hatched bars show direct causes of death, solid bars indicate indirect causes of death;

*Rate for direct sepsis (genital tract sepsis and other pregnancy related infections) is shown in hatched and rate for indirect sepsis (influenza, pneumonia, others) in solid bar

**Rate for suicides (direct) is shown in hatched and rate for indirect psychiatric causes (drugs/alcohol) in solid bar

‡Rate for direct malignancies (choriocarcinoma) shown in hatched and rate for indirect malignancies (breast/ovary/cervix) in solid bar

Source: MBRRACE-UK

Key points

- Venous thromboembolism is the leading cause of direct maternal death in the UK.
- Pregnancy itself is an independent risk factor for venous thromboembolism and can increase the risk by four to five times.
- Signs and symptoms may be non-specific and often mimic normal symptoms of pregnancy.
- Risk assessment tools are useful in the prevention of venous thromboembolism, and risk must be reassessed at each admission.
- Anticoagulation with low molecular weight heparin is the treatment of choice, although caution must be exercised around its timing and delivery.

Questions