Thrombosis and Women's Health

Risk factors, contraceptive pill, HRT and your doctor

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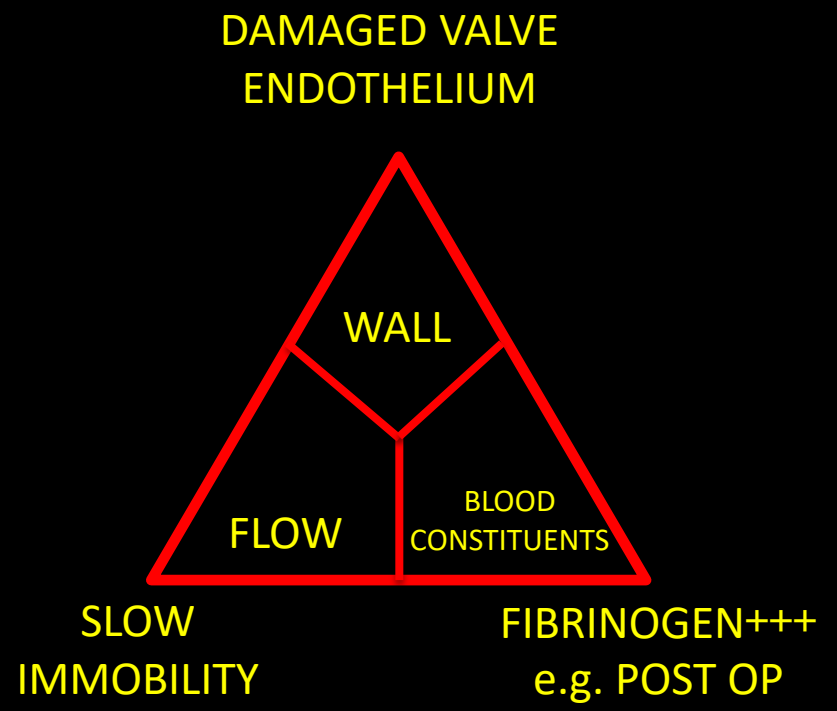
VENOUS THROMBOSIS: AETIOLOGY

PREDISPOSING FACTORS FOR DEEP VENOUS THROMBOSIS

Immobility, bed rest
Post op coagulability changes
Pregnancy
OC pill
Severe burns and trauma
Cardiac failure
Disseminated malignancy
Economy class syndrome



Deep vein thrombosis

- Incidence of VTE 2-3 per 1000
- Incidence is higher in men than in women (above the age of 45).
  - Overall adjusted incidence:
    - Men is 130 : 100,000
    - Women 110: 100,000
    - Men : Women is 1.2 : 1.0

Risk Factors

- Illness or injury that causes prolonged immobility increases the risk of a DVT
- Age >40 years (VTE risk increases with advancing age)
- Contraceptive pills and hormone replacement therapy
- Cancer and its treatment
- Major surgery (example: abdomen, pelvis, or hip or knee replacement)
- Obesity
- Previous DVT or PE
- A family history of blood clots
- Certain heart problems
- Varicose veins
- Faulty blood clotting is an uncommon cause
  - an example is an inherited condition that causes the blood to clot more easily than usual (factor V Leiden)

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Oral Contraceptives-Combined Pill

- 20, 30 or 35 micrograms of ethinyloestradiol
- Different progestogens
- 21 day and every day formulations
- Fixed dose or phasic
- 4 or 12 week withdrawal
- Continuous pill

Oral Contraceptives-Combined Pill

- Advantages
  - Suppress ovulation
  - High efficacy
  - Give predictable ‘periods’
- Disadvantages
  - Increased risk of thrombosis
  - Hypertension in some

Oral Contraceptives-Combined Pill

- Can we reduce risk by Reducing Dose?

Oral Contraceptives-Combined Pill

- Loss of efficacy
- Loss of cycle control (depends on both oestrogen and progesterone)
- Wide range of blood levels via oral route

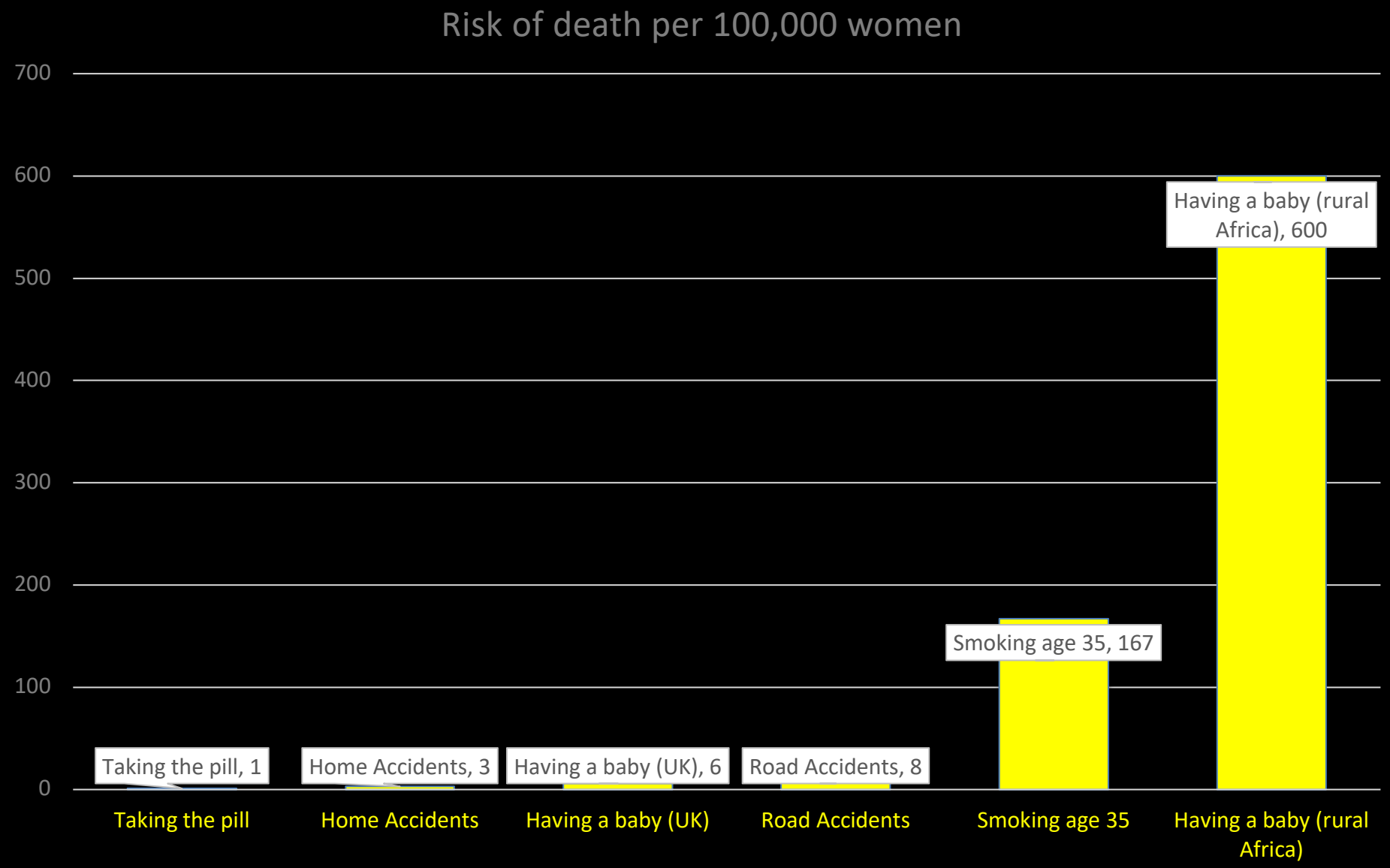
Oral Contraceptives-Combined Pill-Risk

- VTE risk in data sheets:

  15 per 100,000 - second generation

  25 per 100,000 - third generation

Oral Contraceptives-Combined Pill-Risk



Progestogen-only methods

- Advantages
  - Greater safety
- Variable efficacy (from extremely low to better than COC)
- Some measure of loss of cycle control (varies with route, type and dose)

Routes available

- Progestogen-only pill (POP)
- Emergency contraception (Levonelle)
- Injectable (Depo-Provera)
- Intrauterine (Mirena)
- Implant (Implanon)

Desogestrel Progesterone only pill

- 75 micrograms Desogestrel
- Suppresses ovulation
- Lower failure rate
- Different rules for missed pills

Emergency Contraception

- Products
  - Levonelle One Step
  - Any copper IUD, including GyneFix
- Indications
  - Unprotected sex
  - Potential barrier failures
  - Potential pill failure
    - 2 missed pills in first week
    - 4 missed pills in mid-packet
  - Potential IUD failure
  - Increased risk of ectopic in failures

- Awareness of risk may not translate into action

Levonelle One Step

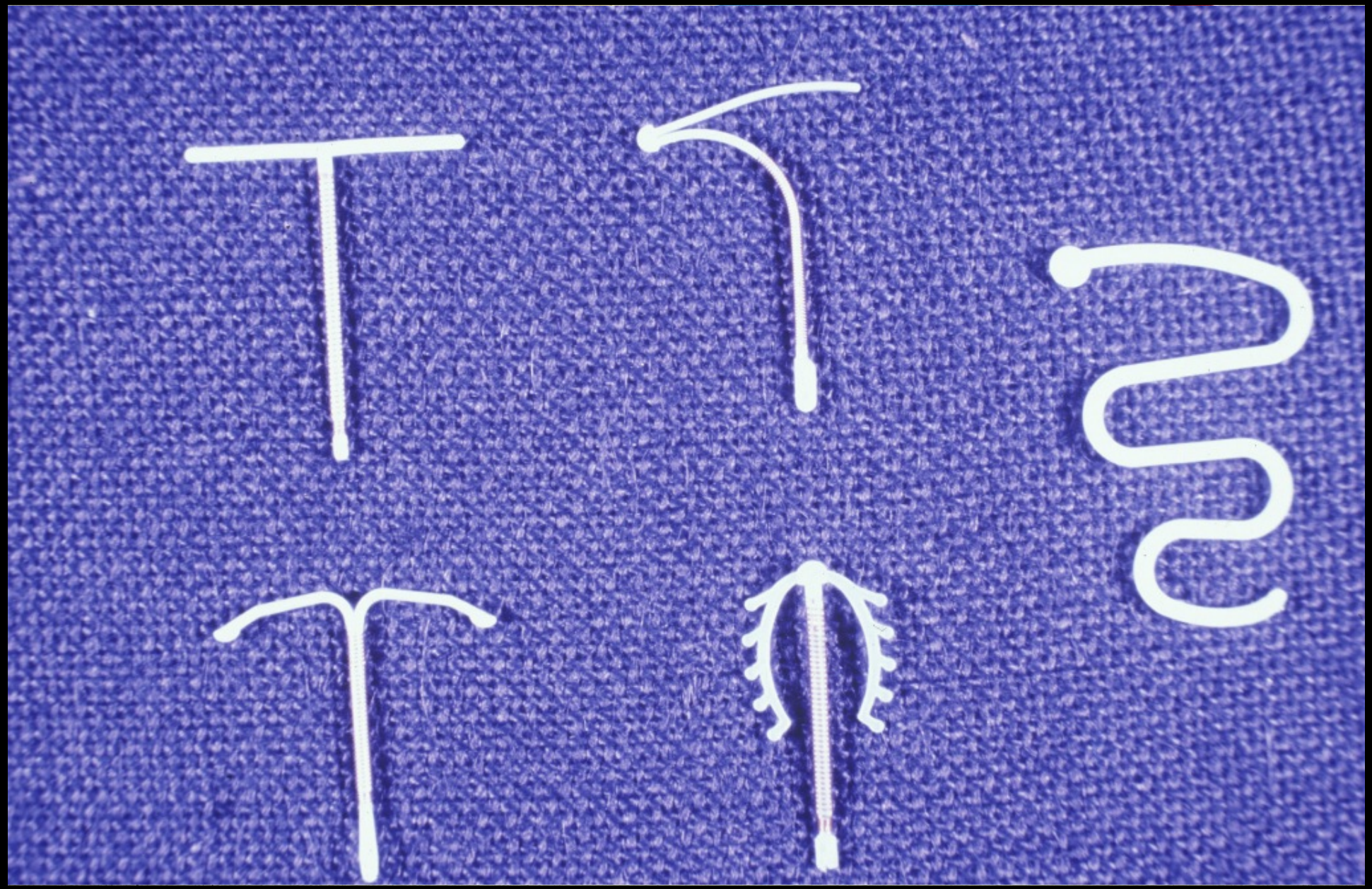
- 1500 micrograms levonorgestrel
- Within 72 hours
- Efficacy
  - < 24 hours 95 %
  - 24-48 hours 85 %
  - 49-72 hours 58 %

Emergency Hormonal Contraception (EHC)

- Side effects
  - 23 % nausea
  - 6 % vomiting
- Contraindications
  - Established pregnancy

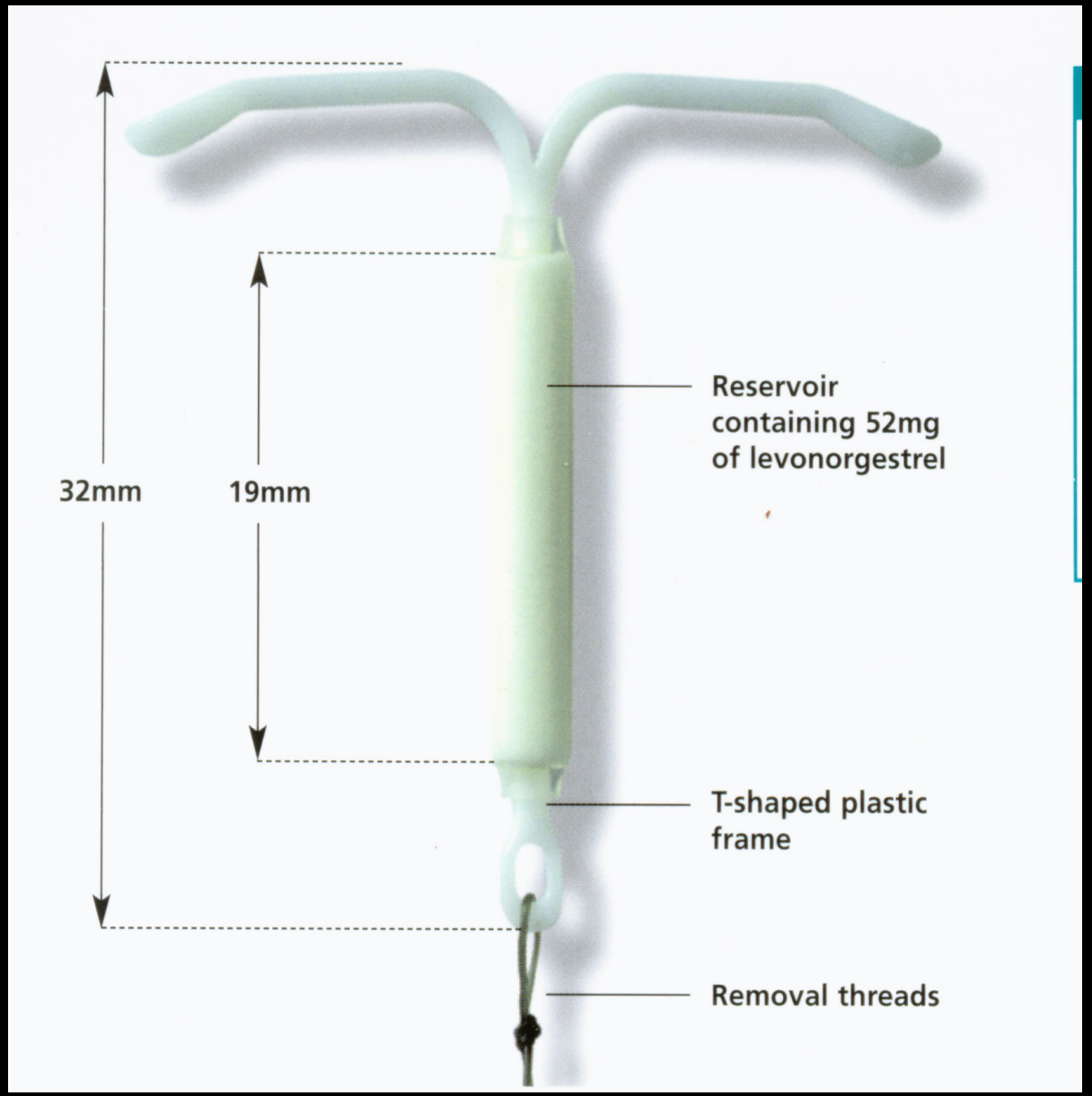
Depo-Provera

- 150 mg medroxyprogesterone acetate
  - IM
  - Every 12 weeks
  - Failure rate approx 0.5%
  - High incidence of amenorrhoea
  - Long-term use associated with reduced bone density which recovers with addback or discontinuation



IUD (Copper devices)

- Gold standard Copper T 380
- Not user-dependant
- Good efficacy (failure rate 1% or less p.a.)
- Requires insertion and removal
- Some increased risk of infection in first 60 days especially when cervix colonised
- Periods may be heavier, longer, more painful


32mm
19mm
Reservoir containing 52mg of levonorgestrel
T-shaped plastic frame
Removal threads

Intrauterine

- Mirena releases 20 mcg levonorgestrel daily for 5 years
- Failure rate equal to or less than female sterilisation
- Reduction in menstrual loss a beneficial side-effect

Mirena

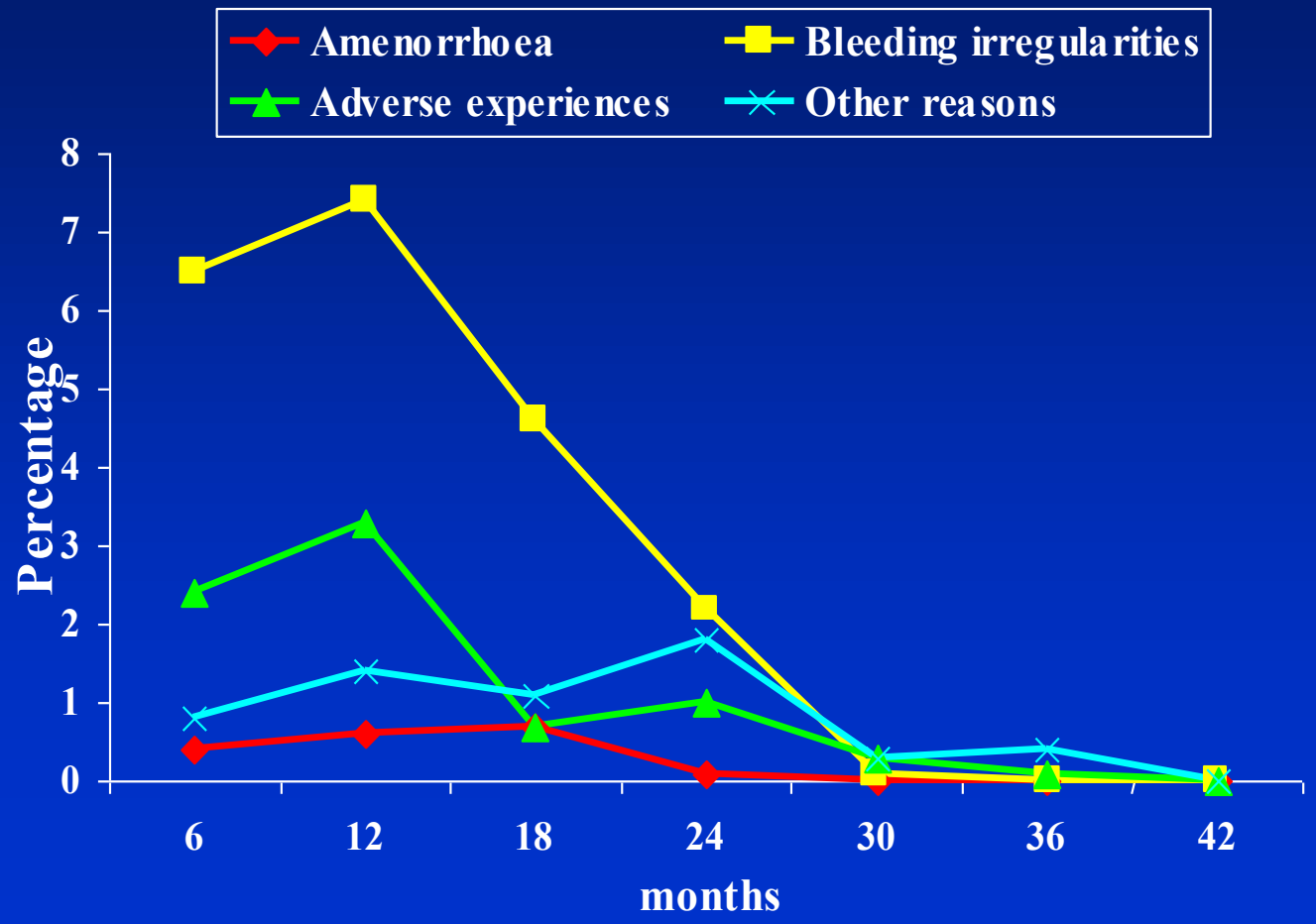
- Good contraception
- Control of menorrhagia
- May help dysmenorrhoea
- Effective endometrial protection

- Some systemic absorption
- Irregular bleeding may persist
- Insertion not always easy

Implanon

- Subdermal
- Etonogestrel
- Menstrual irregularity common
- Failure rate far below that of sterilisation

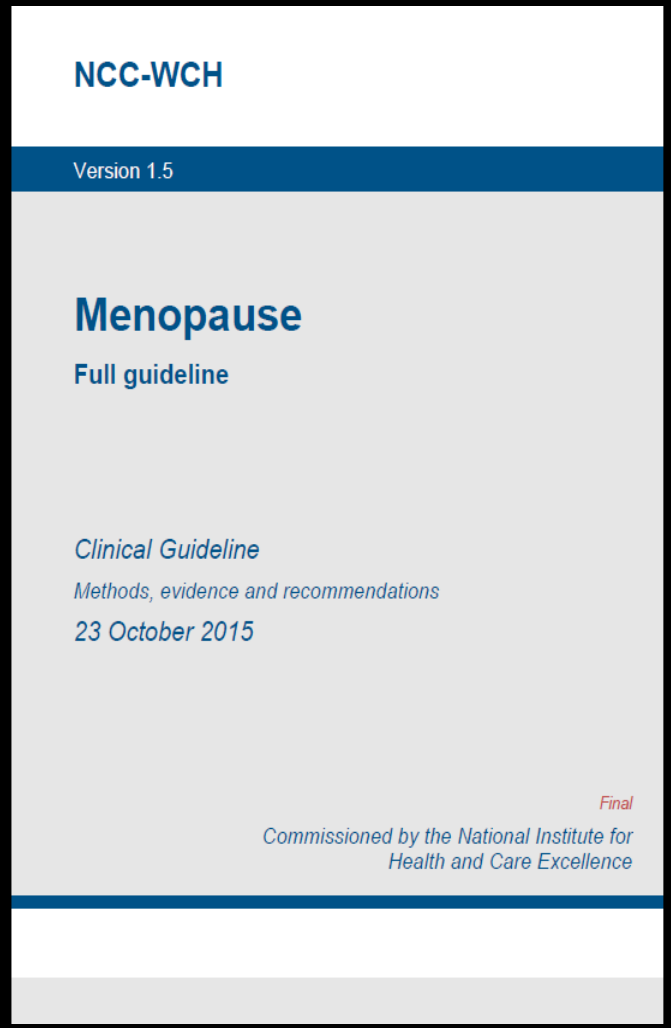
Discontinuation rates with Implanon® (n=720)



Summary

- Combined pill increases the VTE risk
- There are many choices
- Many use Desogestrel first line now
- GPs would prefer ‘LARCs’
  - Long Acting Reversible Contraception

Hormone Replacement Therapy for Menopausal symptoms



Hormone Replacement Therapy for Menopausal symptoms

- Diagnosis and classification of the stages of menopause

- Optimal clinical management of menopause-related symptoms, including:
  - treatments for symptomatic relief (specifically vasomotor, musculoskeletal and psychological symptoms, and altered sexual function), including: -NEXT SLIDE!

Hormone Replacement Therapy for Menopausal symptoms

Hormonal pharmaceutical treatments:

- oestrogen combined with progestogen
    - (oral and transdermal)
- oestrogen
    - (oral and transdermal)
- oestrogen (depot)
- progestogen alone
- testosterone
- tibolone
- bio-identical hormones licensed for use in the UK
- tissue-selective oestrogen complexes
- selective oestrogen-receptor modulators

Hormone Replacement Therapy for Menopausal symptoms

- Non-hormonal pharmaceutical treatments:
  - selective serotonin reuptake inhibitors
  - serotonin–noradrenaline reuptake inhibitors
  - gabapentin
  - clonidine

- Non-pharmaceutical treatments:
  - phytoestrogens
  - herbal preparations (including black cohosh and red clover)
  - acupuncture
  - lifestyle advice

- Psychological therapy:
  - cognitive behavioural therapy

Hormone Replacement Therapy for Menopausal symptoms

- Risks and benefits of treatments;
  - Including the contribution of hormone replacement therapy (HRT) in preventing long-term sequelae of the menopause (especially osteoporosis and cardiovascular disease)
- Timing of treatment
- Monitoring of treatment
- Duration of treatment
- Treatment withdrawal strategies
- Diagnosis and management of premature ovarian insufficiency

Individualised Care

- Adopt an individualised approach at all stages of diagnosis, investigation and management of menopause

- No ‘one size fits all’

Providing information and advice

- Give information to menopausal women and their family members or carers (as appropriate) that includes:
  - an explanation of the stages of menopause
  - common symptoms and diagnosis
  - lifestyle changes and interventions that could help general health and wellbeing

Providing information and advice

- Benefits and risks of treatments for menopausal symptoms
  - Hormonal eg HRT
  - Non-hormonal eg clonidine
  - Non-pharmaceutical eg CBT
- Long-term health implications of menopause.
- Contraception for women who are in the perimenopausal and postmenopausal phase
- NB Young women – normal rules don’t apply
  - Fertility unpredictable

Managing short-term menopausal symptoms - Vasomotor Symptoms

- **Offer women HRT** for vasomotor symptoms after discussing with them the short-term (up to 5 years) and longer-term benefits and risks

- **Do not routinely offer SSRIs, SNRIs or clonidine** as first-line treatment for vasomotor symptoms alone.

Managing short-term menopausal symptoms - Vasomotor Symptoms

- Explain to women that there is some evidence that isoflavones or black cohosh may relieve vasomotor symptoms. However, explain that:
  - multiple preparations are available and their safety is uncertain
  - different preparations may vary
  - interactions with other medicines have been reported

Managing short-term menopausal symptoms - Vasomotor Symptoms

- Consider **HRT** to alleviate **low mood** that arises as a result of the menopause.
- Consider **CBT** to alleviate **low mood or anxiety** that arise as a result of the menopause.
- **there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression**

Stopping HRT

- Offer women who are stopping HRT a choice of gradually reducing or immediately stopping treatment.

- Explain that:
  - gradually reducing HRT may limit recurrence of symptoms in the short term
  - gradually reducing or immediately stopping HRT makes no difference to their symptoms in the longer term.

- NO ARBITRARY TIME LIMIT!

Venous thromboembolism

- HRT affects vascular endothelium
- Oral HRT affects hepatic production and clearance of haemostatic factors

Oral HRT and VTE

Randomized clinical trials

- Oestrogen & Progesterone (age 70–79 years) RR 7.5
  vs. placebo (age 50–59 years)
- Oestrogen & Progesterone(age 50–59 years) RR 0.7
  vs. placebo (age 70–79 years)

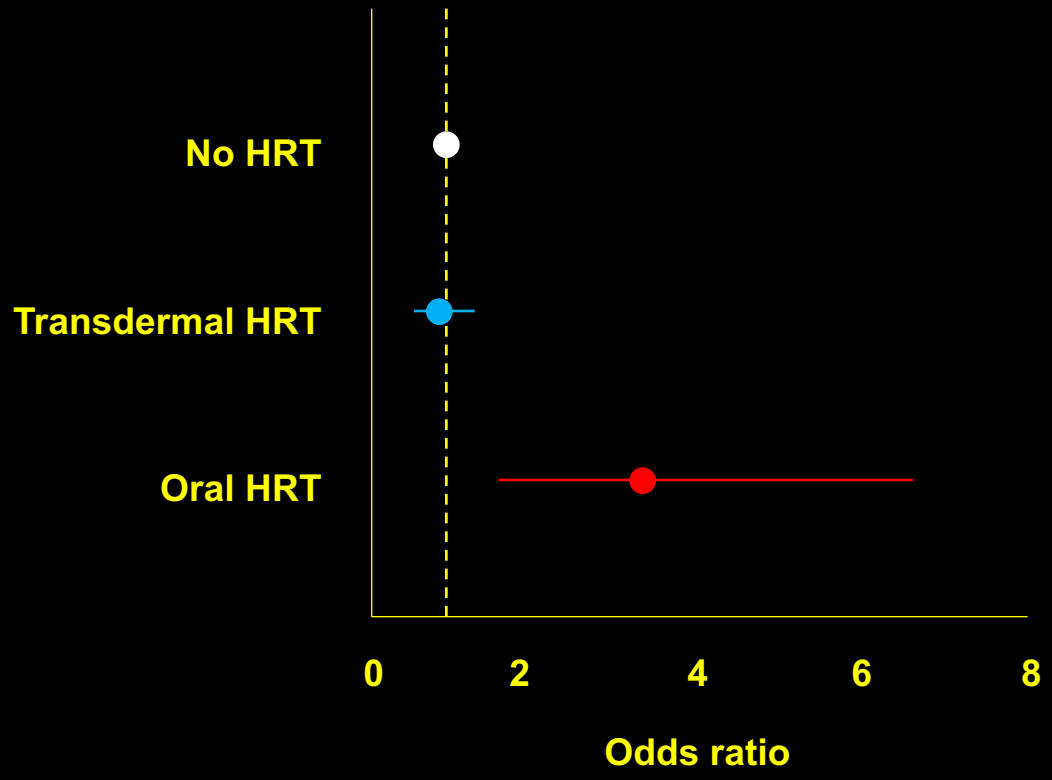
Hulley *et al. J Am Med Assoc* 1998;280:605–13
Cushman *et al. J Am Med Assoc* 2004;292:1573–80
Women's Health Initiative Steering Committee. *J Am Med Assoc* 2004;291:1701–12

Oestrogen Replacement and HRT and VTE risk: absolute risk

- A per oral HRT increases moderately the thromboembolic risk, in particular in presence of hereditary or acquired thrombophilia, and during the first year after initiation of Oestrogen replacement or HRT

  (Age 50–59: 2 additional cases/year per 10,000 women)
- Low-dose transdermal HRT seems not to increase the thromboembolic risk

HRT route and VTE



Scarabin, *et al. Lancet* 2003;362:428–32

Risk of VTE: HRT route of administration and progestogens

(ESTHER study)

Route/progestagen	OR	95% CI
Oral	4.2	1.5–11.6
Transdermal	0.9	0.4–2.1
Micronized progesterone	0.7	0.3–1.9
Pregnanes	0.9	0.4–2.3
Norpregnanes	3.9	1.5–10.0

HRT and thromboembolism:

Misperceptions

- The risk of both venous and arterial thromboembolism is increased during HRT
- Stroke risk is substantially increased in women receiving HRT

Venous thromboembolism

- Explain to women that:
  - The risk of venous thrombosis is approximately two-fold higher with standard doses of oral HRT, but is a rare event in that the background prevalence is extremely low in a healthy woman under 60 years of age. It is also associated with obesity and with thrombophilia
  - the risk of venous thromboembolism (VTE) is increased by oral HRT compared with baseline population risk
  - the risk of VTE associated with HRT is greater for oral than transdermal preparations
  - the risk associated with transdermal HRT given at standard therapeutic doses is no greater than baseline population risk.

Cardiovascular disease

- HRT:
  - does not increase cardiovascular disease risk when **started in women aged under 60 years**
  - does not affect the risk of dying from cardiovascular disease**.**
    - the presence of cardiovascular risk factors is not a contraindication to HRT as long as they are optimally managed.

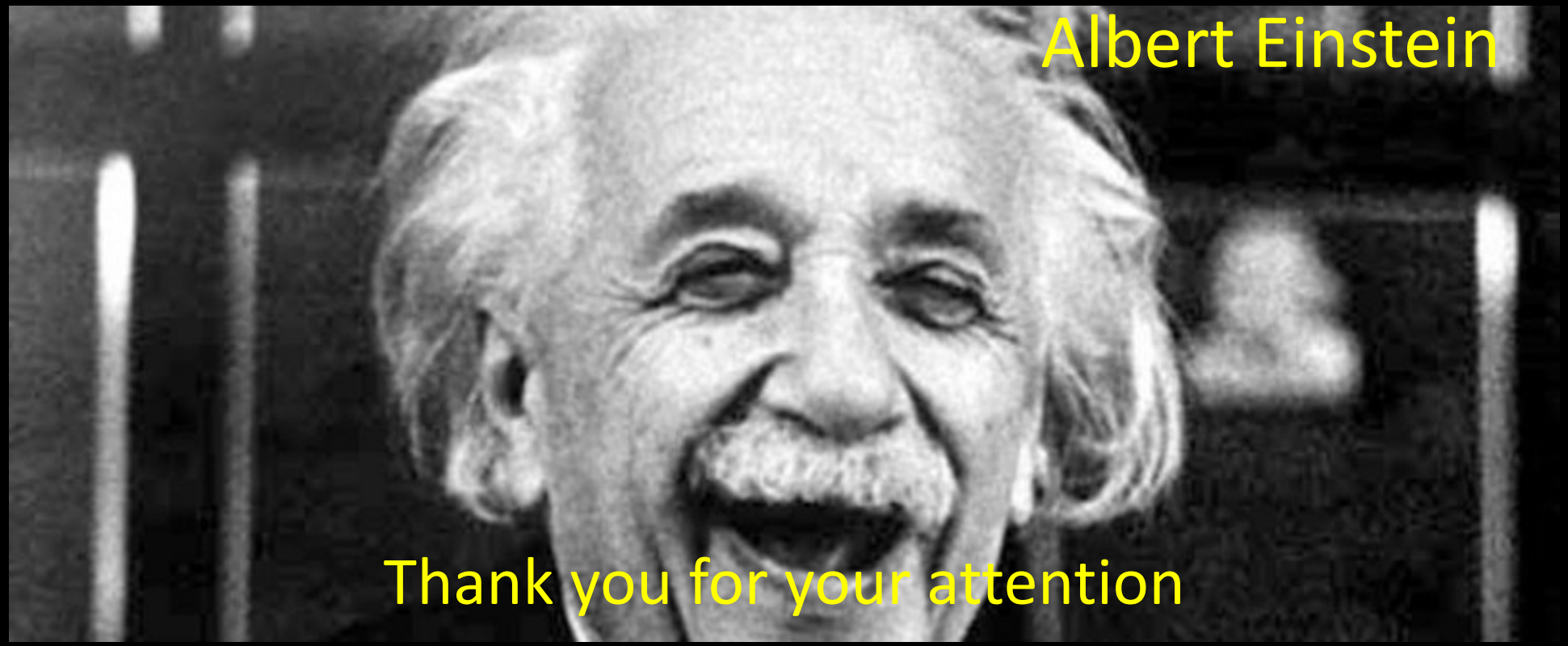
Cardiovascular disease

- The baseline risk of coronary heart disease and stroke for women around menopausal age varies from one woman to another according to the presence of cardiovascular risk factors
  - HRT with oestrogen alone is associated with no, or reduced, risk of coronary heart disease
  - HRT with oestrogen and progestogen is associated with little or no increase in the risk of coronary heart disease.
- Oral (**but not transdermal**) oestrogen is associated with a small increase in the risk of stroke
  - the baseline population risk of stroke in women aged under 60 years is very low .

Summary

- Hormonal manipulation increase thrombotic risk
- Minimise risk by
  - Keeping a good body shape/weight
  - NEVER smoke
  - Consider the mode of absorption
- Pregnancy is much higher risk than the contraception
- Menopausal symptoms can devastate a life, both for the lady suffering and those in her care network

Education is what remains
after one has forgotten what one has learned
in school



Thank you for your attention

Questions?

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