Medical condition
Obesity, family history and VTE

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Part 1 Obesity
1. The Centers for Disease control and Prevention. BMI categories. 
Medical condition Obesity
VTE risk
VTE is rare among women of reproductive age. All COCs are associated with an increased risk for venous thromboembolism (VTE) compared to non-use. A number of studies have found differences in risk for VTE associated with COCs containing different types of progestogens.

Current evidence suggests that COCs containing levonorgestrel, norethisterone and norgestimate are associated with the lowest risk. The absolute differences, however, are very small.

Limited data do not suggest that the small absolute risk for arterial events associated with COC use varies according to the type of progestogen.
1. **Rabe, T. et al.: Contraception and Thrombophilia - A statement from the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF e.V.) and the Professional Association of German Gynaecologists. J Reproduktionsmed Endokrinol 2011; 8: 126-167.**

2. **Dinger, JD. Abstract congress European Society for Contraception, Prague 2008**

VTE risk increases significantly with age and BMI in CHC users. Think about alternatives to CHC. In young women obesity is not an absolute contraindication for CHC use.
Efficacy of contraceptive methods in obese women
CHCs
Obesity has increased dramatically in the United States in recent decades. Our objective was to explore associations of contraceptive choices of US women, aged 20–44 years, with body mass index (BMI) and relevant covariates.

Data are based on interviews with a national sample of 11,300 women in the 2011–2015 National Survey of Family Growth. We analyzed women ages 20–44 at risk of unintended pregnancy. The primary dependent variable was BMI category. Covariates analyzed included age, parity, race/ethnicity, marital status, self-reported health and education. Data were analyzed via cross-tabulation and logistic regression. We determined unadjusted and adjusted odds ratios for three categories of contraceptive method: female sterilization, intrauterine device (IUD) and hormonal contraception.

Results

- Obese women have higher odds of female sterilization compared to women with normal BMI:
  - BMI 30–34.9: aOR: 1.96 (95% CI: 1.45–2.66)
  - BMI > 35: aOR: 1.56 (95% CI: 1.13–2.14)
- Odds of hormonal contraceptive use are reduced:
  - aOR: 0.78 (95% CI: 0.62–0.98)
- Weight concerns and obesity affect contraceptive decision making

1. Mosher WD et al. Contraception 2017

Ref 1
women with normal BMI.

- Odds of IUD use are significantly higher among women with BMI >35 kg/m² (aOR=1.64, 95% CI 1.20–2.25).
- Odds of hormonal contraceptive use are correspondingly reduced (aOR=0.78, 95% CI 0.62–0.98) for women in the highest BMI category.

Conclusions: Contraceptive use varies by BMI category even after adjusting for usual correlates of use. Differences in contraceptive use by BMI category have implications for contraceptive counseling and provision.

Ref 1: Interindividual variability in EE plasma concentrations were 24-64%. A high variability is also known for normal-weight women.
Ref 2: This joint population PK analysis demonstrated reduced systemic COC exposure in obese subjects (Cmax and AUCτ) but no difference in trough LNG and EE concentrations.
Ref 3: OC hormone peak levels are lower among obese women compared to normal-weight women, but their trough levels are similar. In this small study, the observed PK differences did not translate into more ovarian follicular activity among obese OC users and are unlikely to have an impact on effectiveness.


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Obese women did not have lower etonogestrel plasma levels, than normal-weight women. EE levels were lower but until week 6 in the therapeutic range. Therefore efficacy of the CVR seems not to be reduced.

CHCs, on the whole, do not appear to adversely affect body weight; furthermore, they provide important non-contraceptive benefits including regulation of menses and a significant reduction in endometrial and ovarian cancer risk. Nevertheless, there is a controversy about the efficacy of these methods in obese women and there is concern with regard to safety (thromboembolic and cardiovascular risk), especially in CHCs containing EE. No post-marketing surveillance studies are available yet for estradiol-containing pills.
Access to efficient and safe alternatives to CHCs for obese women is of importance when weighing up benefits and risks of contraceptive choices. Access differs across Europe.
Medical condition: Obesity
Progestin only methods and IUDs

- There are limited data on the efficacy of desogestrel 75 μg in obese women. The WHO Medical Eligibility Criteria for progestin-only pills do not include any restriction on the use of POPs in obese women. Desogestrel 75 μg is not associated with an increased risk of thromboembolic events or arterial embolic events 26, 35. The impact of desogestrel 75 μg on plasma lipids and glucose metabolism is minimal
- **Implant:** In the CHOICE study the efficacy of the was not reduced in obese women. Plasma levels of ENG are lower in obese women and come close to the concentration which is necessary to effectively prevent ovulation. In a comparative 12 month study of three different progestin-only methods including the ENG implant, a small increase in weight (2.1 kg) was observed but with no difference between the three methods vs the copper IUD. The implant has little and clinically a non-relevant impact on fasting glucose and insulin in obese women. In women with diabetes, HbA1c did not change in implant users, nor did the daily insulin requirement. Triglycerides and HDL
decrease but stay within the normal clinical range. In one study there was a small but significant decrease in cardioprotective high molecular weight adiponectin. On the other hand, inflammatory markers decreased or were unchanged. Preliminary epidemiological data do not suggest an increased risk of thrombotic stroke or myocardial infarction with this implant. From a theoretical standpoint, given the low progestin dosage in the implant, the occurrence of such events is unlikely. On the other hand, ENG plasma levels in obese women are lower. Thus, even if epidemiological and clinical data at present do not indicate decreased efficacy in obese women, caution is recommended. As ENG plasma levels decline over time an earlier replacement of the implant after 24 months instead of 36 months may be considered in some obese women, in particular those with concomitant use of hepatic enzyme inducers.

- Several studies found that DMPA (i.m. and s.c.) is highly effective in normal-weight and overweight women. Jain et al. demonstrated no difference in efficacy in obese DMPA s.c. users, but showed a trend towards decreasing trough medroxyprogesterone acetate (MPA) levels as BMI increased. This observation caused uncertainty in regard to the effectiveness in women with BMI >35 kg/m². However, median MPA concentration remained consistently above levels needed for suppression of ovulation (200 pg/ml) in participants with all classes of obesity (I–III). Even in extremely obese women, median MPA levels remained above the level needed to prevent ovulation, but when compared with normal-weight women they were lower among class I–II obese women and lowest among class III obese women, with a higher risk of ovulation at the end of the first injection. DMPA is frequently used all over the world in women with obesity and other cardiovascular risk factors. Haemostatic risk markers do not indicate changes and therefore do not suggest an increased risk of VTE. One observational study reported an elevated VTE risk with DMPA, but was limited by a small number of cases. HDL and insulin sensitivity were found to be reduced in one trial.

- **Copper-IUDs** neither affect metabolic parameters nor the risk of VTE. They are highly efficient and their efficacy is not affected by weight or BMI, because the contraceptive acts locally in the uterus. Contraindications, such as ongoing pregnancy, uterus malformation and active pelvic inflammatory disease, must be excluded. Increased STI risk, hysterometer >9 cm and nulliparity indicate need for caution before prescription and insertion, or should be weighed against other benefits.

- **LNG-IUS**: Plasma levels with the LNG-releasing intrauterine system are lower in obese women compared with non-obese women. Because of the local effects of this system in the uterine cavity the efficacy should not be compromised in obese women. The system is not associated with an increased risk of VTE and exerts only minimal effects on plasma lipids and glucose metabolism. An advantage might be protection of the endometrium in obese women. In an observational study the removal rate was >20% in obese women.

**Three options are available for EC after unprotected intercourse** in the majority of European countries:
(1) Levonorgestrel 1.5 mg orally within 72 h after unprotected intercourse.
(2) UPA 30 mg orally within 120 h after unprotected intercourse.
(3) T-shaped copper IUD: to be inserted within 120 h after unprotected intercourse.

Insertion of a copper IUD is the most efficient method, but access is not available everywhere; insertion requires a trainer provider, is uncomfortable and costs are high. Furthermore, the method is not acceptable to all women. UPA 30 mg appeared superior to LNG 1.5 mg especially when administered after the LH surge and between 72 and 120 h following unprotected intercourse. Besides the lower pregnancy rate, the longer window for use and the higher capacity to prevent ovulation in the presence of follicles measuring 18–20 mm are important additional advantages of UPA. In most countries, LNG but not UPA are available over the counter. Side effects are similar with
both methods. One meta-analysis indicated that in obese women the efficacy of both methods is reduced, but the efficacy of LNG was more reduced than that of UPA (OR 4.4 [CI 2.0–9.4] vs OR 2.6 [CI 0.9–7.0]) compared with women with normal BMI.

From Ref 1: The medical eligibility criteria of the US Centers for Disease Control and Prevention (CDC) recommend against the use of COCs or POPs in post-bariatric patients due to possible decreased efficacy secondary to malabsorptive procedures. However, a systematic review of the literature concluded that no substantial decrease in effectiveness was identified from available studies 74. In cases of surgical procedures not including malabsorption there is no reason to restrict COC use. In women who have returned to a BMI < 30 kg/m², non-oral CHCs are a possible alternative, although data on efficacy and safety in this population is limited.

From Ref 3: Etonogestrel pharmacokinetic was investigated before and after Roux-en-Y gastric bypass surgery in nine women aged 18-45 years using 75 micrograms desogestrel. study did not reveal any clinically significant changes
in etonogestrel pharmacokinetics, suggesting that oral desogestrel may be used by women after RYGB surgery. As the number of participants is small, desogestrel should nevertheless used with some caution in this patient group. The advantage is, that this POP is not associated with and elevated VTE risk in obese women.
Case
Medical condition: Obesity

17 year old adolescent with a BMI of 31 kg/m², non-smoker, no further risk factors, wants hormonal contraception with regular cycles. She does not use tampon and does not like to touch her vagina. For her only CHC are acceptable.

Which CHC might be the preferred option in this teenager?

- Does use of a 20μg EE pill decrease VTE risk?
- What type of progestin should be chosen?
- Will a long-cycle be more efficient in obese women?
- Is a pill containing 30EE μg/150 μg LNG more efficient?
- Is the CTP an option?
- What should be discussed in addition?
Medical condition: Obesity, VTE, efficiency
Case 1

Is the VTE risk with CHC use acceptable in this young woman, who wants to use a method with regular bleeding?

Yes, if she refuses all other methods and has no further risk factors.
Medical condition: Obesity, VTE, efficiency
Case: Counselling aspects

Discuss the long-term risks associated with her weight and advice her to exercise and visit a nutrition course to learn, how to lose weight

- COC containing ≤ 20 μg EE are not associated with a lower VTE risk than those with 30-35 μg EE. Therefore use 30μg EE COCs to increase efficacy.
- Advise use of a COC with EE/LNG (lower VTE risk CHC containing third or fourth generation progestins)
- As steady state is achieved delayed, use of condoms can be recommended for the initial 10 days in new starters.
**Medical condition: Obesity, VTE, efficiency**

**Case: Efficacy of non-oral CHC**

**CTP and CVR**
- Efficacy of the CTP may be reduced. Her BMI is just a bit above 30 kg/m². The CTP could be used, if she would not accept oral contraception
- The CVR could be used if she would prefer vaginal application
- Both methods are associated with a twofold VTE risk in relation to a COC with levonorgestrel (6-12/10000 woman-years vs 5-7/10000 woman-years)
Part 2 Family history and VTE
Medical condition
Contraception after VTE

**Efficient and safe options**
- Copper IUD and LNG-IUS
- POP Desogestrel
- Implant
- DMPA
- Permanent methods
**Definition of Family history for VTE**

**Positive family history**
Having a member of your family who has had a blood clot, a deep vein thrombosis, ischaemic stroke or pulmonary embolism

**Strong-risk family history**
If the first-degree relative had the event at age <50 years the VTE risk is especially high and CHCs should be avoided

Only 30% of women with a positive family history suffer from any type of thrombophilia
Medical condition
Positive family history

Efficient and safe options for contraception

- Copper IUD and LNG-IUS
- POP Desogestrel
- Implant
- DMPA
- Permanent methods


The vTE risk in women with a positive family history increases with younger age of the affected relative and number of relatives.

Second degree relatives also play a role. More than one first degree relative with VTE results in a OR of 4!!

**WHO definition**: Family history is positive if a first-degree relative has experienced a VTE. A family history is a condition where the advantages of using the method generally outweigh the theoretical or proven risks.

Ref 1: Data source: Swedish Registry 1987–2007, siblings with VTE vs siblings without VTE. Among 45,362 VTE cases, 2393 affected siblings were identified. The role of age was taken into account.
• The DVT risk in women with a positive family history increases with younger age of the affected relative and number of relatives.
• If CHC users with a family history have not experienced a VTE in the first year of use, the probability of developing a DVT in the future is smaller than in new users.
Medical condition
Positive Family history - VTE risk
Case: How to handle siblings

Risk balancing in women with positive FH

No genetic mutations were found.
Can she continue with COC?
Can her sister continue with the pill, she is 21 years old and started pill with 18 years?
Can her younger sister, today 14 years old use CHCs in the future?

siblings of 14, 17 and 21 years
Medical condition
Positive Family history - VTE risk
Case: How to handle siblings

Risk balancing in women with positive FH
What has to be considered?

- 17 year old girl after DVT
- DVT event in 17 year old new starter occurred typically in the early phase of use
- No thrombophilia
- No other cases of VTE in first or second degree relatives
- 17 year old cannot use CHC after having had DVT (WHO 4)
Medical condition
Positive Family history - VTE risk
Case: How to handle siblings

• VTE risk in 21 year old sister
  o With a 1 first degree relative < 50 years the DVT risk is 15-fold.
  o She already used the pill without problems, which decreases the probability that she suffers from a genetic predisposition in the family
  o She might continue with the CHC, but changing to a POC or IUD would reduce her nevertheless elevated DVT risk

• For the sister aged 14
  o She will be a newstarter
  o Her VTE risk with CHC use and a 1. first degree relative < 50 y is 15 fold!
  o Do not start with CHC recommend POC or IUD.