TOPIC : POC Overview

Progestin-only contraception (POC) Overview

An advanced slide kit complementing the WHO training tool is available from www.fptraining.org

Update January 2020

TOPIC : POC Overview

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This session discusses the most commonly used POCs in Europe

- Desogestrel 75 µg pill (POP)
- Drospirenone 4 mg pill (POP)
- Etonogestrel-releasing 3 year implant (Implant)
- Depot medroxyprogesterone acetate (DMPA)

Information about the levonorgestrel-releasing intrauterine system (LNG-IUS) will be given in the IUD/LNG-IUS sessions

TOPIC : POC Overview

Contents

- Progestin generations and properties
- Mechanisms of action
- Contraceptive efficacy and return to fertility
- Safety
- Use in women with medical conditions (incl. breastfeeding)
- Health benefits
- Contra-indications
- Adverse events: bleeding, breast tenderness, weight, acne, BMD

TOPIC : POC Overview

Progestins frequently used in POC
Generation and some properties

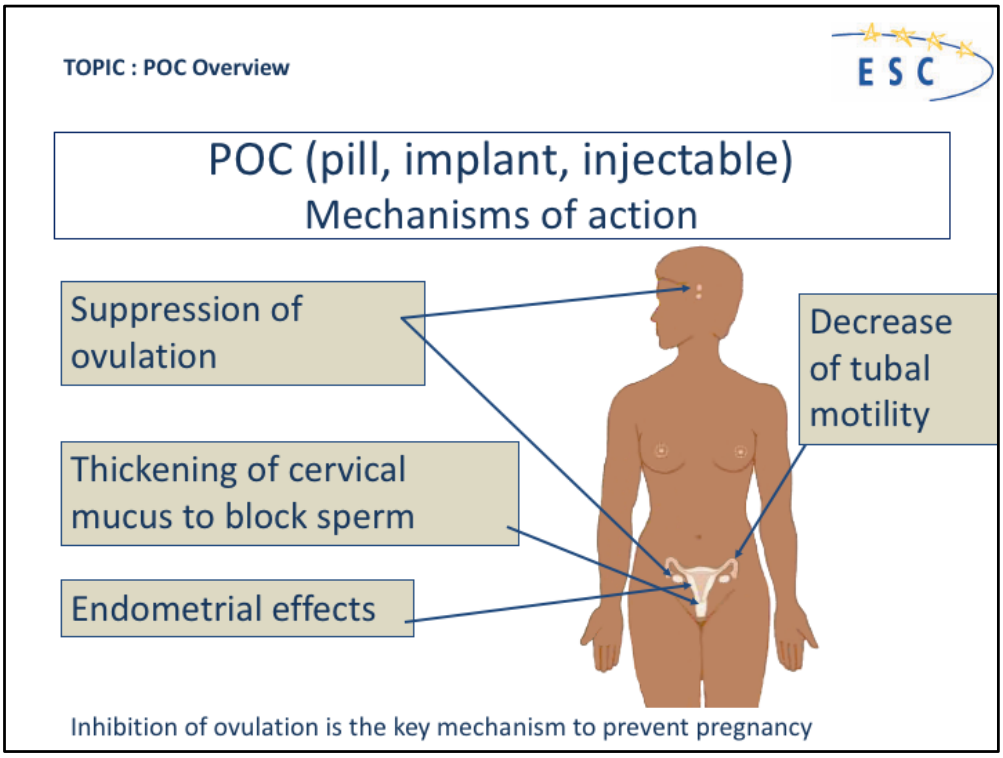
Progestin	Generation	Anti-androgenic	Andro-genic	Anti-mineralo-corticoid	Gluco-corticoid
Progesterone		(+)		(+)	
Levonorgestrel	2nd		+		
Desogestrel metabolite: etonogestrel	3rd		(+)		
Drospirenone	4th	+	-	+	-
Medroxypro-gesterone acetate	Derived from progesterone		(+)		+

+, Strong binding; (+), less strong binding to the steroid receptor

Ref 1

1. *Mueck AO et al. Nomegestrol acetate, a novel progestogen for oral contraception. Steroids 2011; 76: 531–9.*

Antiandrogenic properties are used to treat hyperandrogenism. Risk of VTE is lowest with the second generation progestins.



POCs (pill, injectable and implant) act in different ways:

- The primary mechanism of action is to **suppress ovulation**. Progestins causes the hypothalamus and the pituitary gland to reduce production of the hormones that are necessary for ovulation. Without ovulation, there is no egg to be fertilised.
- Progestins also **thickens the cervical mucus**. The thickened mucus makes it more difficult for sperms to enter the uterine cavity. In the unlikely event that a woman does ovulate, this mucus barrier greatly reduces the chance that the egg will be fertilised.
- Ciliary action in the fallopian tubes is altered.
- Endometrial effects decrease success of implantation.

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POC: Contraceptive efficacy

Method	% of women experiencing an unintended pregnancy within first year of use	
	Typical use	Perfect use
No method	85	85
Condom male	18	2
Combined pill	9	0.3
POP (DSG-DRSP)	9	0.7
Implanon	0.05	0.05
DMPA	6	0.2
IUD Copper T380Ag*	0.3	0.3
LNG-IUS 5 years*	0.2	0.2
Female sterilisation	0.5	0.5
Male sterilisation	0.15	0.1

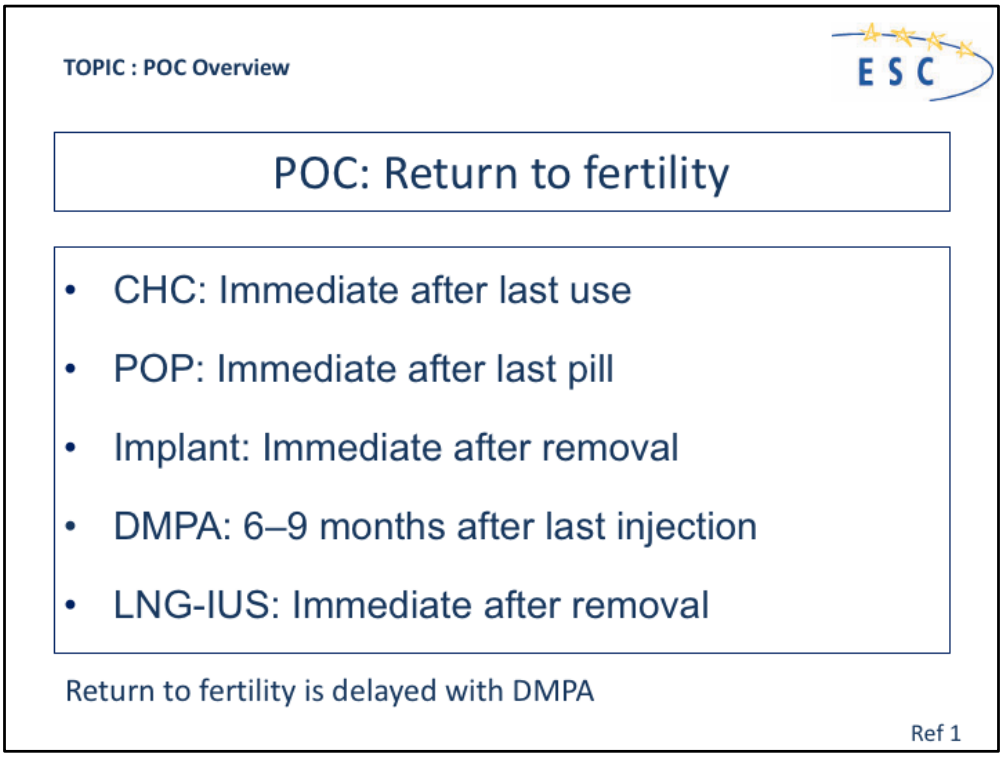
*Source I.Sivin, Contraception 1990; Vol.42NO 4.; adapted from Trussell Contraception 2011;

Ref 1,2

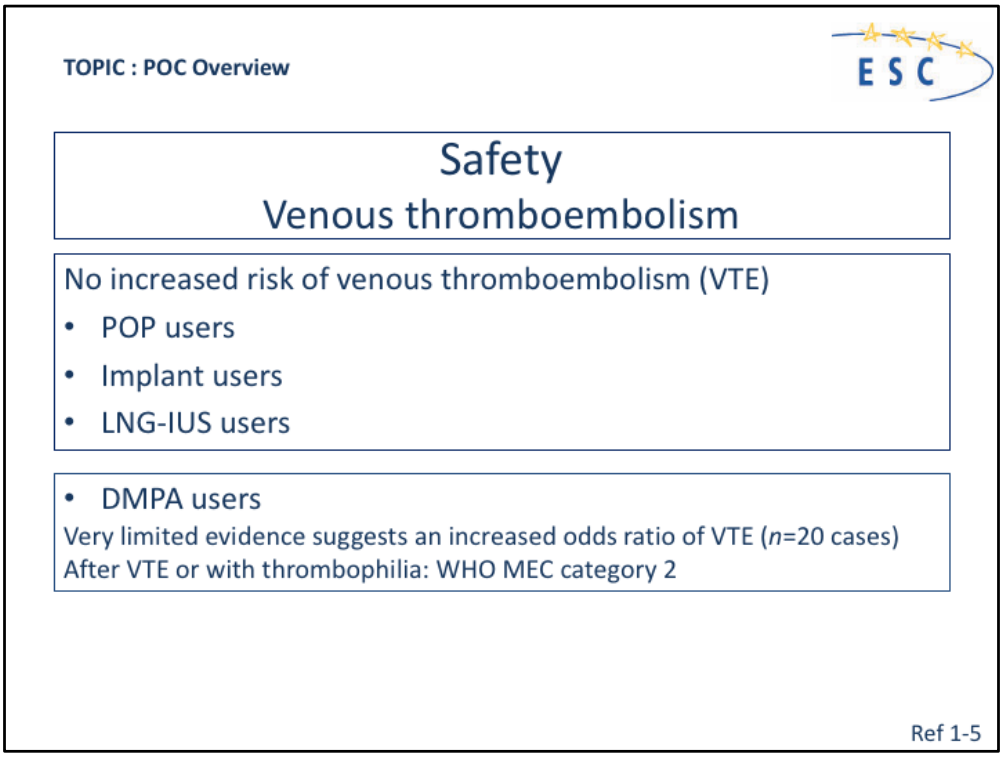
When we discuss with a women the efficacy of a contraceptive method we must consider typical use of the method, which means use in normal life by a typical user. In this slide we look at how effective contraceptive methods are as they are commonly used.

The slide shows the number of women who would get pregnant if 100 women used a method for 1 year. In 100 fertile women who were having sex without contraception, 85 would become pregnant. If the same 100 women were using an injectable, only six would become pregnant. If 100 women were using the COC, nine or 0.3 would become would become pregnant depending of the woman`s reliability to use a COC correctly.

Calculations on pooled studies with 1571 patients gave an overall Pearl index (based on 14 329 cycles) of 0.7258 (95%CI 0.3133 to 1.4301) for the DRSP-only pill *(Palacios et al. 2019 Acta OG Scan 1549-1557).* The PI in another study was 0.7 (*Archer DF, et al. Drospirenone-only oral contraceptive: results from a multicenter non-comparative trial of efficacy, safety and tolerability. Contraception 2015;92: 439–44).*

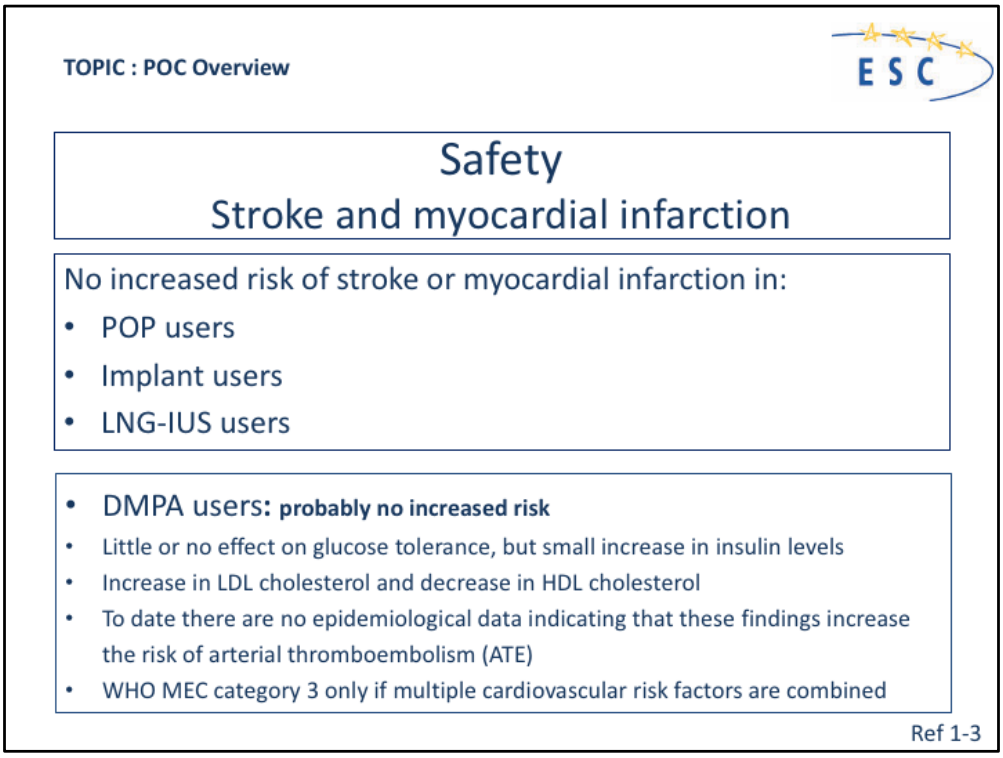


1. *Jain J et al. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. Contraception 2004; 70: 11.*



1. *Lidegaard Ø et al. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. BMJ 2012; 344: e2990.*
2. *Lidegaard Ø et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009; 339: b2890.*
3. *Lidegaard Ø et al. Hormonal contraception and venous thromboembolism. Acta Gynecol Scand 2012; 91: 769–78.*
4. *Tepper NK et al. Progestin-only contraception and venous thromboembolism: a systematic review. Contraception 2016; 94: 678–700.*
5. *Van Hylckama Vlieg A et al. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arteriscler Thromb Vasc Biol 2010; 30: 2297–300.*

Ref 3: **The incidence rate of VTE in non-pregnant women** not using hormonal contraception increased from 0.7 per 10,000 woman-years in women 15–19 years of age to 5.8 per 10,000 woman-years in women 45–49 years of age, or 8.3-fold in reproductive age women.



1. *Lidegaard Ø et al. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012; 366: 2257–66.*
2. *Westhoff C et al. Depot medroxyprogesterone acetate contraception. Metabolic parameters and mood changes. J Reprod Med 1996; 41 (5 suppl): 401–6.*
3. *Anonymous. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case–control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Contraception 1998;* 57: 315–24.

Ref 1: The risk of VTE is related to the dose of ethinylestradiol or estradiol. One of the main benefits of POC is the safety related to thromboembolic risk.

Ref 3: Although limited by the small number of cases and control subjects using the types of contraceptives under investigation, the data suggest that there is little or no increased risk of stroke, VTE or acute myocardial infarction associated with the use of oral or injectable progestogen-only or combined injectable contraceptives. However, further investigation into a possible adverse effect of POC used by women with very high blood pressure is indicated.

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POC is an important option

for women with medical conditions that do not allow use of (CHCs)

Medical condition	CHC	POP	Implant	Injectable	LNG-IUS
Postpartum (<21 days, no BF)	3-4	1	1	1	1-2*
Postpartum (21-42 days, no BF)	2-3	1	1	1	3*
Breastfeeding <6 weeks postpartum	4	2	2	3	3*
Breastfeeding 6 weeks-6 months pp	3	1	1	1	1
Smoking ≥ 35 years old	3-4	1	1	1	1
Multiple risk factors for arterial cardiovascular disease#	3-4	2	2	3	2
Diabetes (>20 years)	3-4	2	2	3	2
Diabetes with complications	3-4	2	2	3	2
Hypertension (sBP ≥160 mmHg or dBP ≥100 mmHg)	4	2	2	3	2
Thrombophilia	4	2	2	2	2
History of DVT/PE	4	2	2	2	2

Ref 1-2

1. *World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO, 2015.*
2. *Philips SJ. Progestogen-only contraceptive use among breastfeeding women: a systematic review. Contraception 2016; 94: 226-252*

* WHO 3: ≥ 48 hours to < 4 weeks postpartum
2. POCs do not compromise a woman's ability to breastfeed, and do not adversely affect infant growth, health or development during the first year postpartum. POC does not exert an effect on pre-existing pregnancy.

- Most users are young and healthy when they start contraception, but they are likely to be long-term users.
- Confident users are better users.
- POC is a very good option for contraception in high-risk women.
- In contrast to progestin-only injectables, the advantages of **progestin pills and implants** generally outweigh the theoretical or proven risks (WHO category 2) in conditions such as breastfeeding before 6 weeks postpartum, multiple risk factors for arterial cardiovascular disease (#such as older age, smoking, diabetes, hypertension and known dyslipidaemias), untreated severe hypertension (≥160/≥100 mmHg), and complicated diabetes.

- *WHO 1: < 48 hours including insertion immediately after delivery of the placenta

in non-BF women;
- *WHO 2: < 48 hours including insertion immediately after delivery of the placenta in BF women;
- *WHO 3: ≥ 48 hours to < 4 weeks postpartum in both BF and non-BF women

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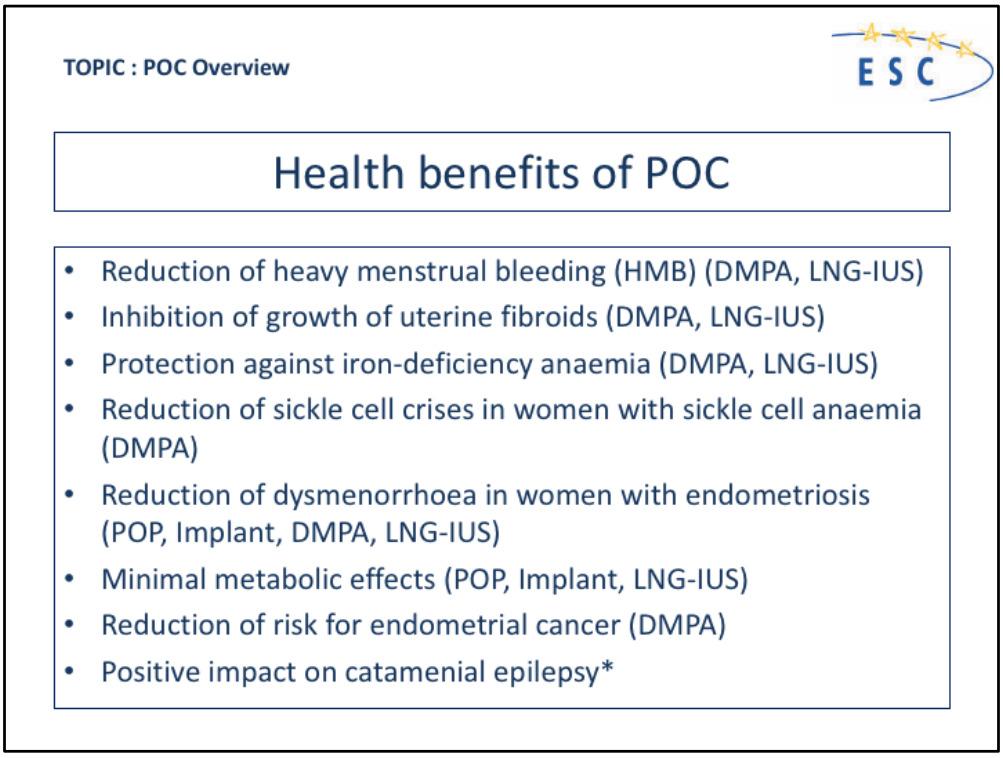
Most important contraindications of POC

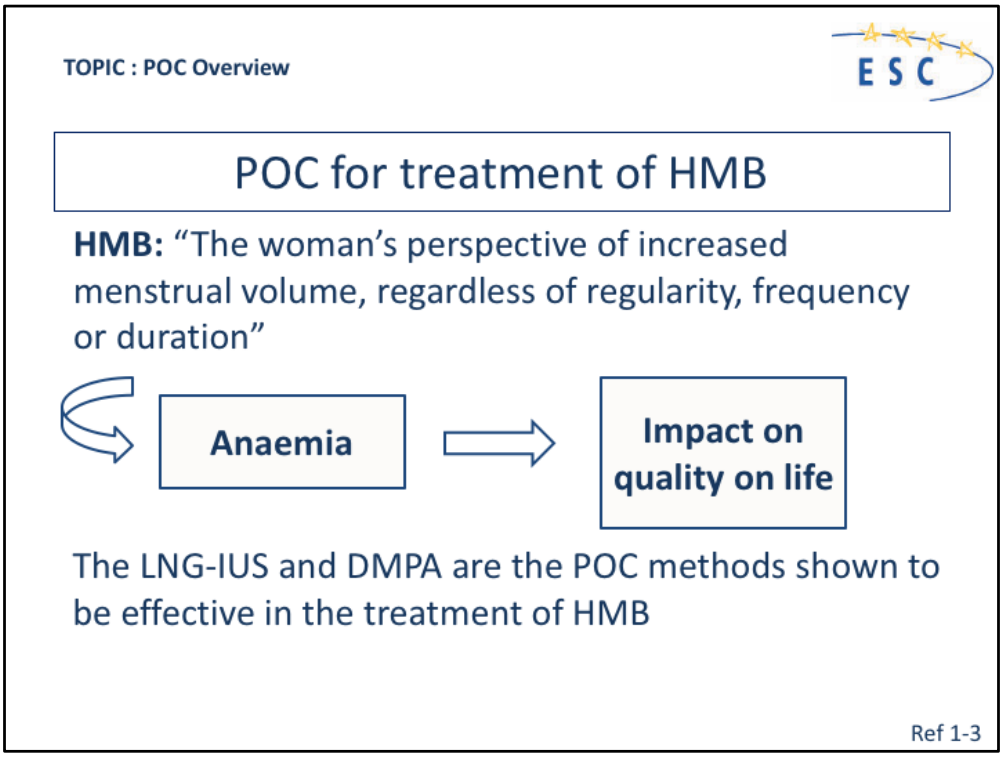
Medical condition	CHC	POP	Implant	Injectable	LNG-IUS
Acute DVT/PE	4	3	3	3	3
Unexplained vaginal bleeding	2	2	3	3	4
Severe liver disease	4	3	3	3	3
Malignant liver tumors	4	3	3	3	3
Current breast cancer	4	4	4	4	4
Past breast cancer (NED >5 years)	3	3	3	3	3

Ref 1

1. *World Health Organization. Medical eligibility criteria for contraceptive use. Fifth edition, 2015 . Geneva: WHO.*

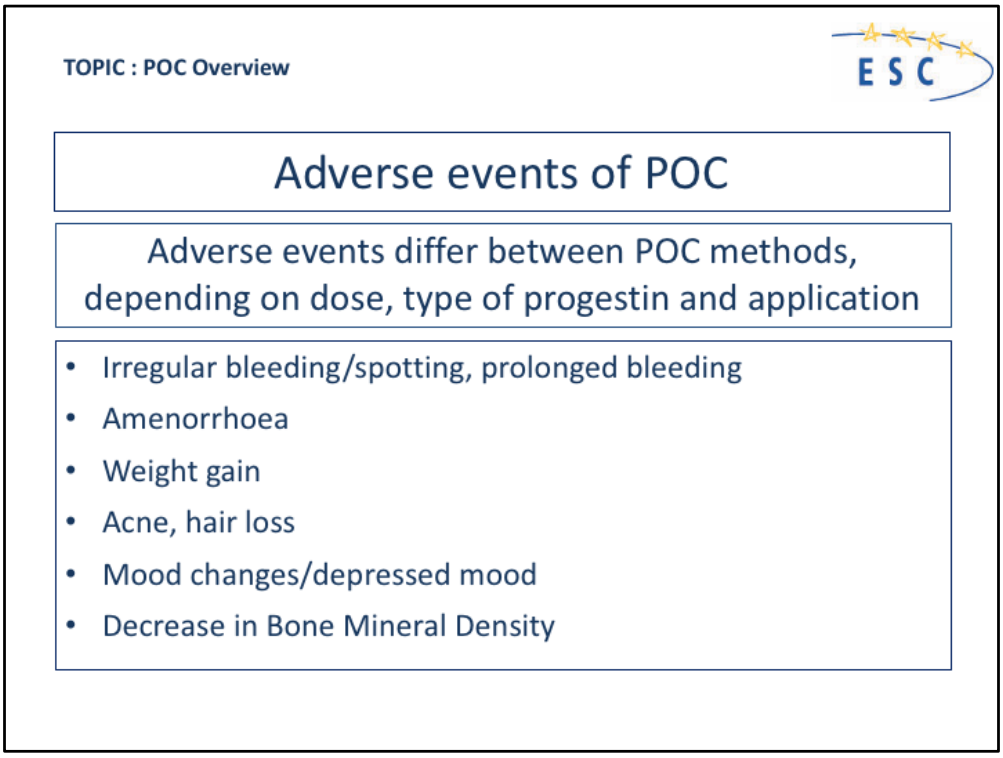


Not all POC methods exert the same health benefits, as progestin dose and type vary between different formulations.
*DRSP is not appropriate because of its discontinuous use.

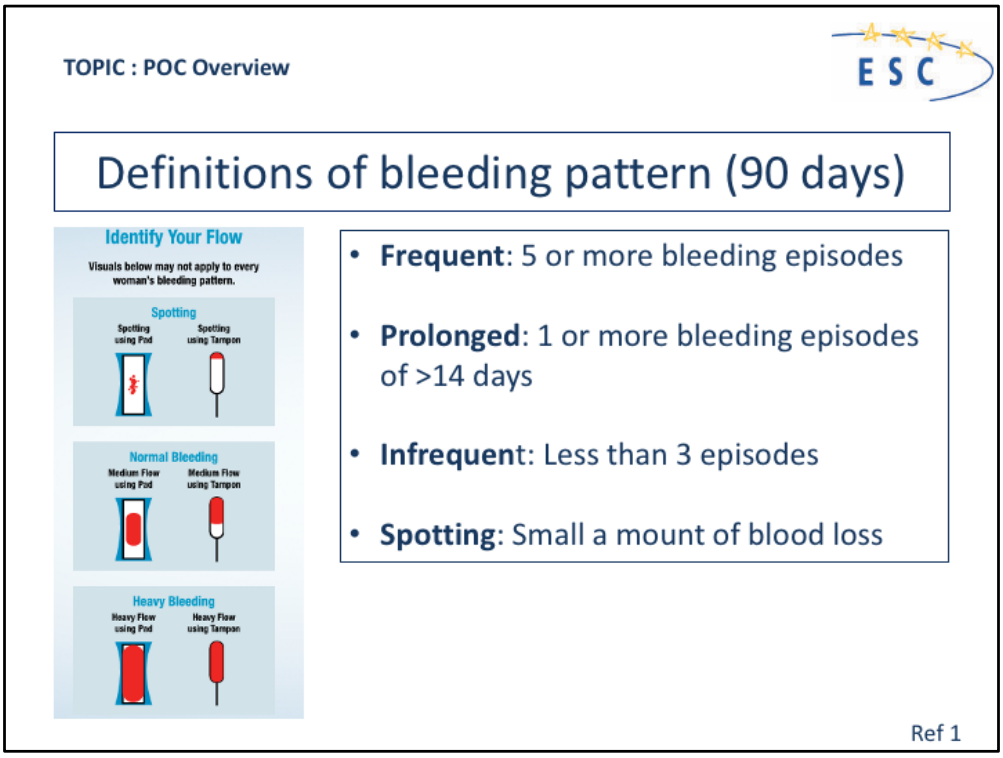


1. *Munro MG et al. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011; 113: 3–13.*
2. *Hoaglin DC et al. Use of mixed-treatment-comparison methods in estimating efficacy of treatments for heavy menstrual bleeding. Eur J Med Res 2013; 18: 17.*
3. *Kücük T et al. Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomized, prospective, controlled clinical trial in female smokers. Clin Exp Obstet Gynecol 2008; 35: 57–60.*

Ref 2: A systematic review and mixed-treatment-comparison (MTC) meta-analysis were carried out of available data from randomised controlled trials (RCTs) to derive estimates of efficacy for eight classes of treatments for HMB (COC, danazol, endometrial ablation, LNG-IUS, placebo, progestins given for <2 weeks out of 4 during the menstrual cycle, progestins given for close to 3 weeks out of 4, and tranexamic acid. Thirty-four RCTs were identified, with follow-up from 1 to 36 months. Efficacy at 3 months of follow-up ranged from 87.5% for the LNG-IUS to 14.2% for progestins administered for <2 weeks out of 4 in a menstrual cycle.



Counselling is very important for the compliance of women for the progestin only methods; women who want a predictable bleeding pattern may not find POC acceptable.



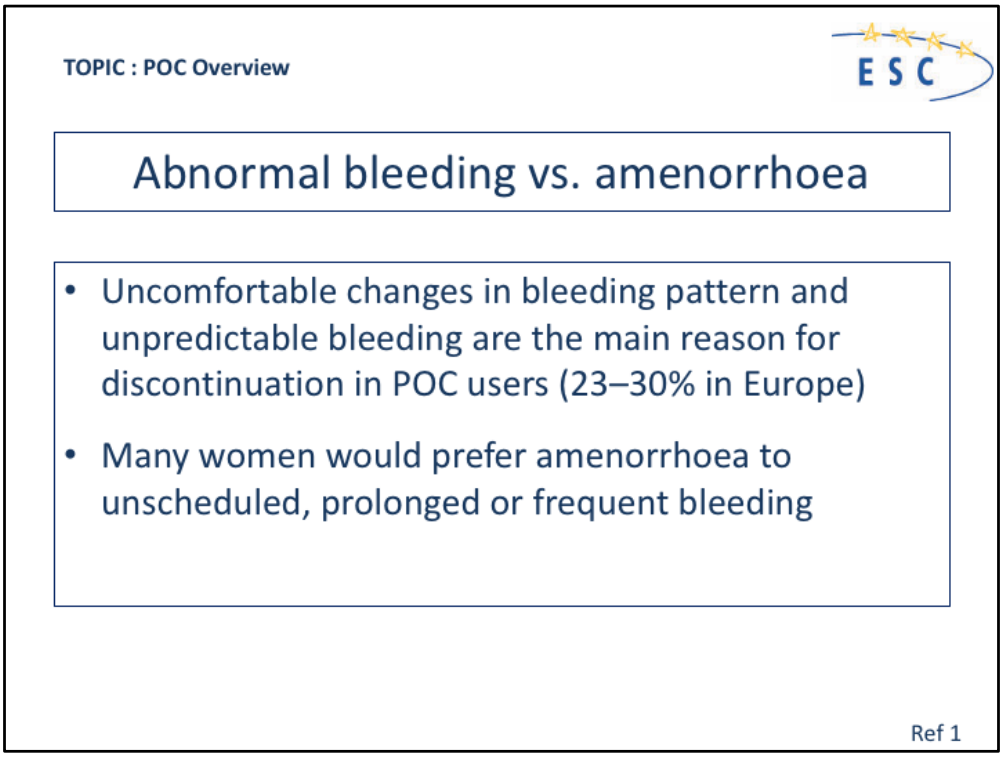
1. *Belsey EM et al. Vaginal bleeding pattern among women using one natural and eight hormonal methods of contraception. Contraception 1998; 38: 181–206.*

Before using POC, ensure that the patient understands the most common side effects, especially changes in bleeding patterns.

Definitions of vaginal bleeding (reference period: 3 months).

1. Normal and regular blood loss: mainly related to the natural cycle or CHC use.
2. Unpredictable blood loss:

- Frequent (more than five episodes of blood loss).
- Prolonged (one or more episodes of blood loss lasting ≥14 days).
- Spotting (small amount of blood loss, no need for sanitary protection).
- Not frequent (of blood loss less than three episodes).

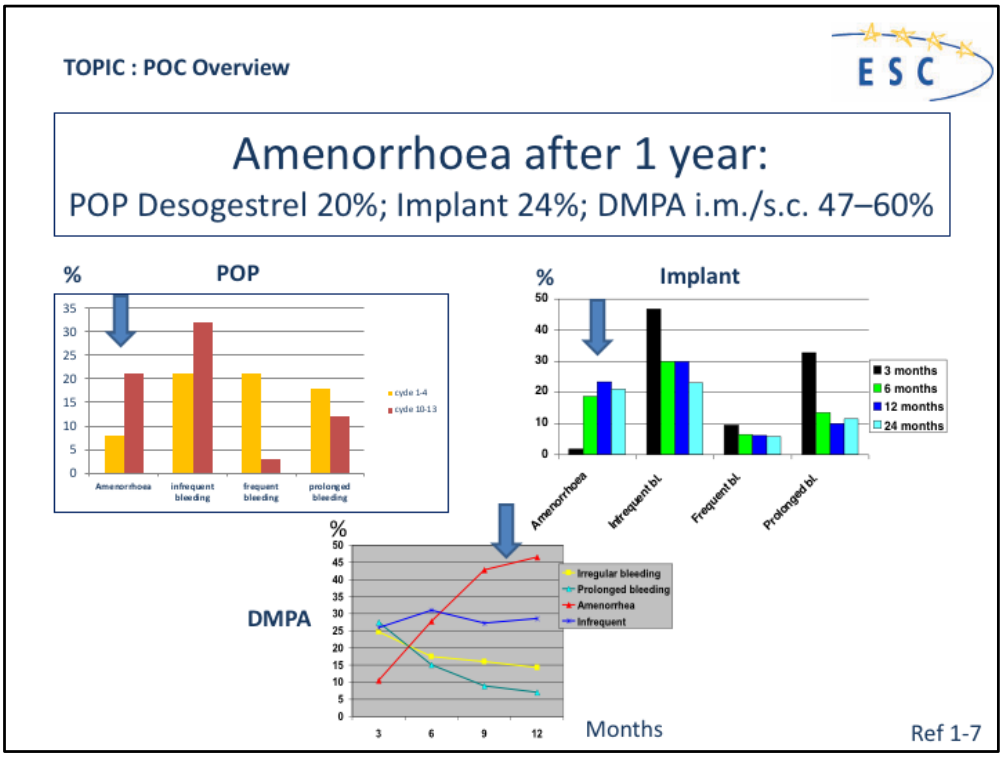


1. *Merki-Feld GS et al. A survey on Swiss women's preferred menstrual/withdrawal bleeding pattern over different phases of reproductive life and with use of hormonal contraception. Eur J Contracept Reprod Health Care 2014; 19: 266–75.*

Bleeding pattern with POC methods

Method	Bleeding/spotting days over time	Amenorrhoea after 1st year
POP Desogestrel	Decreasing	20%
Implant	Decreasing	19–25%
DMPA	Decreasing	47–60%
LNG-IUS	Decreasing	43%

Frequency of frequent and prolonged bleeding decreases over time; therefore, reassurance is important if women find it troublesome



1. *Anonymous. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Collaborative Study Group on the Desogestrel-Containing Progestogen-Only Pill. Eur J Contracept Reprod Health Care 1998; 3: 169–78.*
2. *Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. Contraception 1998; 58 (6 suppl): 99–107S.*
3. *WHO Special Programme of Research, Development and Research Training in Human Reproduction: Task Force on Long-Acting Agents for Fertility Regulation (WHO). A multicentered phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg. II: The comparison of bleeding patterns. Contraception 1987; 35: 591–607.*
4. *Arias RD et al. Changes in bleeding patterns with depot medroxyprogesterone acetate subcutaneous injection 104 mg. Contraception 2006; 74: 234–8.*
5. *Hubacher D et al. Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: systematic review and evidence-based comparisons. Contraception 2009; 80: 113–18.*
6. *Archer DF, et al. Drospirenone-only oral contraceptive: results from a multicenter non-comparative trial of efficacy, safety and tolerability. Contraception 2015;92: 439–44.*

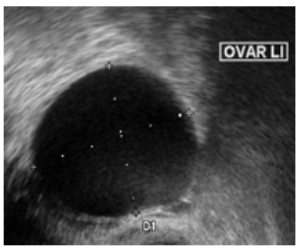
   A total of 713 participants with 7638 DRSP treatment cycles were analyzed. The proportion of participants with any bleeding decreased from 72.7% in Cycle 1 to

40% in Cycle 6 and 32.1% in Cycle 13. Unscheduled bleeding decreased from 49.1% in Cycle 1 to 27.8% in Cycle 6 and to 22.8% in Cycle 13. Prolonged bleeding was reported by 6.5% during Cycles 2 to 4 decreasing to 4.2% during Cycles 11 to 13.

7. *Palacios S, et al. A multicenter, double-blind, randomized trial on the bleeding profile of a drospirenone-only pill 4 mg over nine cycles in comparison with desogestrel 0.075 mg. Archives of Gynecology and Obstetrics (2019) 300:1805–1812.*

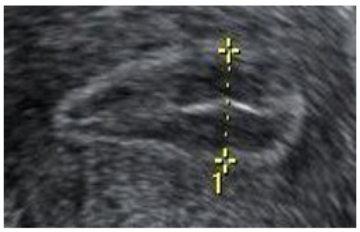
   This report describes the improvement in bleeding profile of women using the new DRSP-only oral contraceptive in comparison to DSG: the proportion of women with unscheduled bleeding was statistically significantly lower in the DRSP group than in the DSG group (p = 0.0001, Chi-square test). Importantly: Scheduled bleeding or spotting was defined as any bleeding or spotting that occurred during hormone-free intervals (defined as days 25–28 ± 1). Up to eight consecutive bleeding/spotting days were considered as scheduled bleeding days. Unscheduled bleeding or spotting day was defined as any bleeding/spotting that occurred while taking active hormones (days 2–23), except days which were classified as scheduled bleeding days. As desogestrel is administered without any free period, no scheduled bleeding is expected.

Breakthrough bleeding: by persistent unruptured follicles

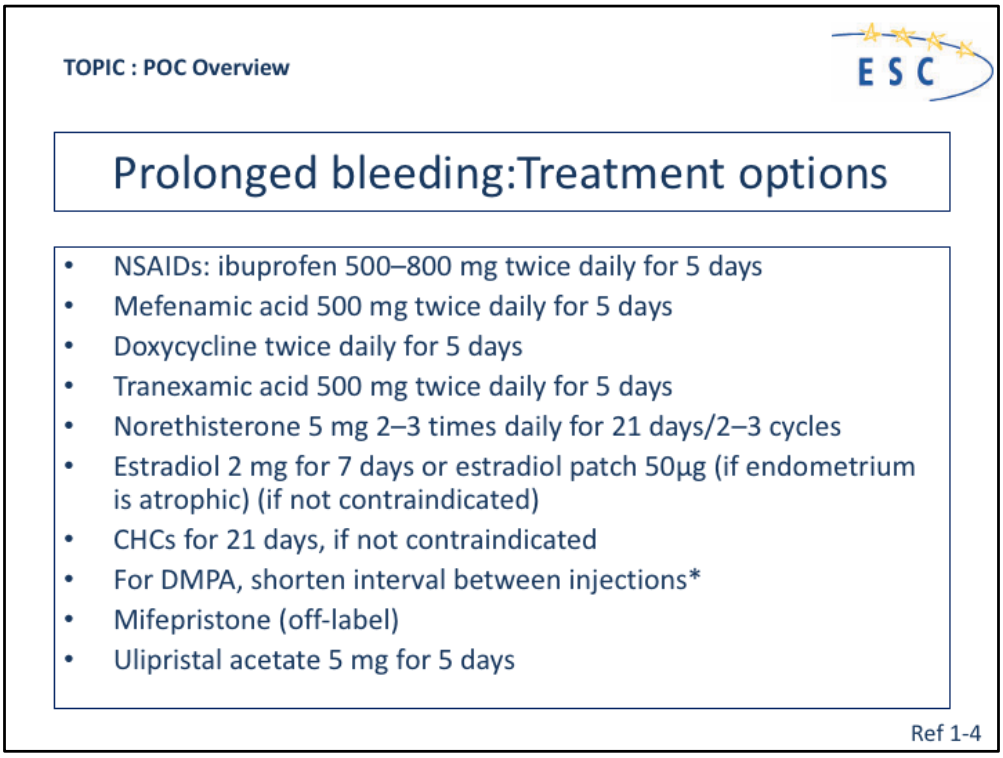


- Reason for breakthrough bleeding (and breast tenderness) in users of very-low-dose POC ,such as the POP or the LNG-IUS, can be unruptured follicle cysts which produce estradiol
- These cysts resolve spontaneously
- Reassure the patient

Frequent and irregular bleeding: Treatment

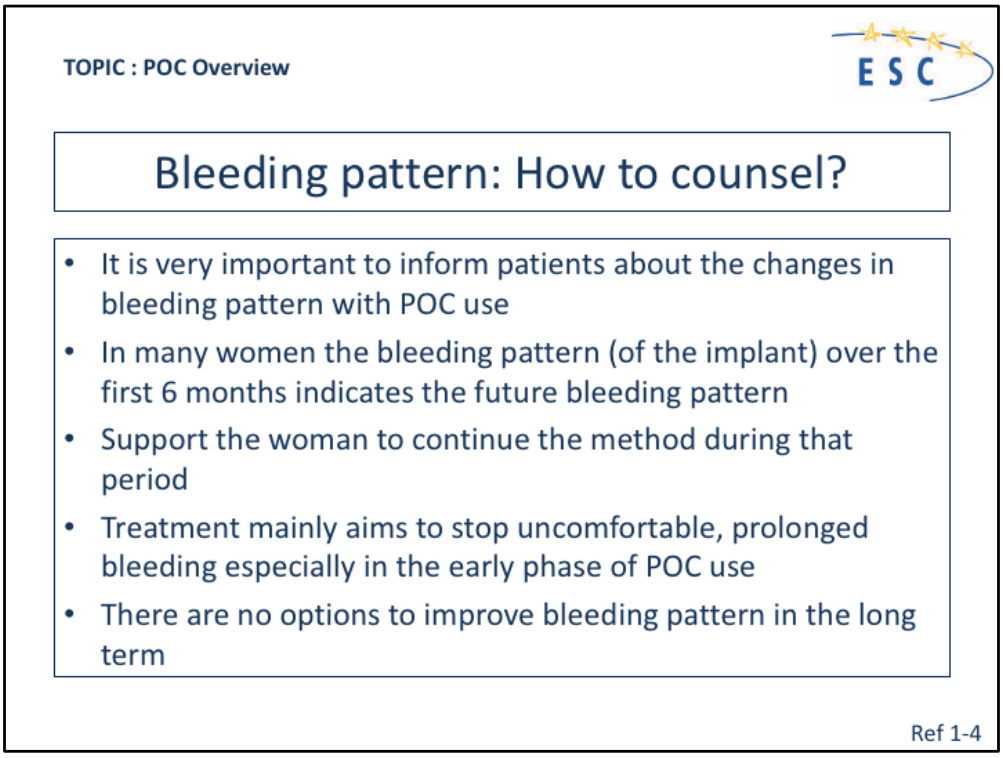


If ultrasound is available, you can check whether the endometrium is high or low. Fragile vessels in atrophic endometrium will respond better to oestrogen treatment

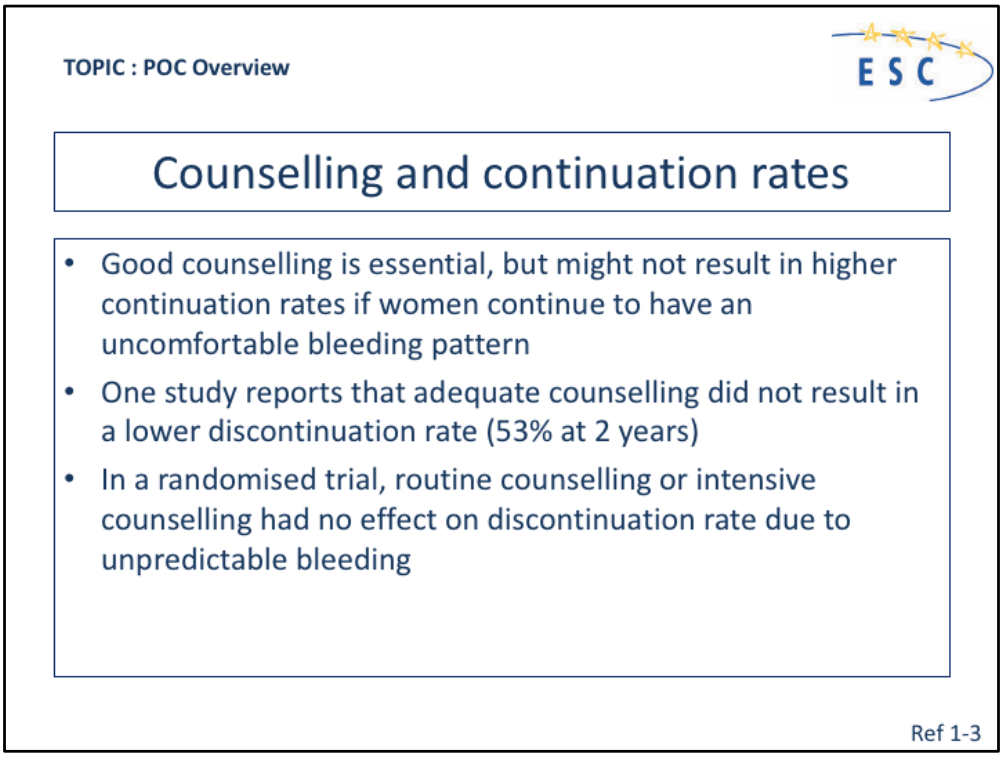


1. *Zigler RE et al. Unscheduled vaginal bleeding with progestin-only contraceptive use. Am J Obstet Gynecol 2016; Dec 14 [Epub ahead of print].*
2. *Mansour D et al. The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users. Contraception 2011; 83: 202–10.*
3. *Abdel-Aleem H et al. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev 2013; CD003449.*
4. *Zigler RE et al. Ulipristal Acetate for Unscheduled Bleeding in Etonogestrel Implant Users: A Randomized Controlled Trial. Obstet Gynecol 2018; 132(4): 888–894.*

* Clinical experience.



1. *Modesto W et al. A randomized clinical trial of the effect of intensive versus non-intensive counselling on discontinuation rates due to bleeding disturbances of three long-acting reversible contraceptives. Hum Reprod 2014; 29: 1393–9.*
2. *Teunissen AM et al. Continuation rates of the subdermal contraceptive Implanon and associated influencing factors. Eur J Contracept Reprod Health Care 2014; 19: 15–21.*
3. *Weisberg E et al. A three-year comparative study of continuation rates, bleeding patterns and satisfaction in Australian women using a subdermal contraceptive implant or progestogen releasing-intrauterine system. Eur J Contracept Reprod Health Care 2014; 19: 5–14.*
4. *Mansour D et al. Can initial vaginal bleeding patterns in etonogestrel implant users predict subsequent bleeding in the first 2 years of use? Contraception 2019; 100(4): 264-268.*
   Implant users with favorable bleeding in the first reference period are likely to continue with favorable bleeding over the next 2 years. Initial bleeding patterns predict overall continuation rates in years 1 and 2. Implications Statement: When evaluating vaginal bleeding in any 90-day reference period over 2 years of etonogestrel implant use, approximately 80% of women with favorable and 40% with unfavorable bleeding patterns will have favorable bleeding in the next reference periods. These findings can facilitate counseling regarding bleeding for women using the etonogestrel implant.



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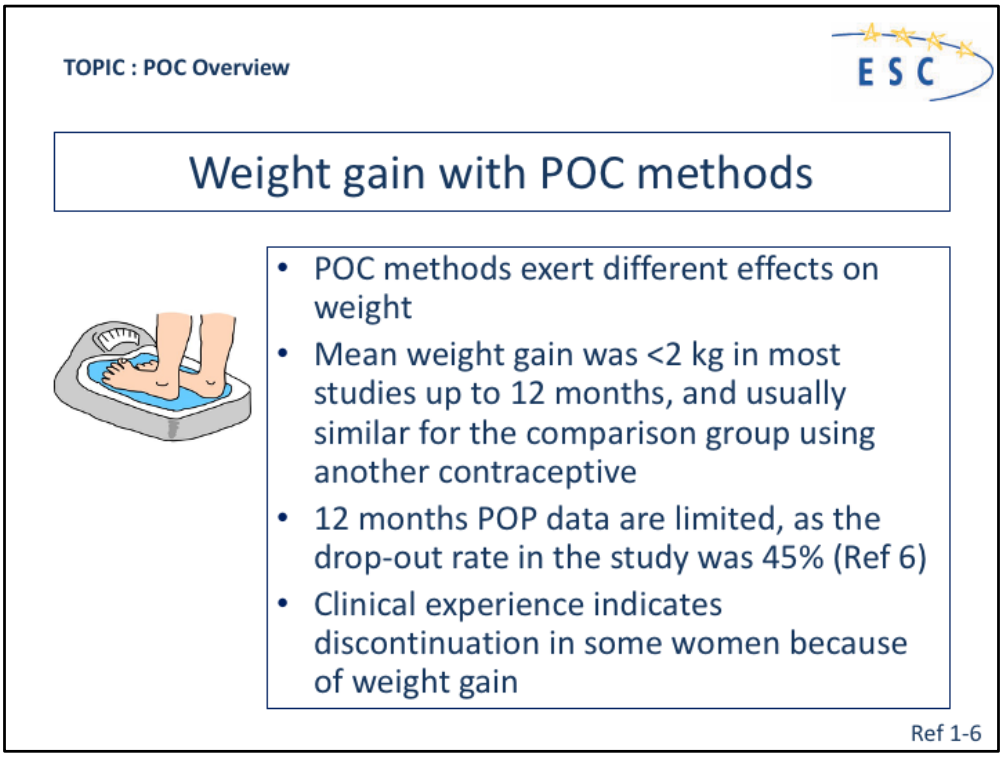

1. *Lopez LM et al. Progestin-only contraceptives: effects on weight. Cochrane Database Syst Rev 2016; 8: CD008815.*
2. *Westhoff C et al. Changes in weight with DMPA subcutaneous injection 104 mg. Contraception 2006; 74: 234–8.*
3. *Bahamondes L et al. Comparison of weight increase in users of DMPA and copper-IUD up to 5 years. Contraception 2001; 64: 223–5.*
4. *Vickery Z et al. Weight change at 12 months in users of three progestin-only contraceptive methods. Contraception 2013; 88: 503–8.*
5. *Urbancsek J. An integrated analysis of nonmenstrual adverse events with Implanon. Contraception 1998; 58 (6 suppl): 109–15S.*
6. *Korver T et al. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestagen-only pills containing desogestrel 75 µg/day or levonorgestrel 30 µg/day. Eur J Contracept Reprod Health Care 1998; 3: 169–78.*

Ref 1: The Cochrane Database found little evidence of weight gain with progestin-only contraceptives. Some differences were noted when a POC was compared with no hormonal contraceptive. Actual mean weight gain was low for 6–12 months, i.e. less than 2 kg for most studies.

However, prospective studies demonstrate that in some DMPA and implant users,

there can be a relevant increase in weight, which may lead to discontinuation.

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Weight gain compared with other contraceptives

Contraceptive method	Weight change (kg)	Percentage of women with particular weight increase
POP DSG (13 months)	No change	
Implant (24 months)	No change (31%) Increase >5 kg (20% W)	10% increase in body weight in 21% of users
DMPA (12 months)	2.4 kg	
DMPA (36 months)	5.8 ± (8.7) kg	20% increase >5 kg
DMPA (36 months)	3 kg	
LNG IUS (12 months)	1.03 kg	
Copper IUD (12 months) (36 months)	0.2 kg 0.6 kg	

A subgroup of women experiences a relevant increase of weight with use of the Implant and DMPA, what can result in discontinuation.

Ref 1-7

1. *Lopez LM et al. Progestin-only contraceptives: effects on weight. Cochrane Database Syst Rev 2016; 8: CD008815.*
2. *Westhoff C et al. Changes in weight with DMPA subcutaneous injection 104 mg. Contraception 2006; 74: 234–8.*
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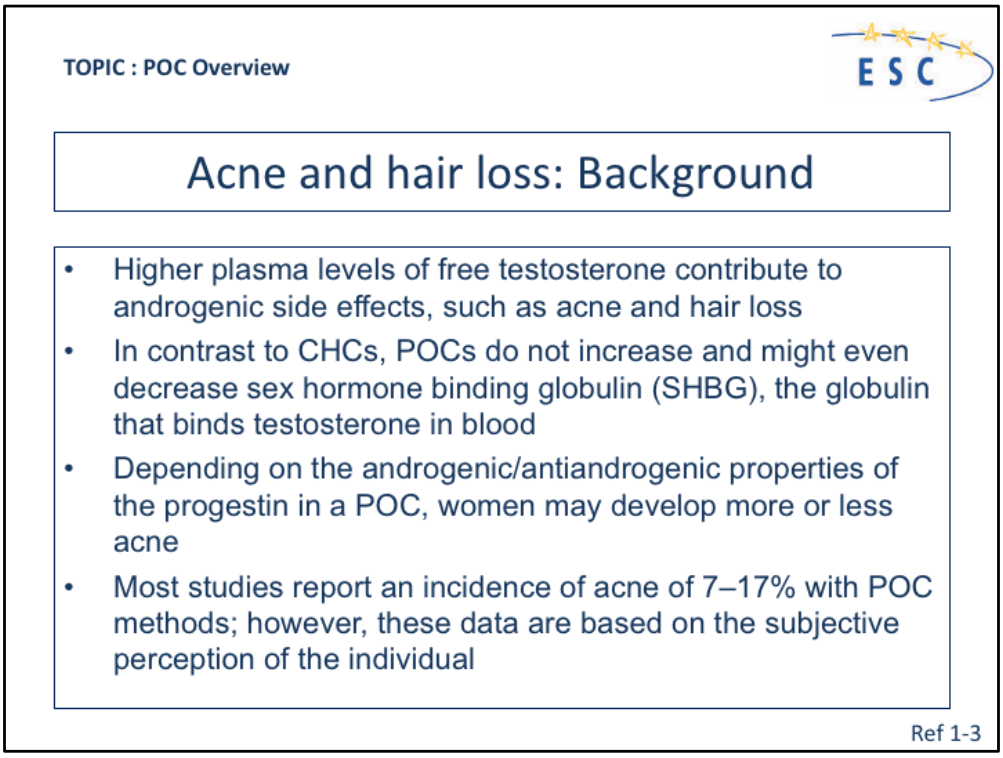
TOPIC : POC Overview

Acne, skin problems

A typical problem in adolescents, who are the biggest group of new contraceptive users



COCs decrease free testosterone levels by 40–50%, on average (*Fotherby, 1994*; *Thorneycroft, 1999*). This is partly due to reduced production of the androgen testosterone, achieved by the suppression of luteinising hormone, which causes decreased androgen synthesis. Androgen bioavailability is also reduced when COCs increase the level of the protein that binds free androgens (SHBG), which in turn, increases binding of testosterone.
Second, testosterone has to be converted in the hair follicles and skin to dihydrotestosterone by the enzyme 5α-reductase to lead to acne (*Cassidenti, 1991*). COCs prevent the conversion of free testosterone to dihydrotestosterone. SHBG in circulation binds the free testosterone. If plasma levels of testosterone decrease, androgenic symptoms can improve. If we want to use a hormonal contraceptive to improve the androgenic signs, it is very important to use a CHC (CHC session 3).

TOPIC : POC Overview

Mood changes, depression

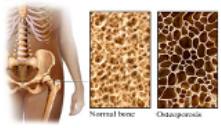
- POCs very rarely initiate depression in predisposed women (clinical report and some studies)
- POCs and progestin-releasing devices should not be initiated in women suffering from major depression (copper IUD might be a better alternative)
- If a woman complains of developing depressed mood while using POC, stop the method
- If no other option is available, inform the patient that mood can worsen and she should come back immediately if this happens (start a method which can easily be stopped)
- This is also true for the LNG-IUS
- For DMPA and DRSP evidence is lacking; therefore recommendations are based on clinical observations with all POC

Ref 1-4

1. *Westhoff C et al. Depot medroxyprogesterone acetate contraception. Metabolic parameters and mood changes. J Reprod Med 1996; 41 (5 suppl): 401–6.*
2. *Pagaino HP et al. Safety of hormonal contraception and intrauterine devices among women with depressive and bipolar disorders: a systematic review. Contraception 2016; 94: 641–9.*
3. *Berenson AB. Continuation rates and complications of intrauterine contraception in women diagnosed with bipolar disorder. Obstet Gynecol 2011; 118: 1331–6.*
4. *Scholes CD et al. Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. Contraception 2000; 61: 285–90.*

Take a good history and ask actively about depressive episodes. It is not prudent to start a POC or LNG-IUS in women with major depression. If there is no other choice, close follow-up is needed. A pill might be a better option to test tolerability.

TOPIC : POC Overview



Bone Mineral Density

- During the reproductive years maintenance of bone mineral density (BMD) is important to decrease fracture risk in later life
- Estrogen depletion can cause a decrease in BMD
- There is some concern that DMPA might have a negative impact on BMD by suppressing ovarian function
- Short-term studies do not indicate a negative effect of the desogestrel POP or implant on BMD
- For the DRSP POP no prospective data are available yet

For the DRSP POP no prospective data are available yet, so it is unknown if DRSP may cause a clinically relevant loss of bone mineral density. However, associated to the low suppression of the ovarian estradiol production in comparison with DMPA there are no concerns for detrimental effect on the bone.

ESC

POC: Summary (1)

Advantages

- High efficacy
- Efficacy not user-dependent (except POP)
- No increase in VTE or ATE risk (DMPA WHO 2-3)
- Minimal metabolic effects
- No adverse effects of ethinyl-estradiol
- Safe in many medical conditions
- Improvement of HMB (DMPA, LNG-IUS)
- No negative impact on lactation

ESC

POC: Summary (2)

Disadvantages

- Unpredictable/prolonged bleeding
- Impact on body weight in some women
- Hormonal side effects (skin, hair)
- Negative, but probably reversible, impact on bone density with DMPA
- Return to fertility delayed with DMPA
- Impact on mood, especially in predisposed women