TOPIC : POP

Progestin-only pill (POP)

Desogestrel 75 µg (DSG)
Drospirenone 4 mg (DRSP)

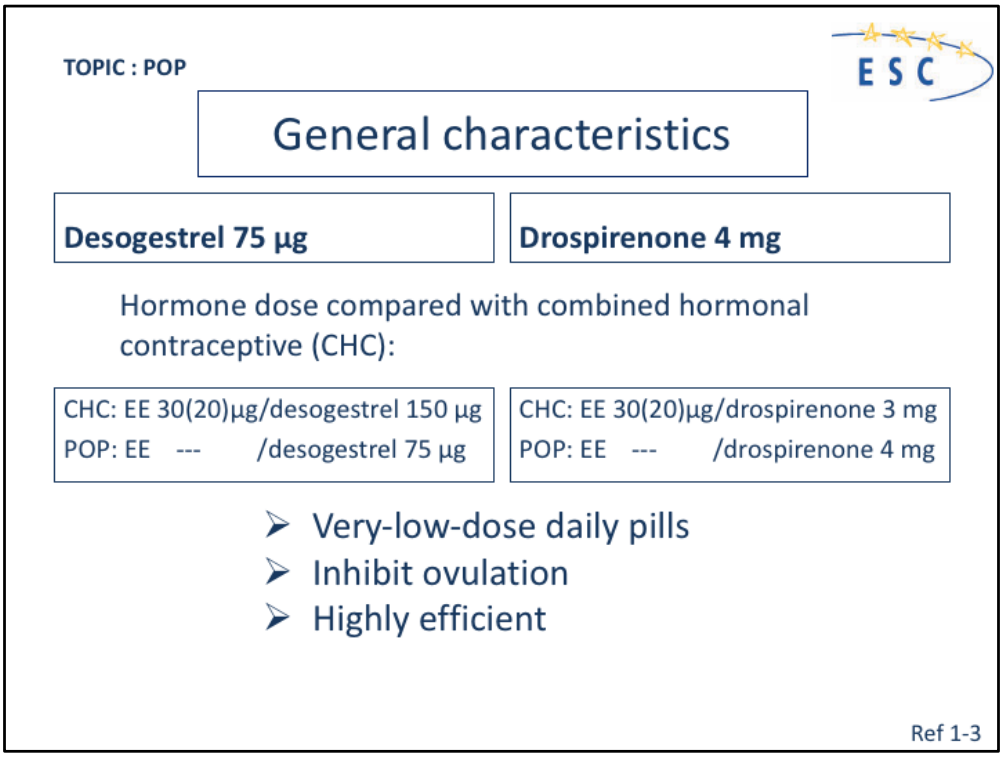
An advanced slide kit complementing the WHO training tool is available from:
www.fptraining.org

Update January 2020

TOPIC : POP

POP: Contents

- General characteristics
- Mechanism of action
- Contraceptive efficacy
- Health benefits, migraine
- Adverse events, bleeding
- Emergency contraception
- Breastfeeding
- Summary



1. *Duijkers IJ, et al. A randomised study comparing the effect on ovarian activity of a progestogen-only pill (POP) containing desogestrel and a new POP containing drospirenone in a 24/4 regimen. Eur J Contracept Reprod Health Care 2015;20:419–27.*
2. *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.*
3. *Palacios S, et al. Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone-only pill. Acta Obstet Gynecol Scand 2019;98:1549–1557.*

TOPIC : POP

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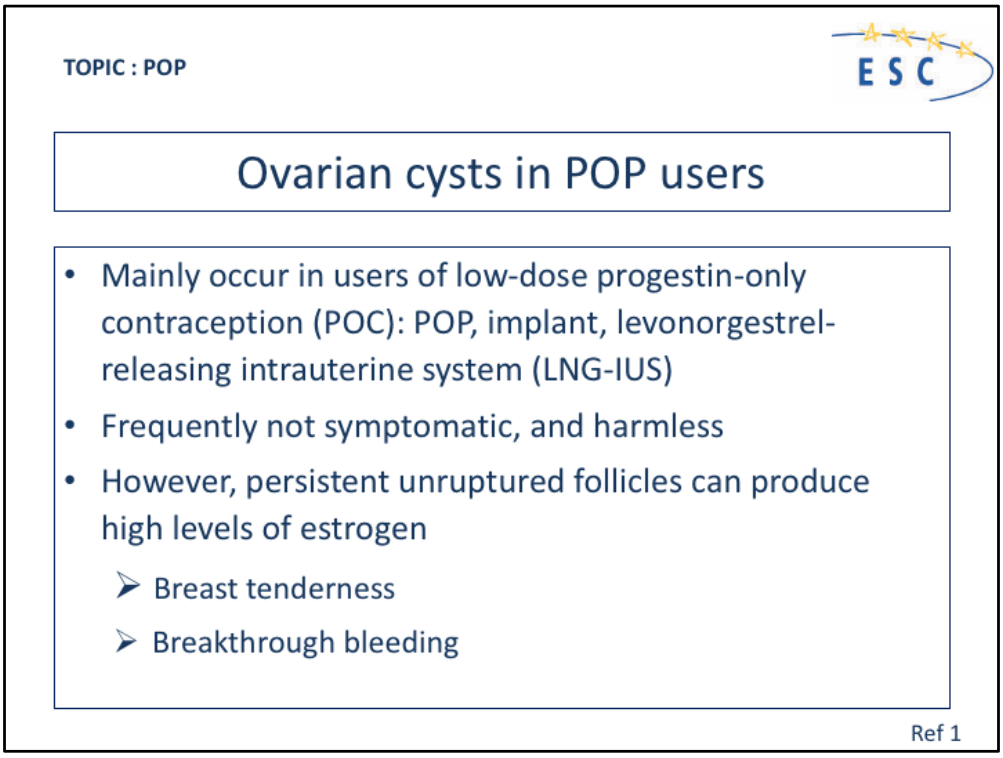
Suppression of ovarian function is less strong in comparison with CHC

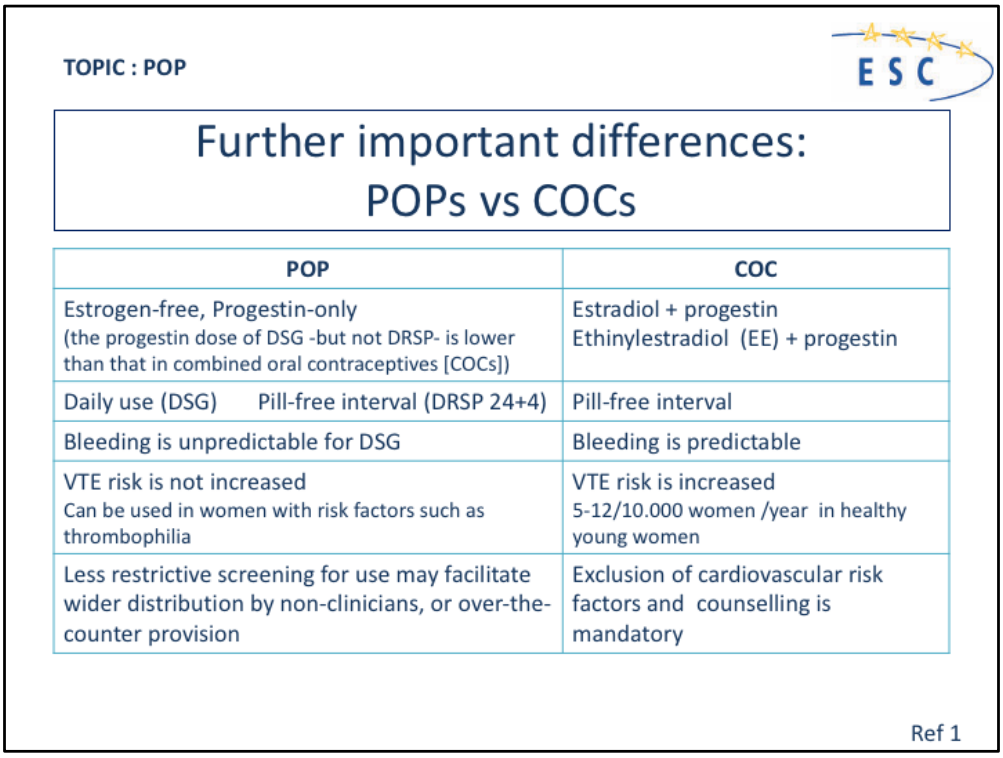
- Ovulation is inhibited
- The low dose allows, however, more follicular development
- Women have higher oestradiol concentration in comparison with DMPA users
- Occasionally follicles will develop and not rupture, resulting in ovarian cysts

Ref 1

1. Rice C et al. A comparison of the inhibition of ovulation achieved by desogestrel 75 micrograms and levonorgestrel 30 micrograms daily. Hum Reprod 1999 Apr;14(4):982-5.



1. Rice C et al. A comparison of the inhibition of ovulation achieved by desogestrel 75 micrograms and levonorgestrel 30 micrograms daily. Hum Reprod 1999 Apr;14(4):982-5.



1. *Grimes DA et al. Progestin-only pills for contraception. Cochrane Database Syst Rev 2013; 11: CD007541.*

- POPs have both advantages and disadvantages when compared with COCs. The pill-taking regimen (of DSG) is simple and fixed: no pill colour changes or days without pill-taking occur. The 24+4 pill-taking regimen (of DRSP) includes a pill-free interval of 4 days. Fertility returns promptly upon discontinuation. POPs are appropriate for all women, but especially those who cannot or should not take estrogen in COCs; for example, a woman older than 35 years who smokes cigarettes (*ACOG, 2006*).
- Lacking estrogen, POPs may have a lower risk of complications. A WHO case–control study found no significant increase in the risk of stroke, myocardial infarction and VTE among POP users compared with non-users (*WHO, 1998*). A cohort study from Denmark also found no statistically significant association between POPs and VTE (*Lidegaard, 2009*).
- Although the literature is unclear concerning the potential impact of COCs on lactation, no concern exists for POPs (*Moggia, 1991*; *Dunson, 1993*; *McCann, 1994*; *Bjarnadóttir, 2001*; *FFPRHC, 2004*). No data are available concerning a potential effect on infant brain or liver.
- Like DMPA injections for contraception (*Manchikanti, 2007*), POPs may reduce the frequency of sickle cell crises.
- Less restrictive screening for use may facilitate wider distribution by non-clinicians,

or over-the-counter provision.

- Disadvantages include the recommendation for careful compliance and the disruption of normal menstrual patterns (*FSRH, 2008*). These changes include irregular bleeding, short or long cycles, bleeding and spotting, prolonged bleeding, or no bleeding at all. Overall, POPs are associated with more days of bleeding and spotting compared with COCs (*Raymond, 2011*).

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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
DMPA	6	0.2
Implanon	0.05	0.05
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;

- Randomised controlled trials published to date are inadequate to compare POPs with each other or with COCs. Since POPs are commonly used during breastfeeding, when fertility is low, the impact of better efficacy of any pill would be small in this setting. No trial has addressed the question of consistent timing of ingestion.
- Any potential benefit of better contraceptive efficacy with desogestrel 75 µg vs LNG 30 µg (*Collaborative, 1998*) may be offset by worse bleeding patterns. These include prolonged bleeding and absence of bleeding. For every one pregnancy that might be prevented with desogestrel, five women will discontinue early because of irregular bleeding. The trade-off between efficacy and continuation may be viewed differently in different settings, and amongst women in the same settings. For some women efficacy will be the chief consideration, while for others regular bleeding will be more important.
- Little information was available about the advice given as to the timing of administration of the pills or whether back-up contraception should be used in case of a late or missed pill. Although accurate timing of administration is considered important for POPs, little empirical evidence supports this hypothesis, and interindividual variation in the metabolism of progestins is wide (*Goldzieher, 1994*; *Wallach, 2000*).
- 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).*

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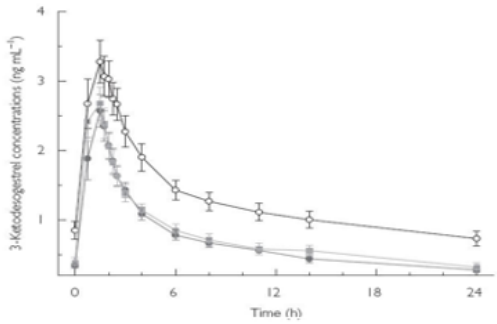
POPs are efficient but the dose is very low
So: Caution with concomitant use of enzyme-inducing drugs such as St John's wort

Recommendation:
Use back-up method

Grey points/squares,
cycles with St John's wort



3-ketodesogestrel levels are significantly lower in users of a CHC containing EE 20 µg / desogestrel 150 µg during concomitant treatment with St John's wort. This resulted in this study in more intracyclic bleeding episodes. **Users of the much lower dosed POP will be more vulnerable to increased metabolism and loss of efficacy.**

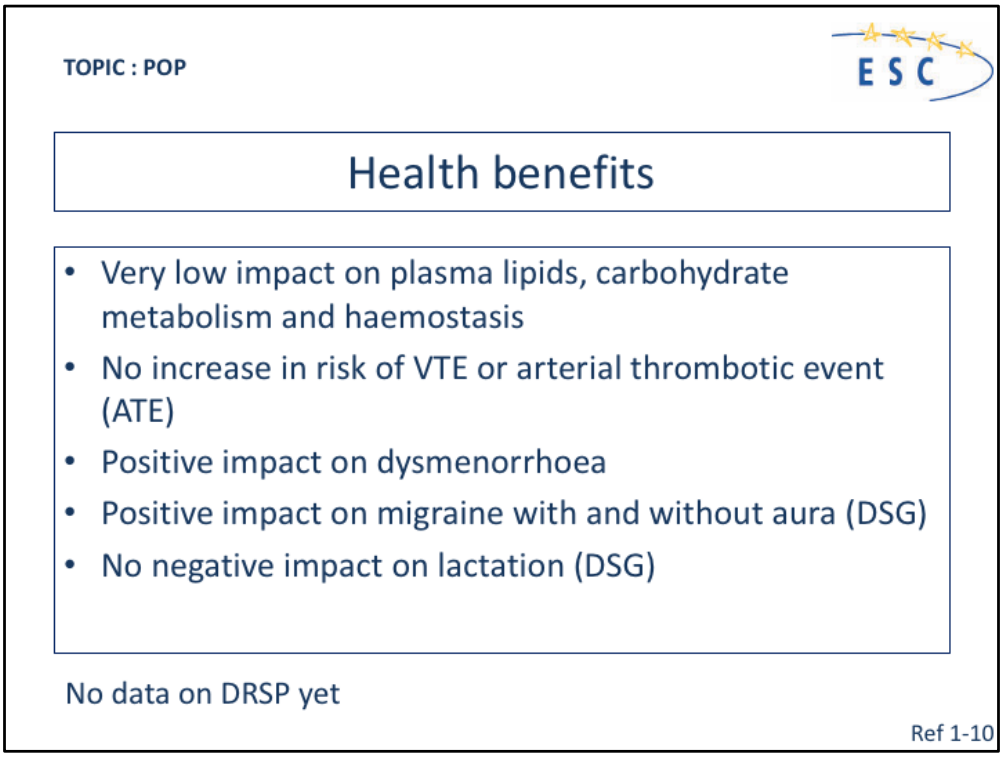
Ref 1,2

1. *Pfrunder A et al. Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. Br J Clin Pharmacol 2003; 56: 683–90.*

St John's wort (*Hypericum perforatum*) is a popular herbal medicine marketed as a dietary supplement and widely used for the treatment of mild-to-moderate depression. St John's wort was reported to have efficacy comparable to that of selective serotonin reuptake inhibitors and tricyclic a
ntidepressants for the treatment of mild-to-moderate depression, as well as a better side effect profile.

2. Ginstman C et al. Plasma concentrations of etonogestrel in women using oral desogestrel before and after Roux-en-Y gastric bypass surgery: a pharmacokinetic study. BJOG 2019;126:486–492.

This study did not reveal any clinically significant changes in etonogestrel pharmacokinetics, suggesting that oral desogestrel may be used by women after RYGB surgery. Peak serum concentrations (Cmax) increased after 52±2 weeks compared with preoperative values (0.817 ng/ml versus 0.590 ng/ml, P=0.024).



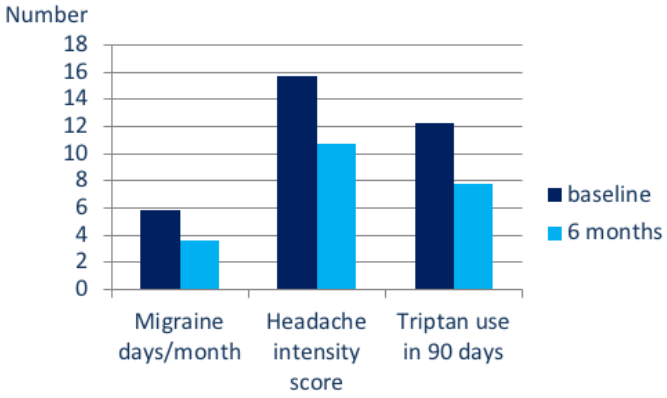
1. *Winkler UH et al. A randomized controlled double-blind study of the effects on hemostasis of two progestogen-only pills containing 75 microgram desogestrel or 30 microgram levonorgestrel. Contraception 1998; 57: 385–92.*
2. *Anonymous. A double-blind study comparing the contraceptive efficacy, acceptability 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.*
3. *Kivelä A et al. The effects of two progestogen-only pills containing either desogestrel (75 microgram/day) or levonorgestrel (30 microgram/day) on carbohydrate metabolism and adrenal and thyroid function. Eur J Contracept Reprod Health Care 2001; 6: 71–7.*
4. *Merki-Feld GS et al. Headache frequency and intensity in female migraineurs using desogestrel-only contraception: a retrospective pilot diary study. Cephalalgia 2013; 33: 340–6.*
5. *Morotti M et al. Progestin-only contraception compared with extended combined oral contraceptive in women with migraine without aura: a retrospective pilot study. Eur J Obstet Gynecol Reprod Biol 2014; 183: 178–82.*
6. *Merki-Feld GS et al. Desogestrel-only contraception reduces headache frequency and improves quality of life in female migraineurs. Eur J Contracept Reprod Health Care 2013; 18: 394–400.*
7. *Merki-Feld GS et al. Positive effects of the progestin desogestrel 75 µg on migraine*

frequency and use of acute medication are sustained over a treatment period of 180 days. J Headache Pain 2015; 16: 522.

8. *Nappi RE et al. Effects of an estrogen-free, desogestrel-containing oral contraceptive in women with migraine with aura: a prospective diary-based pilot study. Contraception 2011; 83: 223–8.*
9. *Lidegaard Ø et al. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012; 366: 2257–66.*
10. *Regidor PA et al. Drospirenone as estrogen-free pill and hemostasis: coagulatory study results comparing a novel 4mg formulation in a 24+4 cycle with desogestrel 75mg per day. Gynecol Endocrinol 2016; 32(9): 749–751.*

TOPIC : POP

Health benefits: migraine



Positive impact of desogestrel 75 µg on migraine frequency and use of acute medication over 180 days

Ref 1-5

1. *Merki-Feld GS et al. Headache frequency and intensity in female migraineurs using desogestrel-only contraception: a retrospective pilot diary study. Cephalalgia 2013; 33: 340–6.*
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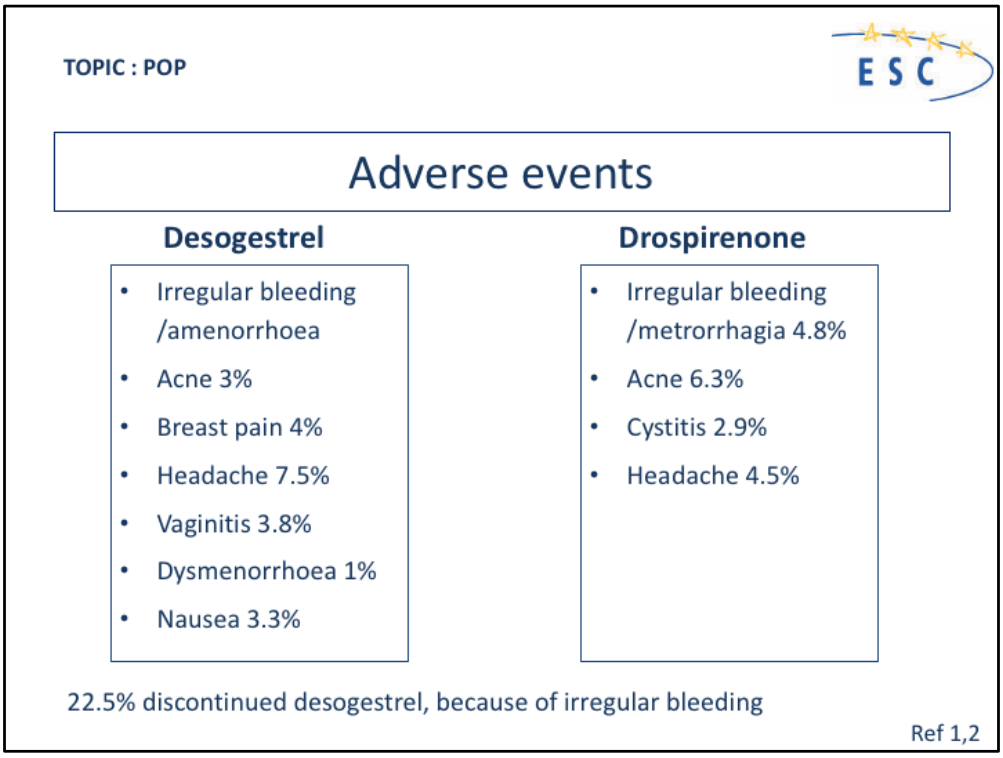

1. *Anonymous. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 micrograms/day or levonorgestrel 30 micrograms/day. Collaborative Study Group on the Desogestrel-Containing Progestogen-Only Pill. Eur J Contracept Reprod Health Care 1998; 3: 169–78.*
2. *Archer, D.F. et al. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability 2015;92: 439-44.*

The desogestrel study lists adverse events occurring in more than 3% of patients, the drospirenone study adverse events in more than 3% of the users.

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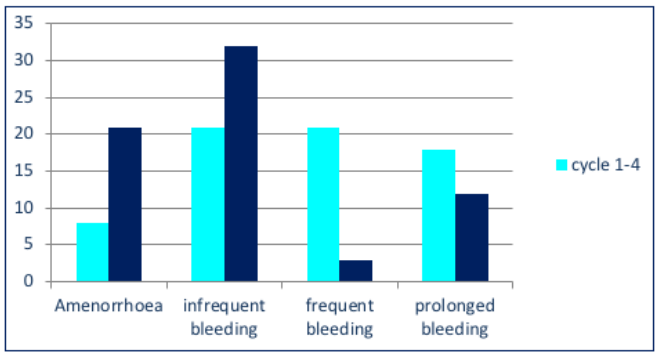
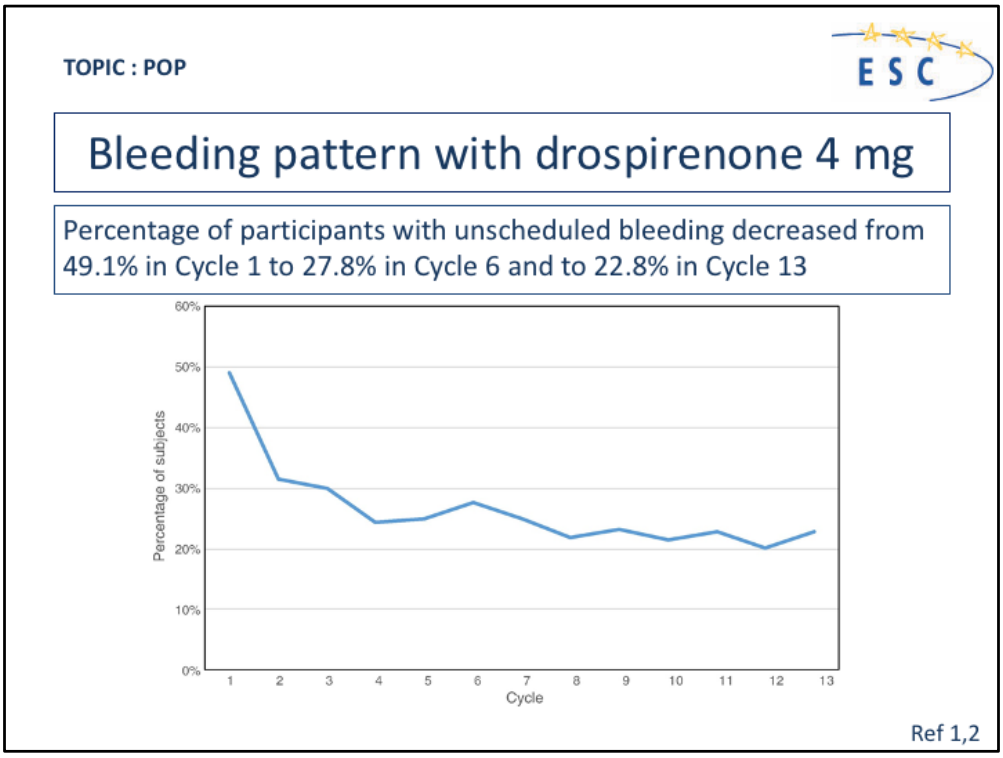
Bleeding pattern with desogestrel 75µg

- The rates of prolonged and frequent bleeding decrease with duration of use (15% after 1 year)
- Amenorrhoea after 1 year occurs in around 21% of users



Ref 1

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.*



1. *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.
2. *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.

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Desogestrel 75 µg POP: Breastfeeding

Medical condition	Desogestrel 75 µg POP	Contraceptive counselling
Postpartum: • **Not breastfeeding**	POP may be started immediately postpartum	No additional method is necessary
• **Breastfeeding** a. <21 days postpartum	Category 2 (WHO, CDC, 2015)	No additional method is necessary
b. ≥21 days -6 months postpartum	Category 1 (WHO, CDC, 2015)	No additional method is necessary
c. >6 months	Category 1 (WHO, CDC, 2015)	Use additional method in first 7 days

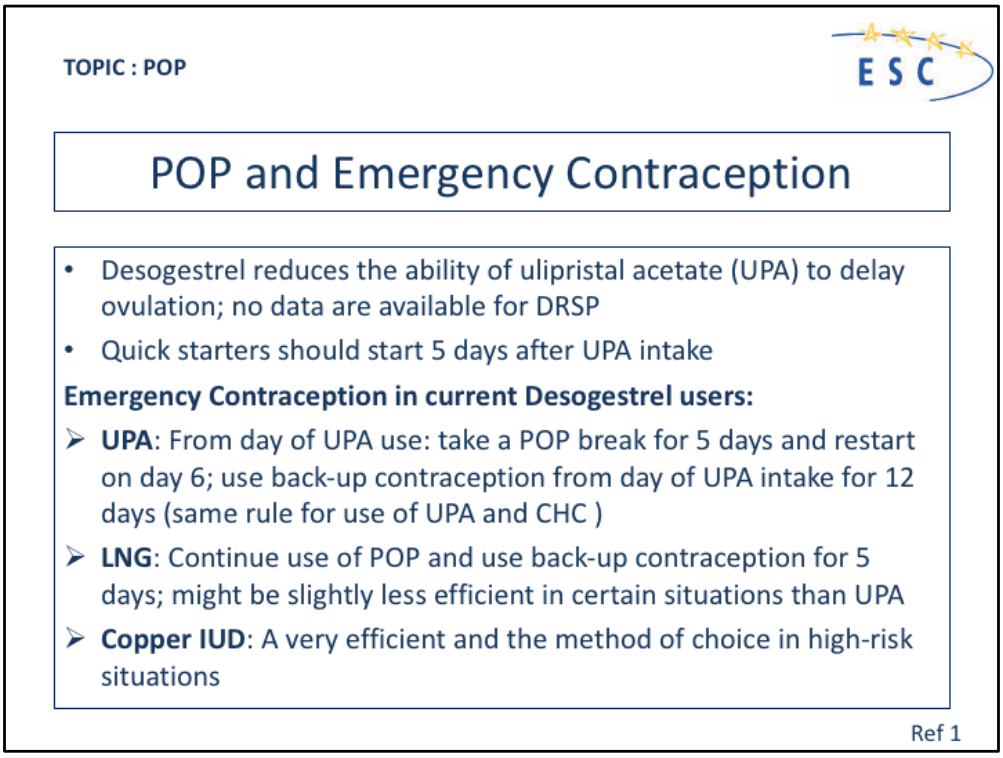
POPs can be started any time during breastfeeding and do not have a negative impact on the baby. There are no data on DRSP available yet.

Ref 1

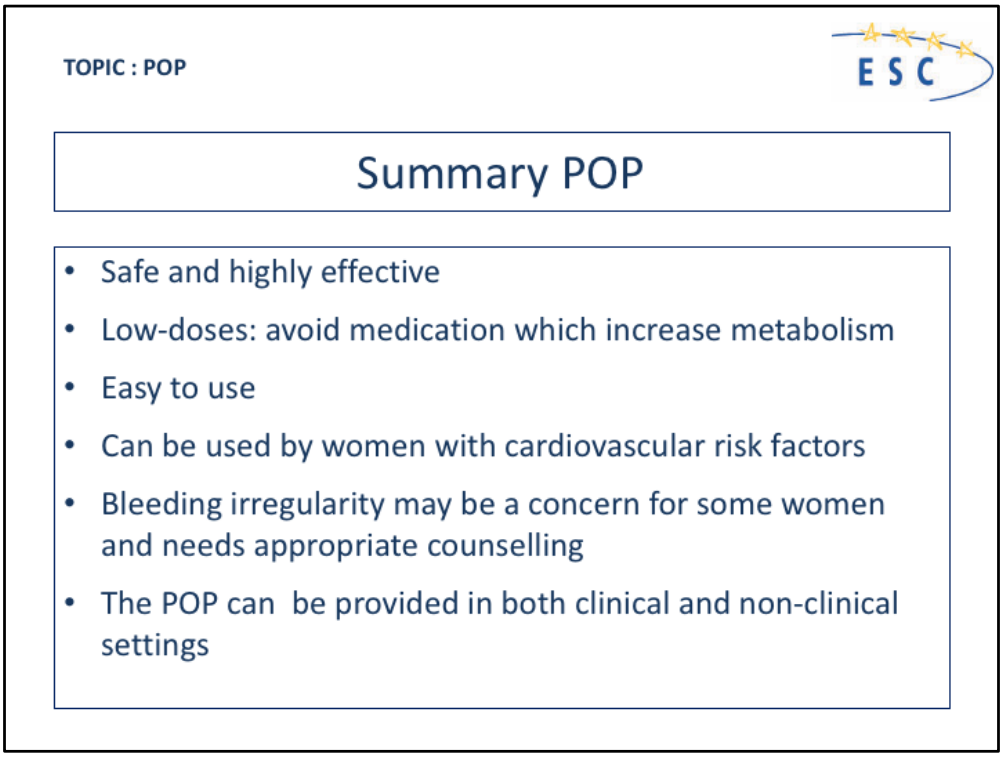
1. *World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. Geneva: WHO, 2015.*

Direct evidence demonstrates no harmful effect of POC on breastfeeding performance, and generally demonstrates no harmful effects on infant growth, health or development; however, these studies have been inadequately designed to determine whether a risk of long-term effects exists.

No data on DRSP available yet, but the amount of DRSP 4 mg in breast milk is negligible as it is only 0,11% of the daily use of the 4 mg.



1. *Brache V et al. A prospective, randomized, pharmacodynamic study of quick-starting a desogestrel progestin-only pill following ulipristal acetate for emergency contraception. Hum Reprod 2015; 13: 2785–93.*



- They are safe.
- They are highly effective.
- They are easy to use correctly.
- They can be delivered in both clinical and non-clinical settings.