TOPIC : DMPA

Depot medroxyprogesterone acetate (DMPA)

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

Update January 2020

TOPIC : DMPA

DMPA: Contents

- General characteristics
- Contraindications
- Safety
- Adverse events (bleeding pattern, weight gain, acne, mood changes, BMD, HIV acquisition)
- Reasons for discontinuation
- Summary

TOPIC : DMPA

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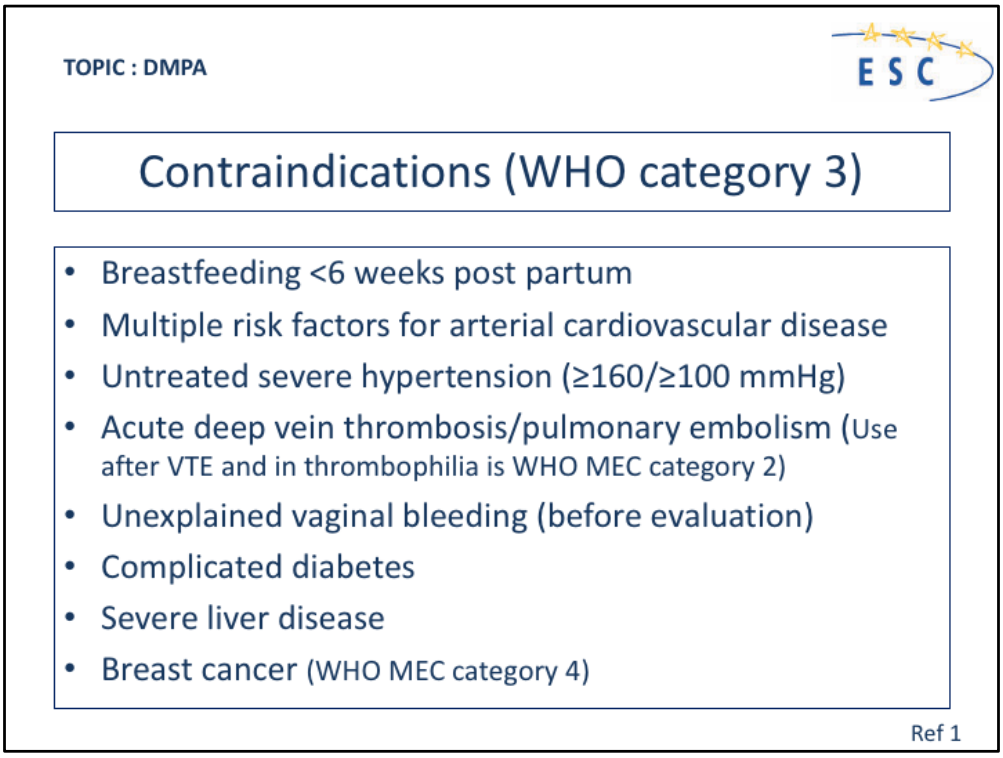
General characteristics

- 12 weekly injections of 150 mg i.m. or 104 mg s.c.
- Highly efficient and user-independent
- Protects immediately from pregnancy if started on day 1–7 of the cycle
- Can be started after day 7 if pregnancy is excluded; additional protection is needed (7 days)
- Has no negative impact on lactation or on the baby
- DMPA self-administration can improve contraceptive access, continuation, and autonomy

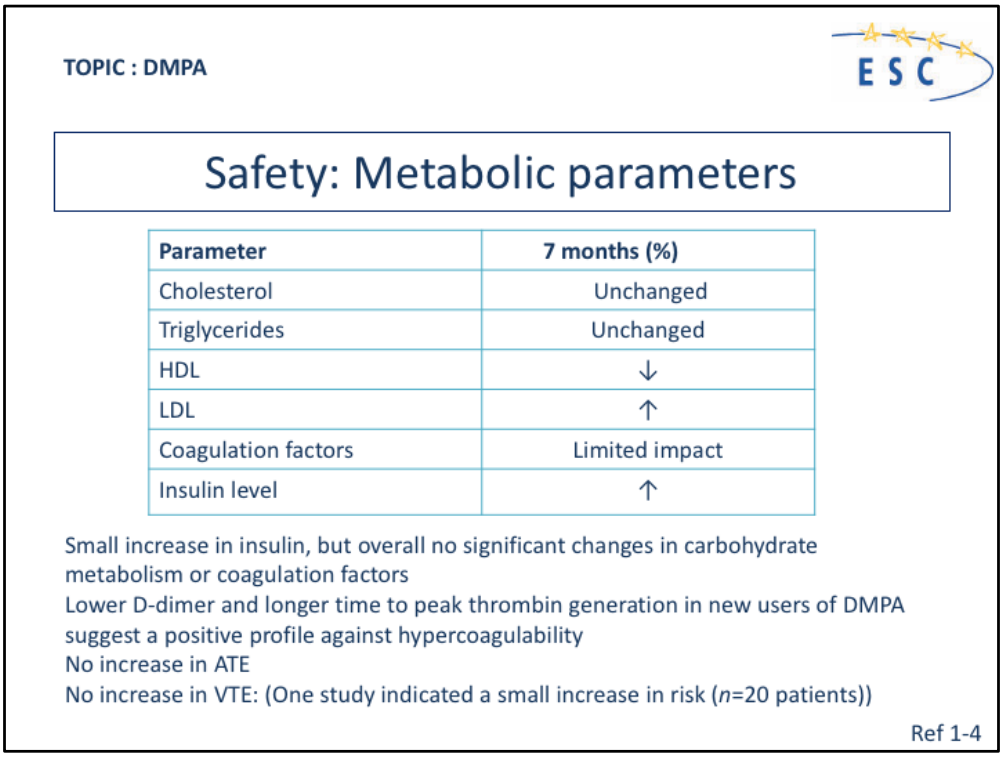
Ref 1-3

1. Burke HM, et al. Effect of self-administration versus provider-administered injection of subcutaneous depot medroxyprogesterone acetate on continuation rates in Malawi: a randomised controlled trial. Lancet Glob Health 2018; 6: e568–78.
2. Burke HM, et al. Factors Affecting Continued Use of Subcutaneous Depot Medroxyprogesterone Acetate(DMPA-SC):A Secondary Analysis of a1-Year Randomized Trial in Malawi. Global Health,Science and Practice 2019; 7: 54-65.
3. Kohn JE, et al. Increased 1-year continuation of DMPA among women randomized to self-administration: results from a randomized controlled trial at Planned Parenthood. Contraception 2018; 97(3): 198-204.



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

Although progestin-only injectables are safe for most women, there are some exceptions. According to the WHO MEC, progestin-only injectables are not generally recommended for women with category 3 conditions. In these situations, the risks of using this method usually outweigh the advantages. Category 3 conditions include: 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), acute blood clot in deep veins of legs or lungs, unexplained vaginal bleeding, complicated diabetes, severe liver disease and most liver tumours, and current breast cancer (WHO 4).



1. Westhoff C et al. Depot medroxyprogesterone acetate contraception. Metabolic parameters and mood changes. J Reprod Med. 1996 May;41(5 Suppl):401-6.
2. Fahmy K et al. Effect of depo-medroxyprogesterone acetate on coagulation factors and serum lipids in Egyptian women. Contraception 1991; 44: 431–44.
3. Fahmy K et al. Effect of long-acting progestagen-only injectable contraceptives on carbohydrate metabolism and its hormonal profile. Contraception 1991; 44: 419–30.
4. Melhado-Kimura V, et al. Effect of the injectable contraceptive depot-medroxyprogesterone acetate on coagulation parameters in new users. J Obstet Gynaecol Res 2017; 43(6): 1054-1060.

No negative impact on cardiovascular outcome according to present evidence.

TOPIC : DMPA

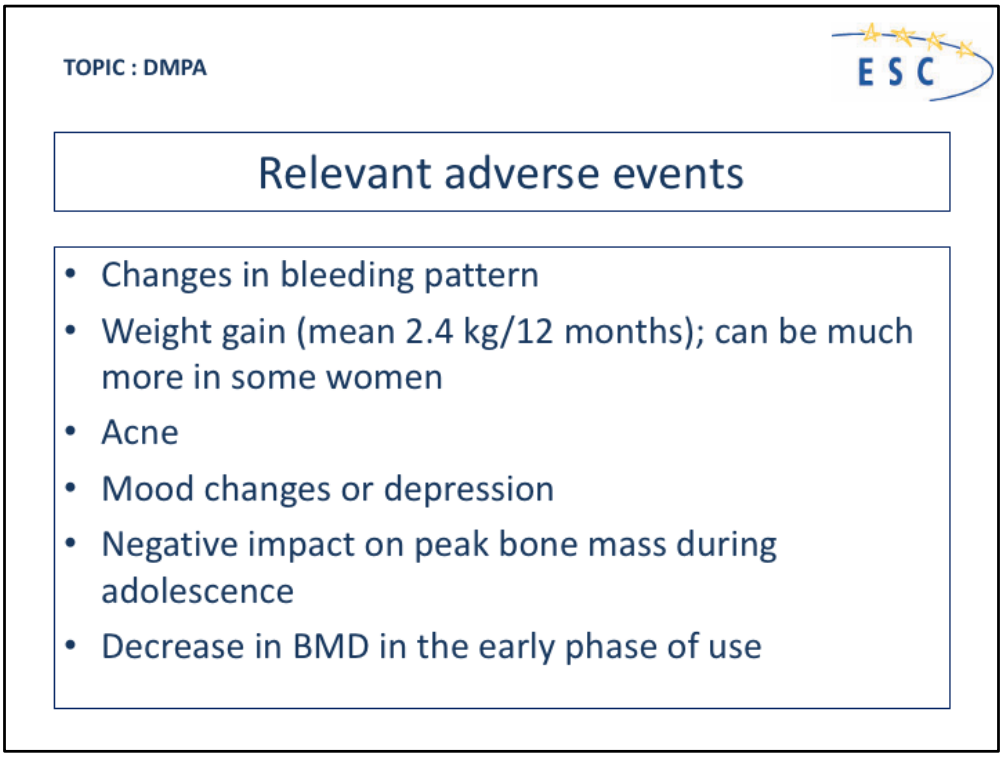
Adverse events do not differ between DMPA i.m. and s.c.

Adverse event occurring in >5%	DMPA i.m. users, n (%) (n=266)	DMPA s.c. users, n (%) (n=263)
Weight increase	**39 (14.7)**	**33 (12.5)**
Headache	**33 (12.4)**	**35 (13.3)**
Nausea	24 (9.0)	15 (5.7)
Acne	**20 (7.5)**	**20 (7.6)**
Depression or mood changes	**19 (7.1)**	**20 (7.6)**
Decreased libido	**16 (6.0)**	**8 (3.0)**
Abdominal pain	16 (6.0)	6 (2.3)
Intermenstrual bleeding	15 (5.6)	15 (5.7)
Abnormal cervical smear	14 (5.3)	9 (3.4)
Injection site reaction	**1 (0.4)**	**21 (8.0)**

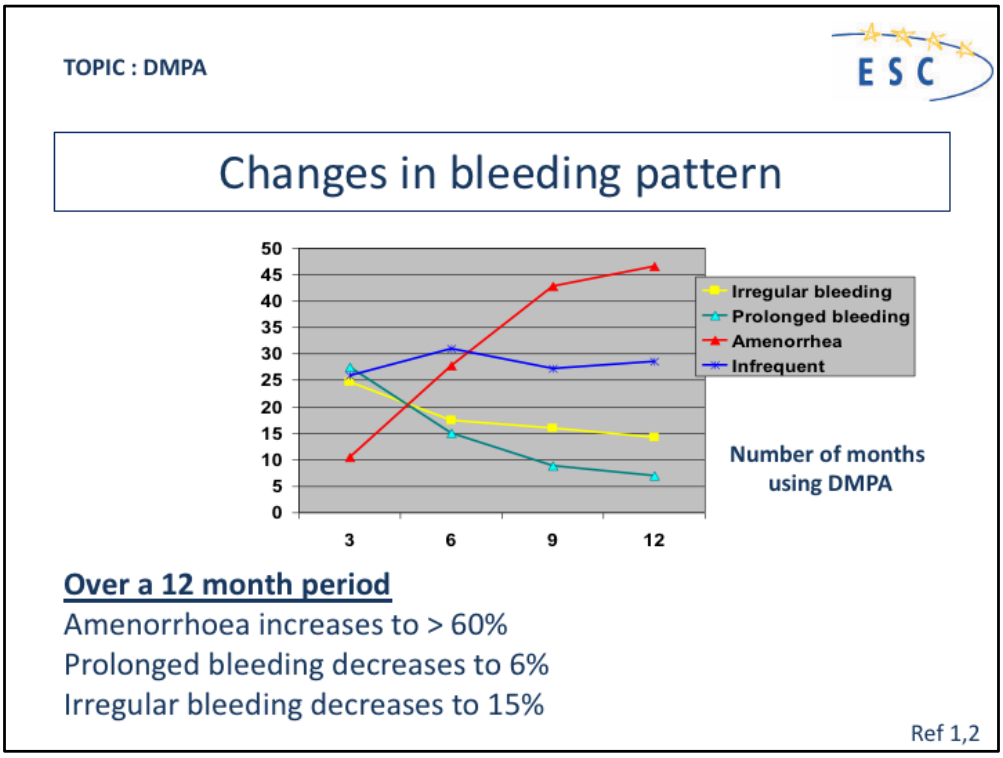
Ref 1

1. *Kaunitz AM et al. Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. Contraception 2009; 80: 7–17.*

Data not available for three women in the DMPA s.c. group and for two in the DMPA i.m. group.



Acne is less frequent in DMPA users than in users of other POC including LNG-IUS (clinical experience).
Peak bone mass, which can be defined as the amount of bony tissue present at the end of skeletal maturation, is an important determinant of osteoporotic fracture risk in later life.

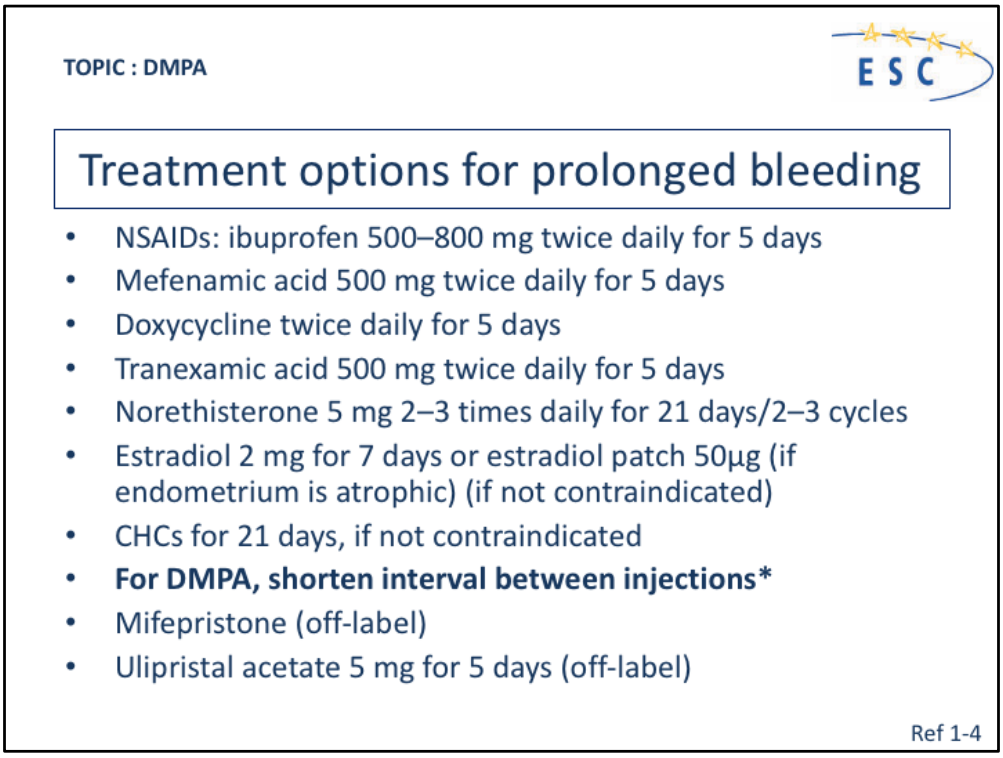


1. *Source of slide: WHO, 1987.*
2. *WHO Special Programme of Research, Development and Research Training in Human Reproduction: Task Force on Long-Acting Agents for Fertility Regulation (WHO). A multicentered phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg. II: The comparison of bleeding patterns. Contraception 1987; 35: 591–607.*

- The majority of women using DMPA experience menstrual changes as a result of the high level of progestin. During the months after the first-second injection, episodes >7 days of unscheduled bleeding/spotting are common. This is potentially due to endometrial instability and subsequent capillary leakage from scant uterine lining. The frequency/duration of these episodes decreases with continued use. Forty-six percent of users will be amenorrhoeic by 1 year; 70% with longer use.
- Endometrial biopsy studies show a predominance of endometrial atrophy and chronic endometritis. The latter is most often due to atrophy rather than to an infectious process.
- The most reliable information on bleeding patterns among women using injectables and other hormonal contraceptives comes from a WHO-coordinated multicentre clinical trial in which women kept detailed menstrual diaries. Less than 10% of DMPA users have normal cycles in the first year of use. As indicated on the graph, many DMPA users can expect to have irregular or prolonged bleeding in the

first 6 months and then infrequent bleeding or amenorrhoea in the next 6 months and beyond. About 47% of women are amenorrhoeic (have no monthly bleeding) after 1 year of DMPA use and, although not reflected on this graph, about 80% are amenorrhoeic after 2 years of DMPA use.

- The original data from the WHO trial described the percentages of women in the trial who experienced eight types of bleeding changes at 3, 6, 9 and 12 months of DMPA use. This graph collapses those eight categories of data into four. Data from each of the four categories of prolonged bleeding were added together to form one category of prolonged bleeding. The data on frequent bleeding were added to the data on irregular bleeding and are displayed here as *irregular bleeding.* The data shown here for amenorrhoea and infrequent bleeding are as originally published.



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.

Ref 1:
Literature was identified through database searches, reference lists, organisations and individuals, covering the period until December 2006. Twenty-three randomised controlled trials enrolling 2674 participants were included. Seventy percent were determined to reflect low to moderate risk of bias.

- **Estrogen treatments** reduced the number of days of an ongoing bleeding episode in DMPA and Norplant users. However, treatment frequently led to study discontinuation due to gastrointestinal upset. Estrogen 50 50 µg patch

for 7 days is another option based on clinical experience.

- **Combinations of oral ethinylestradiol and levonorgestrel** improved bleeding patterns in Norplant users, but method discontinuation rates were unchanged. One trial reported successful use of combined oral contraceptives in treating amenorrhoea among DMPA users.
- **Tranexamic acid, mifepristone combined with an estrogen, and doxycycline** were more effective than placebo in terminating an episode of bleeding in women using progestin-only contraceptives, according to three small studies.

Norplant users, but not Implanon users, administered the anti-progestin mifepristone reported fewer days of bleeding than those given placebo. Mifepristone used monthly by new Norplant users reduced bleeding when compared with placebo.

A variety of NSAIDS have been evaluated for their ability to treat abnormal bleeding, with mixed results.

Norplant users receiving tamoxifen had less unacceptable bleeding after treatment and were more likely to continue using Norplant than those receiving placebo.

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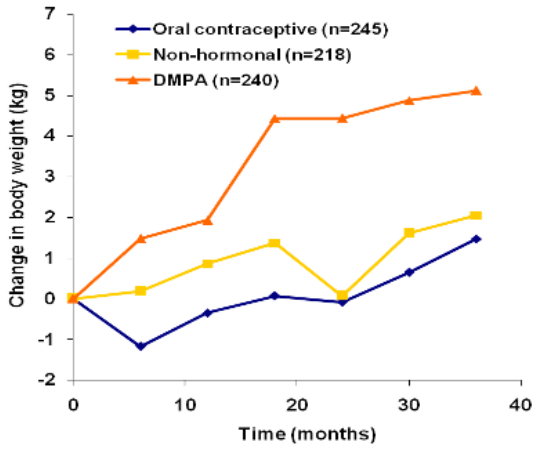
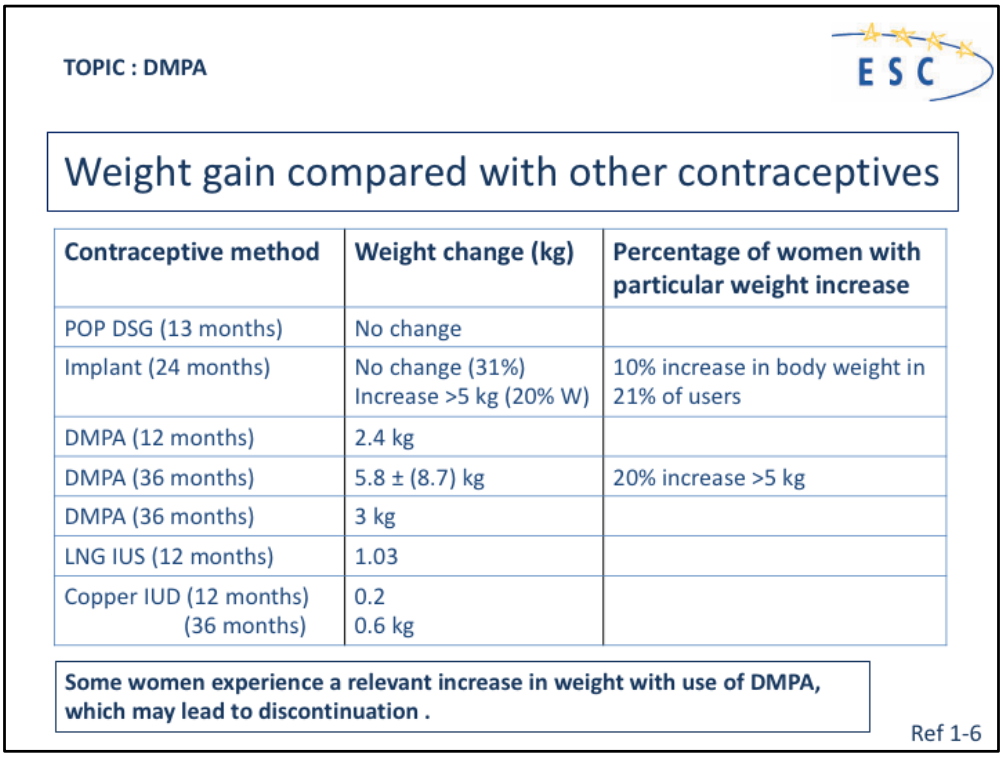
Weight gain over 3 years in DMPA users in comparison with COC users



Estimated absolute change in body weight from baseline to month 36

Ref 1

1. *Berenson AB et al. Changes in weight, total fat, percent body fat, and central-to-peripheral fat ratio associated with injectable and oral contraceptive use. Am J Obstet Gynecol 2009; 200: 329e.1–8.*



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. *KorverT 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 in DMPA users compared with LNG-IUS and Cu-IUD

Years of use	DMPA	LNG-IUS	Cu-IUD
1	1.3 ± 0.15	0.7 ± 0.18	0.2 ± 0.17
3	3.1 ± 0.21	2.4 ± 0.24	1.4 ± 0.23
6	4.6 ± 0.32	2.5 ± 0.53	3.3 ± 0.36
10	6.6 ± 0.61	4.0 ± 0.97	4.9 ± 0.60

The change in weight gain with the CU-IUD over time can serve as a typical reference for the age-related weight increase in women without hormone use.

* Check notes for information related to weight gain in adolescents

Ref 1

1. Modesto W et al. Weight variation in users of depot-medroxyprogesterone acetate, the levonorgestrel-releasing intrauterine system and a copper intrauterine device for up to ten years of use. The European Journal of Contraception and Reproductive Health Care, 2015; 20: 57–63.

2. Silva P et al. Dietary intake and eating behavior in depot medroxyprogesterone acetate users: a systematic review.

Few studies report dietary intake and eating behavior in DMPA users and the available data are insufficient to conclude whether DMPA use is associated with changes in dietary habits or behavior leading to weight gain.

3. Beksinska ME et al. Prospective study of weight change in new adolescent users of DMPA, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. Contraception 2010; 81: 30–4.

In a study carried out among 490 adolescents followed for 6 years, all groups of women gained weight, but the greatest weight gain was among injectable users. In adolescents who had weight gain >2 kg, the results were similar between those who were non-obese and those who were overweight at baseline.

Variable Weight in kg, mean (SD) over 6 Years:
Non-users 2.8 (7.4) kg
DMPA users 6.2 (8.4) kg
COC users 2.3 (5.5) kg
Discontinuers 2.8 (7.6)

TOPIC : DMPA

Adverse events in users of DMPA and other POCs

Adverse event	POP (%)	Implant (%)	DMPA i.m., s.c. (%)
Headache	7.5	12.7	**13.3**
Weight gain		12.1	**12.5**
Depression		7.3	**7.6**
Libido decrease			**3–6**
Acne	3.1	14.5	**7.6**

- POC cannot be used for treatment of acne (or what patients consider acne)
- DMPA users complain less about skin irritation compared with implant users

Ref 1-3

1. *Kaunitz AM et al. Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. Contraception 2009; 80: 7–17.*
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. *Blumenthal PD et al. Tolerability and clinical safety of Implanon. Eur J Contracept Reprod Health Care 2008; 13 (suppl 1): 29–36.*

TOPIC : DMPA

Acne

- No prospectively conducted studies are available investigating the effect of DMPA on acne
- Especially when changing from a combined pill to a progestin-only method skin problems can appear during the first 3 months
- Skin problems frequently resolve with longer duration of use

TOPIC : DMPA

Mood changes, depression

For DMPA evidence is lacking; therefore recommendations are based on clinical observations with all POC:

- POC very rarely initiate depression in predisposed women (clinical reports)
- POC and progestin-releasing devices should not be initiated in women suffering from depression (copper IUD might be a better alternative)
- If a woman complains of developing depressed mood while using POC, stop the method
- If women have a history of depression and 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)

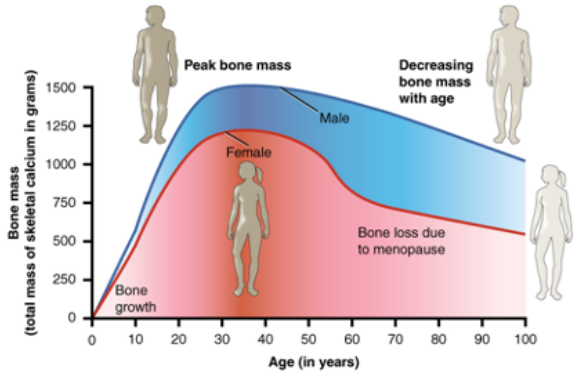
Ref 1-3

1. *Westhoff C. DMPA contraception. Metabolic parameters and mood changes, J Reprod Med 1996; 41: 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.*

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 the better option to test tolerability.

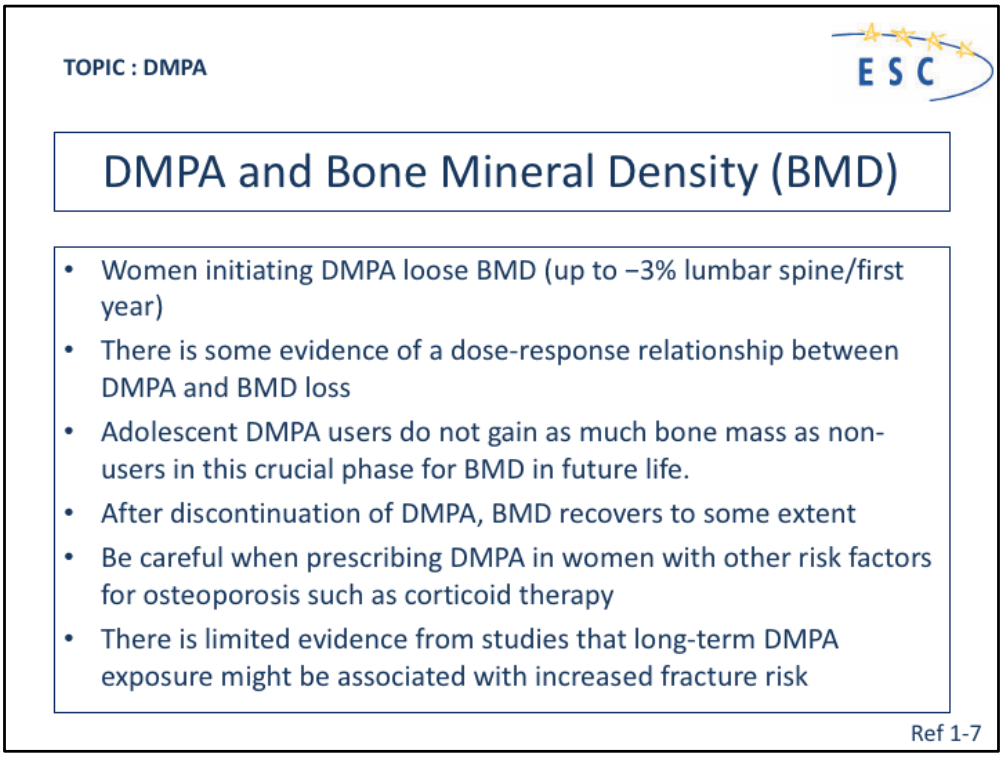
TOPIC : DMPA

Bone mass from adolescence to menopause



- Women should achieve peak bone density during adolescence
- The strongest increase in bone density occurs during the first 2 years after menarche

Women should achieve peak bone density during adolescence. The strongest increase in bone density occurs during the first 2 years after menarche. To achieve peak bone mass is crucial to reduce the fracture risk in later life. Women start to experience some bone loss during early menopause.



1. *Kaunitz AM. Bone density recovery after DMPA injectable contraception use. Contraception 2008; 77: 67–76.*
2. *Cromer BA. Bone mineral density in adolescent and young adult women on DMPA. Curr Opin Obstet Gynecol 2003; 15: 353–7.*
3. *Scholes D et al. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adoles Med 2005; 159: 139–44.*
4. *Scholes D et al. Injectable hormone contraception and bone density: results from a prospective study. Epidemiology 2002; 13: 581–7.*
5. *Merki-Feld GS et al. A prospective study on the effects of depot medroxyprogesterone acetate on trabecular and cortical bone after attainment of peak bone mass. BJOG 2000; 107: 863–9.*
6. *Kyvernitakis I, et al. The impact of depot medroxyprogesterone acetate on fracture risk: a case-control study from the UK. Osteoporos Int 2017; 28(1): 291-297.*
7. *Lange HL, et al. Bone Mineral Density and Weight Changes in Adolescents Randomized to 3 Doses of Depot Medroxyprogesterone Acetate. J Pediatr Adolesc Gynecol 2017; 30(2): 169-175.*

Most studies have found that DMPA users have lower bone density compared with non-users. During adolescence, DMPA prevents the achievement of peak bone density, which is of major importance in decreasing fracture risk after the menopause. A woman's bones normally reach peak bone density during adolescence.

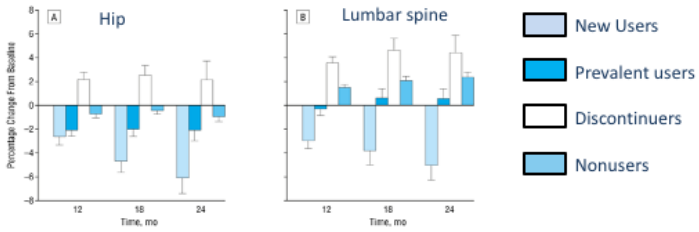
Women who start using DMPA as adults appear to regain most of the lost bone after they stop using DMPA. One study indicated that women who had achieved peak bone mass before the menopause (30–45 years) did not continue to lose bone density at the distal radius. However, it is not yet known whether bone loss in adolescents and young women is completely reversible.

Long-term studies are needed to determine whether DMPA use increases the risk of fracture, especially in women who start use of DMPA during adolescence. Currently, DMPA use is not the method of choice during adolescence. If no other methods are available, preventing the risks associated with unwanted pregnancy at a young age outweigh the theoretical risk of fracture later in life.

TOPIC : DMPA

ESC

DMPA and BMD in adolescents



- These data based on a small number of patients indicate that adolescents regain some BMD after discontinuation of DMPA; whether they regain the complete amount lost is not known
- DMPA use may be considered an option for younger adolescents, after weighing its use against the theoretical risk of fracture later in life; however, with regard to BMD another form of POC is preferable

Ref 1-5

1. *Kaunitz AM. Bone density recovery after DMPA injectable contraception use. Contraception 2008; 77: 67–76.*
2. *Cromer BA. Bone mineral density in adolescent and young adult women on DMPA. Curr Opin Obstet Gynecol 2003; 15: 353–7.*
3. *Scholes D et al. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adoles Med 2005; 159: 139–44.*
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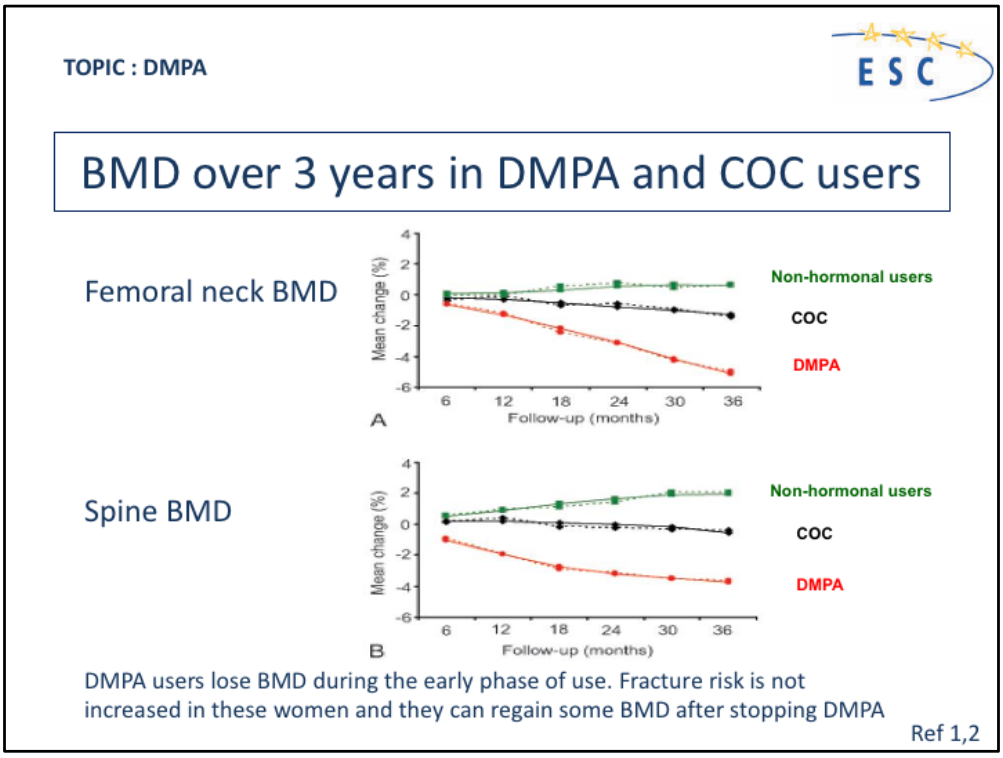
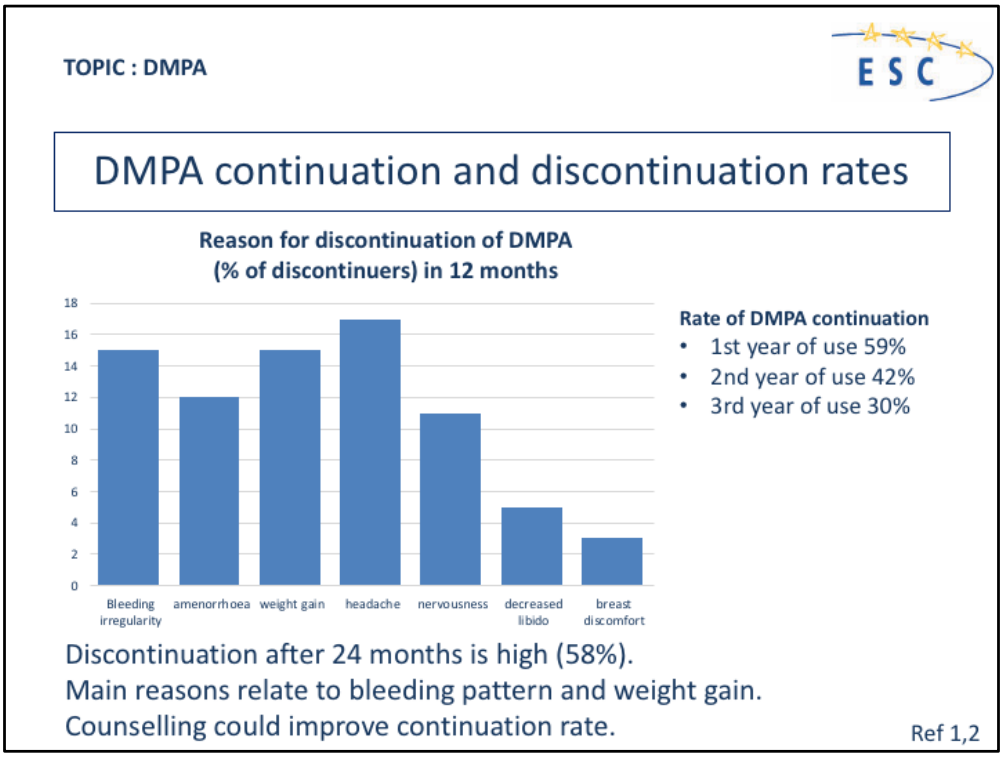


1. *Berenson AB et al. Effects of depot medroxyprogesterone acetate and 20-microgram oral contraceptives on bone mineral density. Obstet Gynecol 2008; 112: 788–99.*
2. *Clark MK et al. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate.* Fertil Steril 2004 Dec;82(6):1580-6

There was a significant difference between DMPA users and non-users in the studies of Berenson et al. and Clark.

The Berenson study included 703 women aged 16–33 years (20 µg EE COC users, DPMA users and non-hormonal contraception [non-HC] users), who were followed for 36 months. DMPA users had the highest BMD loss at the spine during the first year, after which the loss slowed during the second and third years. At the femoral neck, BMD loss was slower during the first year, and increased during the second and third years. COC users had a slight BMD increase at the spine during the first 12 months, followed by a slow and gradual decrease in the second and third years, and had a slow and consistent decrease over time at the femoral neck. For total hip BMD, the changes were −3.5%, −0.3% and +1.6% among DMPA, COC and non-HC users, respectively, over the 3 years. Age was found to be an important determinant of BMD change by contraceptive method. Over 36 months, DMPA users 16–24 years old lost significantly more bone at the spine (4.2% vs 3.2%, p=0.006) and femoral neck (6.0% vs 4.2%, p=0.001) than those aged 25–33 years; however, COC users aged 16–24 years lost significantly less bone density at the spine (0.4% vs 0.8%, p=0.013) than women 25–33 years of age. By contrast, non-HC users aged 16–24 years gained significantly more bone at the spine (3.3% vs 1.3%, p=0.001) than those aged 25–33

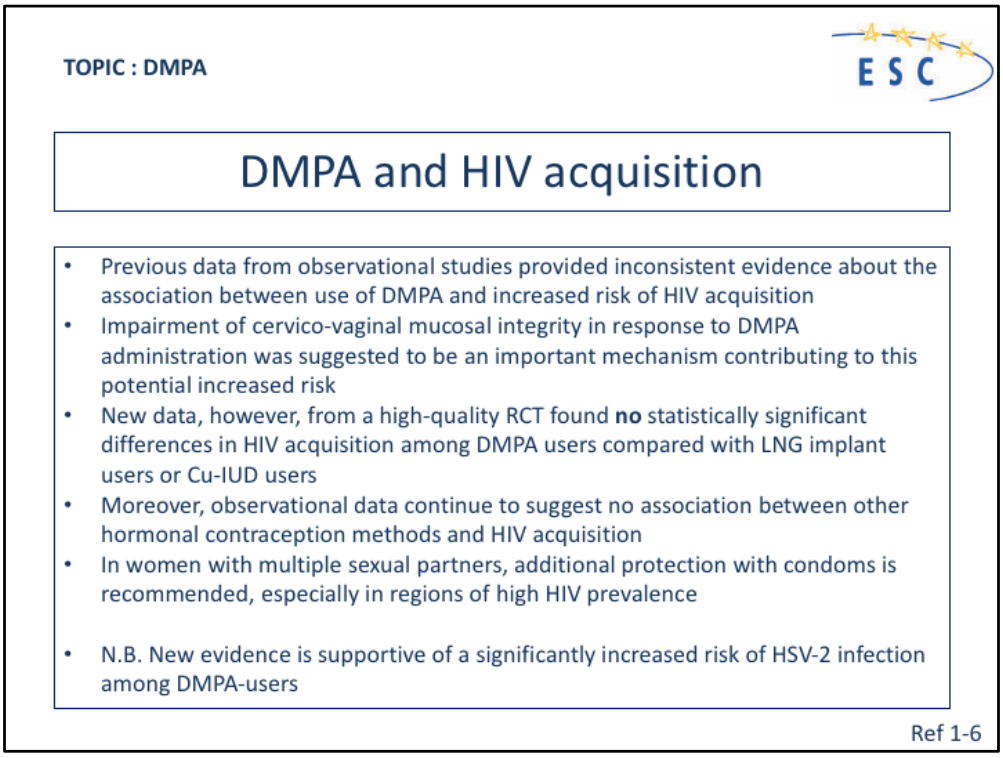
years. The authors concluded that both DMPA and COC containing 20 µg EE caused BMD loss. DMPA-related changes were found to be largely reversible at the spine regardless of the contraceptive method used after DMPA discontinuation and at the femoral neck if no hormonal contraception was used. However, use of a COC immediately after DMPA discontinuation may impede the ability to regain bone at the femoral neck, at least temporarily. This finding appears to have greatest relevance for white women who are at high risk of hip fracture after the menopause. Further studies are needed to confirm these findings and to determine whether they are robust across women of different races and ages.



1. *Canto De Cetina TE et al. Effect of counseling to improve compliance in Mexican women receiving DMPA. Contraception 2001; 63: 143–6.*
2. *Schwallie PC et al. Contraceptive use – efficacy study utilizing DMPA administered as an intramuscular injection once every 90 days. Fertil Steril 1973; 24: 331–9.*

Ref 2: In this large study the continuation rate ranged from 24% to 59%. More recent studies report lower continuation rates: from 26% to 53% at 1 year, with the most frequent reason for discontinuation relating to a lack of adequate user education regarding bleeding disturbances including amenorrhoea. Counselling about the expected hormonal effects could improve the DMPA continuation rate.

Ref 1: In rural Mexico, 175 women who received detailed, structured counselling were compared with 175 women who received routine counselling: the cumulative life table discontinuation rate was 8% for women who received structured counselling vs 32% for those who received routine counselling.



1. *Polis CB et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. AIDS 2016; 30: 2665–83.*
2. *Brind J, et al. Risk of HIV Infection in Depot-Medroxyprogesterone Acetate (DMPA) Users: A Systematic Review and Meta-analysis. Issues Law Med 2015; 30(2): 129-39.*
3. *Zalenskaya IA, et al. Use of contraceptive depot medroxyprogesterone acetate is associated with impaired cervicovaginal mucosal integrity . J Clin Invest 2018; 128(10): 4622–4638.*
4. *Deese J et al. Contraceptive use and the risk of sexually transmitted infection: systematic review and current perspectives. Open Access Journal of Contraception 2018; 9: 91–112*
5. *Baeten et al. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: a randomised, multicentre, open-label trial. Lancet 2019; 394: 303–13*
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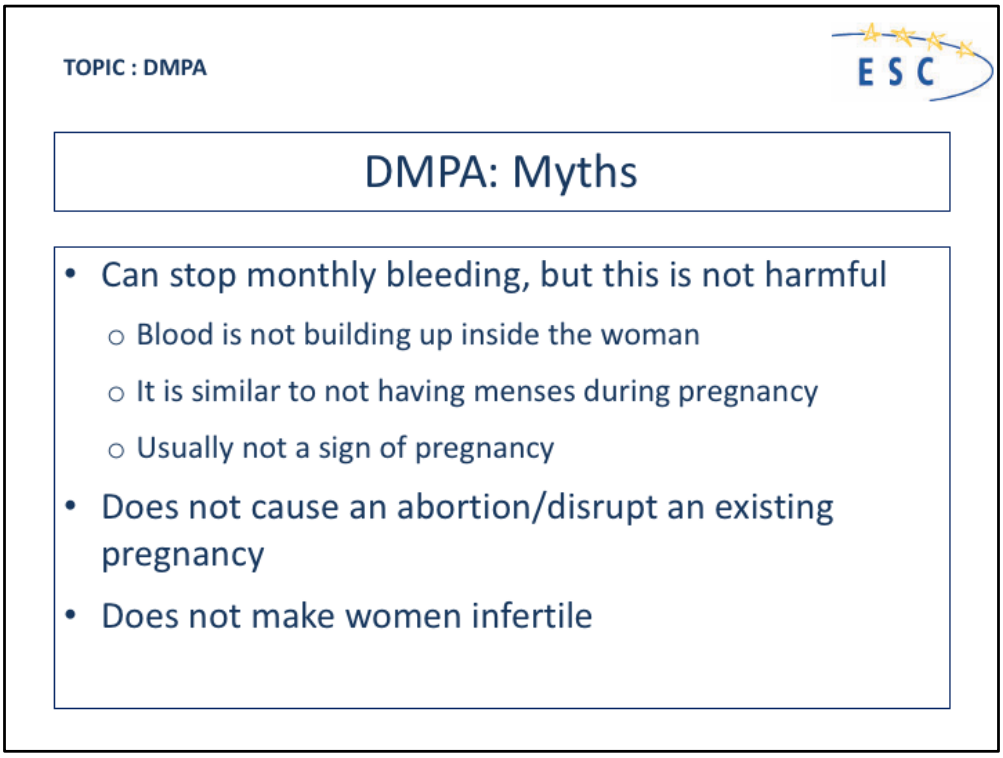
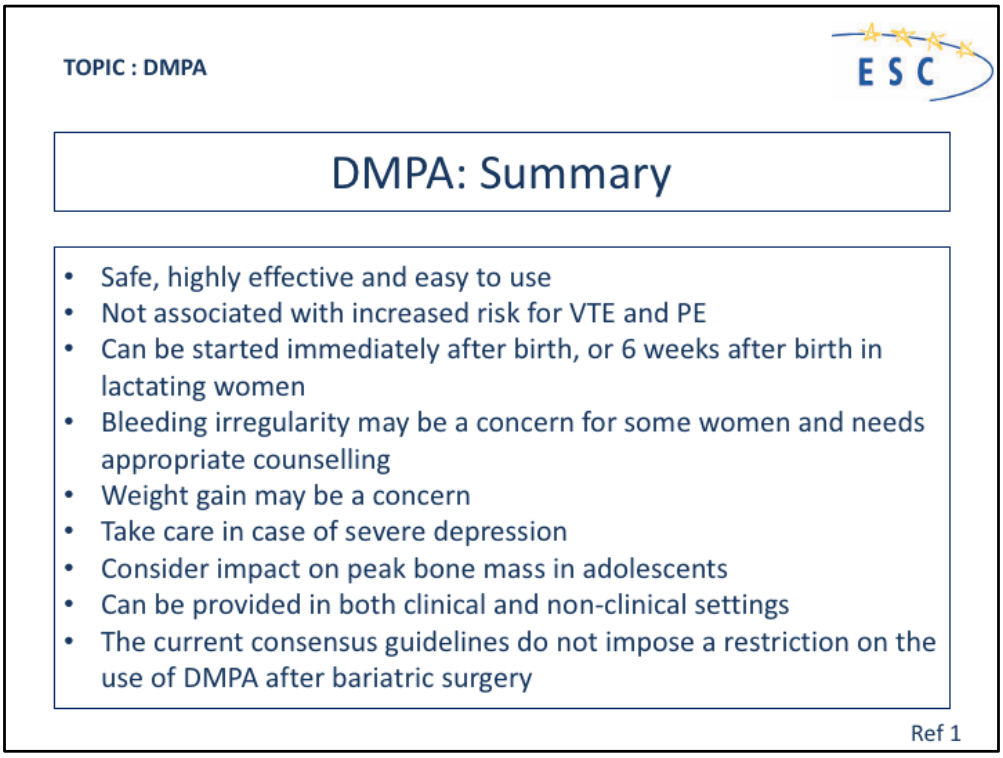


More information: *World Health Organization. Training Resource Package for Family Planning. Progestin-Only Injectable Contraception. Geneva: WHO.*



In conclusion, progestin-only injectables have characteristics that make them a desirable method for many women.

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

Appropriate counselling plays a key role in the provision of injectable contraceptives. While it is relatively simple to administer injectables correctly, providers also need to counsel patients about the characteristics of progestin-only injectable contraceptives, paying special attention to their side effects, and be able to manage side effects.

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