Sixth edition

Medical eligibility criteria for contraceptive use

Web Annex

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Evidence Synthesis Team

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Coordination

Overall coordination for guideline development and evidence synthesis was provided by the WHO Secretariat Team, comprising James Kiarie (Unit Head) and Nancy Kidula (responsible technical officer) from the Contraception and Fertility Care unit at the WHO Department of Sexual and Reproductive Health and Research.

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Abbreviations

ARV	antiretroviral
ART	antiretroviral therapy
BF	breastfeeding
BMD	bone mass density
BMI	body mass index
CHC	combined hormonal contraceptive
Cu	copper
DMPA	depot medroxyprogesterone acetate
ECP	emergency contraceptive pill
EFV	efavirenz
ETG	etonogestrel
GDG	Guideline Development Group
IM	intramuscular
IUD	intrauterine device
LNG	levonorgestrel
MEC	*Medical eligibility criteria for contraceptive use* (WHO publication)
NET-EN	norethisterone enanthate
NNRTI	non-nucleoside/nucleotide reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OC	oral contraceptive
PI	protease inhibitor
PICO	population, intervention, comparator, outcome
POC	progestogen-only contraceptive
POI	progestogen-only injectable contraceptive
POP	progestogen-only pill
PVR	progesterone-releasing vaginal ring
RCT	randomized controlled trial
SC	subcutaneous
SPR	*Selected practice recommendations for contraceptive use* (WHO publication)
UC	ulcerative colitis
UPA	ulipristal acetate
WHO	World Health Organization

1. Introduction

1.1 Background

There are a total of four World Health Organization (WHO) "cornerstones" documents pertaining to contraception: two guidelines focusing on evidenced-based recommendations (primarily targeted towards policy-makers and programme managers) and two guidance documents focusing on application of the recommendations (primarily targeted towards health workers). Regarding the first two cornerstones, *Medical eligibility criteria for contraceptive use* (MEC) provides recommendations and information on *who* can use contraceptive methods safely; while *Selected practice recommendations for contraceptive use* (SPR) *(1)* provides recommendations and information on *how* to use contraceptive methods safely and effectively once they are deemed to be medically appropriate. There are two other cornerstone documents which provide guidance to health workers on how to apply the recommendations in the MEC and SPR in clinical settings: *Decision-making tool for family planning clients and providers (2)* and *Family planning: a global handbook for providers (3)*.

WHO guidelines are based on up-to-date evidence. Therefore, these documents are updated periodically to reflect changes in medical and scientific knowledge. The evidence-based recommendations in the MEC do not indicate a "best" method that *should* be used in a particular medical context; rather, review of the recommendations allows for consideration of multiple methods that *could* be used safely by people with certain health conditions (e.g. hypertension) or physiological characteristics (e.g. age).

The MEC covers the following family planning methods: low-dose combined oral contraceptives (COCs) (i.e. a combination of ≤ 35 µg ethinyl estradiol and a progestogen), combined patch (P), combined vaginal ring (CVR), combined injectable contraceptives (CICs), progestogen-only pills (POPs), depot medroxyprogesterone acetate (DMPA), norethisterone enanthate (NET-EN), levonorgestrel (LNG) and etonogestrel (ETG) implants, emergency contraceptive pills (ECPs), copper-bearing intrauterine devices (Cu-IUDs), levonorgestrel-releasing IUDs (LNG-IUDs), Cu-IUDs for emergency contraception (E-IUD), progesterone-releasing vaginal ring (PVR), barrier methods (BARR), fertility-awareness-based methods (FAB), lactational amenorrhoea method (LAM), coitus interruptus (CI), and female and male sterilization (STER).

This sixth edition of the MEC has two principal components, published separately. The main document contains the new, updated and reaffirmed recommendations on the medical eligibility criteria for contraceptive use in the presence of various medical conditions and medically relevant physiological characteristics. Meanwhile, this web annex contains supplementary material that explains how the recommendations were developed and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables.

Topics prioritized for the sixth edition of the MEC

On 8–10 November 2022, a Guideline Development Group (GDG) scoping meeting was convened in Montreux, Switzerland, to initiate the revision process for the development of the sixth edition of the MEC. At this meeting, the GDG prioritized topics for review and consideration at a later GDG meeting (July 2024) based on meeting one or more of the following criteria: topics identified as controversial or of particular importance to the field; topics with new evidence, for

which the existing recommendation was potentially inconsistent with the updated body of evidence; and new topics for review and possible inclusion in the sixth edition of the MEC based on their global relevance and availability in multiple countries.

Box W.1.1 Prioritized topics reviewed by the Guideline Development Group (GDG) for the sixth edition of the MEC

Existing topics for which new evidence was identified, or topics identified as controversial among stakeholders (four topics):

- progestogen-only contraceptive (POC) use among breastfeeding women
- intrauterine device (IUD) use among breastfeeding women
- hormonal contraceptive use among women using antiretroviral therapy (ART)
- repeated use of emergency contraceptive pills (ECPs).

New topics to consider adding to the MEC for the sixth edition (two topics):

- HIV pre-exposure prophylaxis (PrEP)
- Inflammatory bowel disease (IBD).

For the six prioritized topics outlined in Box W.1.1, the GDG developed questions using the "PICO" format (i.e. questions with specified populations, interventions, comparators and outcomes) (presented in section 2 of this web annex) to serve as the framework for conducting the systematic reviews and compiling the GRADE evidence tables (which are presented in section 3 of this web annex). These tasks were then undertaken by the Evidence Synthesis Team (EST) and the guideline methodologist, respectively. WHO convened the second and final GDG meeting from 23 to 25 July 2024, to review the evidence for the priority topics and, where appropriate, develop or revise specific medical eligibility criteria in the MEC. The guideline development methods are presented in more detail in Annex 2 in the main MEC document.

1.2 Methods for the evidence identification and synthesis

For each of the topics listed in Box W.1.1, systematic reviews were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to answer PICO-formatted questions regarding safety outcomes *(4)*. A protocol for each review was developed and registered in the International Prospective Register of Systematic Reviews (PROSPERO) open access online database *(5)*. The systematic reviews are now published as open access in a special issue of *BMJ Sexual & Reproductive Health (6)*.

In general, multiple databases (e.g. PubMed and Cochrane databases) were searched for studies published in any language in a peer-reviewed journal to inform the new (or updated) systematic reviews. Searches were performed from database inception to 31 August 2023 for the updated reviews on POC and IUD use among breastfeeding women, from 1 January 2015 through 31 December 2023 for the updated review on women using ART (which included the new condition, HIV PrEP), from database inception through 28 February 2024 for repeated ECP use, and from database inception through 15 July 2024 for the updated review on inflammatory bowel disease (IBD).

Reference lists and direct communications with experts in the field were also used to identify other studies, including those accepted by journals but not yet published. Neither grey literature nor conference abstracts were included in the systematic reviews. Due to heterogeneity of study designs, contraceptive formulations and outcome measures, meta-analyses were generally not performed. The risk of bias for each study included in a systematic review was assessed by review authors using version 2 of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2) *(7)* and a modified version of the Cochrane tool to assess risk of bias in non-randomized studies *(8)*.

GRADE evidence profiles were prepared by the guideline methodologist for each PICO question for which evidence was found and clinical outcomes were reported. These evidence tables are used to assess the quality of the summarized evidence, and they include the range of the estimates of effect for each clinical outcome assessed. The systematic review reports were made electronically available to all GDG members prior to the second GDG meeting.

1.3 Decision-making during the final GDG meeting

WHO convened the second and final GDG meeting on 23–25 July 2024, at WHO headquarters in Geneva, to review the evidence for the prioritized topics (Box W.1.1) and, where appropriate, develop or revise specific recommendations for this sixth edition of the MEC. The written and orally presented systematic reviews and GRADE evidence profiles served as the basis for the GDG's deliberations.

The GDG considered the overall quality of the safety evidence, paying particular attention to the strength and consistency of the data, as required by the GRADE approach to evidence review *(9)*. In addition, the GDG applied the GRADE evidence-to-decision (EtD) framework to ensure that recommendations were based on the consideration of the quality of the evidence, the balance of benefits and harms, the values and preferences of contraceptive users and health workers, the priority of the problem, acceptability to clients, cost and resource implications, feasibility of implementation, and health equity. In most cases, the quality of evidence pertaining to each recommendation was low or very low and only addressed potential harms related to contraceptive use.

Systematic reviews of evidence on the values and preferences of contraceptive users and health workers, as well as the findings of a global survey undertaken by the White Ribbon Alliance, were used to incorporate these considerations into the MEC guideline *(10–12)*. The GDG endorsed an approach to client preferences and values that prioritizes the availability of a wide range of contraceptive options and the removal of unnecessary medical barriers.

Since publication of the first edition of the MEC in 1996, the 1–4 scale has been used to categorize medical eligibility for contraceptive use (see section 3 in the main document for the four categories and further details on how to interpret them in practice). These categories are well known by health workers, professional organizations, training institutions and ministries of health as the basis for determining the eligibility of women with specific medical conditions or characteristics to use a range of contraceptive methods. To arrive at a decision on which MEC category to designate (within the range of 1–4), the GDG considered the GRADE evidence profiles and the EtD framework domains. As a result, to avoid confusion and retain consistency, it was determined that recommendations would not be defined as "strong" or "conditional"

according to GRADE methodology and would instead retain the 1–4 scale reflecting eligibility for contraceptive use.

Through consensus, the GDG arrived at new and revised recommendations, as well as upholding most of the existing recommendations using the categories 1–4. For the topics they reviewed during the final GDG meeting in 2024 (see Box W.1.1), the GDG considered the potential benefits and risks of contraceptive method use with respect to each of the medical conditions or personal characteristics assessed.

Information on all new, revised and confirmed recommendations and a summary of changes between the fifth edition of the MEC are presented in the sixth edition of the MEC, to which this document is a web annex.

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2. Reviewed recommendations

The Guideline Development Group (GDG) determined priority topics to be addressed as part of the revision process for the sixth edition of the MEC (see Table 1 in the executive summary of the main MEC guideline, sixth edition). For the six prioritized topics, the GDG developed questions using the "PICO" format to serve as the framework for conducting the systematic reviews and compiling the GRADE evidence tables (see section 3 of this web annex for the GRADE tables).

Sections 2.1–2.6 present, for each reviewed topic, the PICO question(s), recommendations, quality of the evidence and the GDG's application of the evidence-to-decision (EtD) framework.

2.1 Recommendations for progestogen-only contraceptives (POCs) and the progesterone-releasing vaginal ring (PVR) among breastfeeding women

Question 1: Among women who breastfeed, does the use of POCs or the PVR increase the risk of adverse breastfeeding or infant outcomes compared with those who do not use POCs or use a different method of POC?

PICO question for systematic review

Population	Breastfeeding women
Intervention	Use of POCs (POPs, injectable, implant, LNG-IUD or PVR)
Comparator	Non-use of POCs or use of a different method of POC
Outcomes	Adverse breastfeeding or infant outcomes, including breastfeeding continuation, breastfeeding supplementation, duration of breastfeeding, milk production, exclusivity of breastfeeding, problems with breastfeeding, infant growth (weight, height, head circumference), infant illness (infections, comorbidities), infant development

Question 2: Among women who breastfeed, does the initiation of POCs before six weeks postpartum increase the risk of adverse breastfeeding or infant outcomes compared with initiation of POCs at six weeks postpartum or later?

PICO question for systematic review

Population	Breastfeeding women
Intervention	Use of POCs (POPs, injectable, implant, LNG-IUD) initiated before 6 weeks postpartum
Comparator	Use of POCs (POPs, injectable, implant, LNG-IUD) initiated at 6 weeks postpartum or later
Outcomes	Adverse breastfeeding or infant outcomes, including breastfeeding continuation, breastfeeding supplementation, duration of breastfeeding, milk production, exclusivity of breastfeeding, problems with breastfeeding, infant

	growth (weight, height, head circumference), infant illness (infections, comorbidities), infant development

Recommendations

- Women who are less than six weeks postpartum and breastfeeding can generally use progestogen-only pills (POPs), levonorgestrel (LNG) and etonogestrel (ETG) implants, and progestogen-only injectables (POIs) (depot medroxyprogesterone acetate [DMPA-IM and DMPA-SC] and norethisterone enanthate [NET-EN]) (MEC Category 2).
- Women who are at least six weeks but less than six months postpartum and breastfeeding can use POPs, POIs (DMPA and NET-EN), and LNG and ETG implants without restriction (MEC Category 1).
- Breastfeeding women who are at least six months postpartum can use POPs, POIs (DMPA and NET-EN), and LNG and ETG implants without restriction (MEC Category 1).
- Breastfeeding women who are at least four weeks postpartum can use the progesterone-releasing vaginal ring (PVR) without restriction (MEC Category 1).

Quality of the evidence

Question 1: Among women who breastfeed, does the use of POCs or the PVR increase the risk of adverse breastfeeding or infant outcomes compared with those who do not use POCs or use a different method of POC?

Progestogen-only pills (POPs)

Outcome	Quality of the evidence
POPs vs non-hormonal contraception, initiated before 6 weeks postpartum	
Breastfeeding outcomes	
Continuation	Very low
Supplementation	Very low
Initiation	Very low
Duration	Very low
Infant outcomes	
Growth	Very low
POPs vs combined hormonal contraceptive (CHC), initiated before 6 weeks postpartum	
Breastfeeding outcomes	
Continuation	Very low
Supplementation	Very low
Infant outcomes	
Growth	Very low
POPs vs non-hormonal contraception, initiated at 6 weeks postpartum or later	
Breastfeeding outcomes	
Milk volume	Very low
Continuation	Very low
Duration	Very low
Supplementation	Very low

Infant outcomes	
Growth	Very low
Illness	Very low

Progestogen-only injectables (POIs)

Outcome	Quality of the evidence
POIs vs unspecified method, initiated before 6 weeks postpartum	
Breastfeeding outcomes	
Milk volume	Very low
Continuation	Very low
Supplementation	Very low
Duration	Very low
Infant outcomes	
Infant growth	Very low
POIs initiated at 6 weeks postpartum or later vs non-hormonal	
Breastfeeding outcomes	
Continuation	Very low
Duration	Very low
Supplementation	Very low
Infant outcomes	
Growth	Very low

Progestogen-only implant

Outcome	Quality of the evidence
Progestogen-only implant vs non-hormonal contraception, initiated before 6 weeks postpartum	
Breastfeeding outcomes	
Amount of milk ingested	Very low
Continuation	Very low
Duration	Very low
Supplementation	Very low
Infant outcomes	
Growth	Very low
Progestogen-only implant vs non-hormonal contraception, initiated at 6 weeks postpartum or later	
Breastfeeding outcomes	
Supplementation	Very low
Exclusivity	Very low
Infant outcomes	
Growth	Very low

LNG-IUD

Outcome	Quality of the evidence
LNG-IUD vs non-hormonal contraception, initiated before 6 weeks postpartum	
Breastfeeding outcomes	
Continuation	Very low
Duration	Very low
Infant outcomes	
Growth	Very low
LNG-IUD vs non-hormonal contraception, initiated at 6 weeks postpartum or later	
Breastfeeding outcomes	
Duration	Low
Supplementation	Low
Infant outcomes	
Growth	Medium

Multiple POC methods

Outcome	Quality of the evidence
Multiple POC methods vs non-hormonal contraception, initiated before 6 weeks postpartum	
Breastfeeding outcomes	
Continuation	Very low
Supplementation	Very low
Progestogen-only implant or LNG-IUD vs non-hormonal contraception initiated at 6 weeks postpartum or later	
Breastfeeding outcomes	
Continuation	Very low
Duration	Very low
Supplementation	Very low
Infant outcomes	
Growth	Very low
Multiple POCs vs non-hormonal contraception initiated at 6 weeks postpartum or later	
Breastfeeding outcomes	
Duration	Very low
Infant outcomes	
Growth	Very low

PVR

Outcome	Quality of the evidence
PVR vs IUD, progestogen-only implant or POPs, timing of initiation not specified	
Breastfeeding outcomes	
Supplementation	Very low
Duration	Very low
Infant outcomes	
Growth	Very low
Morbidities	Very low

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Question 2: Among women who breastfeed, does the initiation of POCs before six weeks postpartum increase the risk of adverse breastfeeding or infant outcomes compared with initiation of POCs at six weeks postpartum or later?

Progestogen-only implant

Outcome	Quality of the evidence
Progestogen-only implant (immediate postpartum vs delayed initiation)	
Breastfeeding outcomes	
Continuation (randomized controlled trials)	Low
Continuation (cohort)	Very low
Exclusivity	Low
Infant outcomes	
Growth	Low

LNG-IUD

Outcome	Quality of the evidence
LNG-IUD (immediate postpartum vs delayed initiation)	
Breastfeeding outcomes	
Duration	Very low
Continuation	Very low

Multiple POCs

Outcome	Quality of the evidence
Multiple POCs (earlier vs later initiation)	
Breastfeeding outcomes	
Supplementation	Low
Supplementation	Very low
Infant outcomes	
Growth	Very low

Evidence summary

A total of 66 studies provided evidence on the use of POCs in breastfeeding women; 54 of these studies were previously identified in two systematic reviews published in 2016 *(1, 2)*. Eleven studies providing additional evidence on the use of POCs in breastfeeding women and reporting clinically relevant outcomes relating to infant growth, infant health or breastfeeding performance were identified in a systematic review that updates the previous reviews *(3)*. New evidence from nine studies, including four studies on injectables, continues to demonstrate no consistent negative impacts on breastfeeding performance (i.e. time to lactogenesis, milk production, breastfeeding continuation, breastfeeding duration, exclusivity or problems with breastfeeding) or infant health outcomes (i.e. infant weight, infant length, infant head circumference or infant illness) among breastfeeding women who use POCs compared with breastfeeding women who do not using POCs *(4–12)*. New evidence from two studies demonstrates no harmful effects on breastfeeding

performance or infant growth when progestogen-only implant initiation occurs before six weeks postpartum among breastfeeding women compared with later initiation *(13, 14)*. Overall, new evidence on POCs, including injectables, is generally consistent with the previous evidence in demonstrating no consistent harmful effects on breastfeeding or infant outcomes with POC use compared with no POC use. New evidence from one study was also consistent with previous evidence demonstrating no harmful effects on infant growth among breastfeeding women using the PVR compared with copper IUD (Cu-IUD) or POPs *(15)*.

Only two studies included high-risk infants (low birth weight or premature) and no studies included women at risk for breastfeeding difficulties *(12, 14)*. No evidence addressing the long-term effects of POC use on infant growth or development among breastfeeding women was identified. The certainty of the evidence for most outcomes was assessed as being very low quality; however, one trial looking at the use of LNG-IUDs was low quality for breastfeeding outcomes and medium quality for infant outcomes *(16)*, and three randomized controlled trials (RCTs) looking at early versus delayed initiation of POCs were low quality for both breastfeeding and infant outcomes *(13, 14, 17)*. For further detailed information, see the GRADE tables in section 3.1 of this web annex.

Rationale

The GDG reviewed and discussed epidemiological evidence from an updated systematic review on the safety of initiating POC use among breastfeeding women during the first six weeks postpartum *(3)*. In addition, during their deliberations, the GDG considered qualitative and quantitative evidence published in a systematic review of women's contraceptive values and preferences *(18)*.

Direct evidence for most outcomes was assessed as very low quality, while one trial measuring infant growth was determined to be of low quality. Despite the quality of the evidence, the GDG determined there was no evidence demonstrating an increased risk of harms (e.g. adverse breastfeeding or infant outcomes) and this was used as justification for changing the previous recommendation for progestogen-only injectables (POIs) (DMPA-IM, DMPA-SC and NET-EN) from a MEC Category 3 to a MEC Category 2. In addition to the evidence showing no harms, the GDG noted that the purpose of the MEC guideline is to provide options for clients seeking contraceptive services and to enable them to make contraceptive choices that are consistent with their own values and preferences. The GDG further acknowledged that values and preferences regarding contraception may vary according to outcomes. Optimizing available contraceptive choices allows clients to choose a contraceptive method that is more acceptable to them.

New evidence from one study was also consistent with previous evidence demonstrating no harmful effects on infant growth among breastfeeding women using the PVR compared with Cu-IUD or POPs. The GDG reviewed this evidence and upheld the existing PVR recommendations for women who breastfeed.

In making these recommendations, the GDG recognized that supportive policies for providing POCs are essential for successful implementation of these recommendations. The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, availability of required resources, existing service-delivery strategies, and the availability of an adequately trained health workforce.

The GDG also noted that POCs do not protect against sexually transmitted infections (STIs), including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe but are not used as widely by national programmes as male condoms.

Evidence-to-Decision table W.2.1 Breastfeeding and progestogen-only contraceptives (POCs)

Domain	Explanation/evidence	Judgement
Balance of benefits and harms	Contraception is a life-saving intervention with well recognized health, social and economic benefits. All POCs are effective at preventing pregnancy with some variability in effectiveness (contraceptive effectiveness was not addressed in the systematic review). The current body of evidence generally does not demonstrate harms to either breastfeeding outcomes or infant health outcomes among breastfeeding women who initiated POCs prior to six weeks postpartum compared with women who initiated a non-hormonal method or no method. Similarly, initiating POCs prior to six weeks postpartum, compared with initiating a POC at six weeks postpartum or later, did not negatively impact breastfeeding outcomes or infant health outcomes among women who breastfeed. Limited evidence exists on high-risk infants (low birth weight or premature) and no studies included women at risk for breastfeeding difficulties.	Benefits may outweigh harms; there was no evidence of increased harms
Quality of evidence	Evidence was predominantly very low quality for all outcomes among women who breastfeed and initiate POCs compared with women who do not use POCs, though ranged from very low to medium. Evidence was assessed to be of low or very low quality for all outcomes among women who breastfeed and initiate POCs before six weeks postpartum compared with those who initiate POCs at six weeks or later.	Medium to very low
Priority of the problem	Reproductive health and rights are key public health concerns globally. Promoting reproductive agency and ensuring contraceptive choice, while mitigating interaction with other medicines, treatments or physiologic conditions are important in reduction of mortality and morbidity, and to improve health and well-being.	Effective contraception and breastfeeding are both public health priorities.
Values and preferences	Contraceptive users have diverse values and preferences regarding outcomes. Generally, they value having a range of contraceptive methods from which to choose and prefer methods that are effective, easy to use, and have few side-effects. Differences in values and preferences regarding outcomes may impact contraceptive choices	May vary; the MEC supports optimizing informed contraceptive choice – consistent with client

Domain	Explanation/evidence	Judgement
	when the balance of benefits to harms is close; the purpose of the MEC is to provide options for clients so that they can make contraceptive choices that are consistent with their own values and preferences.	values/preferences – from a range of contraceptive options.
Acceptability	The GDG noted that acceptability for different contraceptive methods will vary across and within populations. The purpose of the MEC is to provide a diverse range of contraceptive options that will allow clients to choose a contraceptive method that is more acceptable to them. The GDG underscored the importance of providing appropriate, evidence-based, understandable information and counselling to support each client's decision-making.	May vary; the MEC supports selection of acceptable contraceptives from a range of contraceptive options.
Costs/resources	As a preventive health service, contraception has repeatedly been shown to be a cost-saving intervention. Contraception prevents morbidity and mortality associated with unintended pregnancies and has been shown to reduce costs for the individual, the health system and society. However, costs for different contraceptive options vary. Costs were not formally assessed during the formulation of the recommendations; costs for a particular contraceptive may vary widely throughout different regions of the world and across different contexts within the same region. For a given condition, costs may inform choices among contraceptive alternatives with similar MEC ratings.	While costs may vary across settings, contraception overall is a cost-saving intervention. The MEC supports selection of contraceptives that are less costly from a range of contraceptive options, when cost is a relevant consideration.
Feasibility	The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce. The MEC provides diverse contraceptive options to support selection of contraceptives that are feasible/sustainable in the settings in which they will be used.	May vary; the MEC supports selection of contraceptives that are more feasible in specific settings.
Equity	WHO's nine guiding human rights principles and standards for safeguarding a rights-based approach – which include non-discrimination, availability, accessibility, quality of contraception information and services, informed decision-making, privacy and confidentiality, participation and accountability – were followed by the GDG in its deliberations and formula. The MEC guideline promotes human rights principles and standards by supporting access to diverse contraceptive options across populations. The MEC supports equity and human rights by providing diverse contraceptive options	Increases equity; the MEC supports human rights principles by providing diverse contraceptive options. Contraceptive accessibility for all persons is essential to maximize equity.

Domain	Explanation/evidence	Judgement
	for contraceptive users in different situations and settings. To maximize equity and human rights it is critical that recommended contraceptives be accessible for all persons in whom they are indicated and that their use not preferentially benefit certain groups or have negative impacts on certain groups.	

References for section 2.1

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2.2 Recommendations for intrauterine devices (IUDs) among breastfeeding women

Question 1: Among women using an IUD – either copper-bearing IUD (Cu-IUD) or levonorgestrel-releasing IUD (LNG-IUD) – does breastfeeding compared with not breastfeeding increase the risk of an IUD-related adverse event?

PICO question for systematic review

Population	Women using an IUD (either Cu-IUD or LNG-IUD)
Intervention	Breastfeeding
Comparator	Not breastfeeding
Outcomes	IUD-related adverse events, including bleeding (removals for bleeding, measures of haemoglobin/haematocrit), expulsion (client report, provider diagnosis or chart review; complete or partial expulsion), infection (endometritis or pelvic inflammatory disease according to reported diagnostic criteria), pain (removals for pain or pain scale scores at insertion), perforation (client report, provider diagnosis by imaging, surgery or chart review), pregnancy (client report, provider or laboratory diagnosis, or chart review).

Question 2: Among women who breastfeed, does the use of an IUD (either Cu-IUD or LNG-IUD), as compared with the use of other contraceptive methods (either hormonal or nonhormonal) or no method, increase the risk of an adverse event?

PICO question for systematic review

Population	Breastfeeding women
Intervention	IUD use (either Cu-IUD or LNG-IUD)
Comparator	Use of other hormonal or non-hormonal contraceptives or no contraceptive method
Outcomes	Adverse events, including bleeding (removals/discontinuation for bleeding, measures of haemoglobin/haematocrit), infection (endometritis or pelvic inflammatory disease according to reported diagnostic criteria), pain (removals for pain or pain scale scores at insertion).

Question 3: Among women who breastfeed, does the use of a Cu-IUD, as compared with the use of other non-hormonal methods or no method, increase the risk of adverse breastfeeding or infant outcomes?

PICO question for systematic review

Population	Breastfeeding women
Intervention	Cu-IUD use
Comparator	Use of other nonhormonal methods or no method
Outcomes	Adverse breastfeeding or infant outcomes, including breastfeeding performance (duration or discontinuation, objective change in milk supply, or use of supplementation) and infant growth (comparative objective measures), infant illness (provider diagnosis or chart review), infant development (comparative objective measures).

Recommendations

- Women who breastfeed and are less than 48 hours postpartum can use a Cu-IUD without restriction (MEC Category 1).
- Women who breastfeeding women and are less than 48 hours postpartum can generally use LNG-IUDs (MEC Category 2).

Quality of the evidence

Question 1: Among women using an intrauterine device (IUD) – either copper-bearing IUD (Cu-IUD) or levonorgestrel-releasing IUD (LNG-IUD) – does breastfeeding compared with not breastfeeding increase the risk of an IUD-related adverse event?

Outcome	Quality of the evidence
Cu-IUD, breastfeeding vs not breastfeeding	
Immediate postpartum placement	
Expulsion	Very low
Removal for pain or bleeding	Very low
Interval postpartum placement	
Perforation	Very low
Expulsion	Very low
Removal for pain or bleeding	Very low
Mixed or unspecified timing of placement	
Expulsion	Very low
Perforation	Very low
LNG-IUD, breastfeeding vs not breastfeeding	
Mixed or unspecified timing of placement	
Perforation	Very low

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IUD multiple types, breastfeeding vs not breastfeeding	
Immediate postpartum placement	
Expulsion	Very low
Interval placement	
Perforation	Very low
Expulsion	Very low
Any insertion-related adverse event	Very low
Mixed or unspecified timing of placement	
Perforation	Very low
Expulsion	Very low

Question 2: Among women who breastfeed, does the use of an IUD (either Cu-IUD or LNG-IUD), as compared with the use of other contraceptive methods (either hormonal or non-hormonal) or no method, increase the risk of an adverse event?

Outcome	Quality of the evidence
Cu-IUD vs implant, interval placement	
Removal for bleeding	Very low
Haemoglobin levels	Very low
Adverse events	Very low
Cu-IUD vs progesterone vaginal ring, interval placement	
Discontinuation or removals for bleeding	Very low
Haemoglobin change	Very low
Pelvic inflammatory disease (PID)	Very low

Question 3: Among women who breastfeed, does the use of a Cu-IUD, as compared with the use of other non-hormonal methods or no method, increase the risk of adverse breastfeeding or infant outcomes?

Outcome	Quality of the evidence
Copper IUD vs non-hormonal or no method, early postpartum placement or timing not specified	
Breastfeeding outcomes	
Continuation	Very low
Duration	Very low
Supplementation	Very low
Exclusivity	**Very low**
Lack of milk secretion	**Very low**
Infant outcomes	
Growth	Very low

Evidence summary

The evidence considered for this recommendation included results from 16 studies summarized in a 2016 systematic review *(1)* and 16 additional studies *(2–17)* identified since the previous review

conducted for this update of the MEC guideline. Therefore, a total of 32 studies were considered that provided evidence on the safety of IUD use (either Cu-IUD or LNG-IUD) among breastfeeding women. A separate review of the evidence considered the impact of LNG-IUD use among breastfeeding women on breastfeeding and/or infant outcomes.

Eight new studies assessed the risk of IUD-related adverse events among IUD-users who were breastfeeding compared with those who were not breastfeeding *(2–9)*. Five newly identified studies *(10–14)* assessed the risk of adverse events among breastfeeding women using an IUD compared with breastfeeding women using another contraceptive method. Three newly identified studies assessed the risk of adverse breastfeeding or infant outcomes among breastfeeding women using a Cu-IUD compared with breastfeeding women using a different non-hormonal method or no method *(15–17)*.

The newly identified studies were generally consistent with evidence from the previous systematic review, demonstrating that among women who are using IUDs, breastfeeding may increase the risk of uterine perforation compared with those who are not breastfeeding at the time of IUD insertion; however, the absolute risk of perforation is low regardless of breastfeeding status. Evidence was inconsistent on whether the risk for expulsion was increased, and there was no evidence on other IUD-related adverse events (e.g. expulsion, infection) for breastfeeding versus not breastfeeding women. There was also no evidence for increased risks of adverse events (bleeding or infection) among breastfeeding women using an IUD compared with breastfeeding women using another contraceptive method, and no evidence for increased risk of adverse breastfeeding outcomes (e.g. relating to supplementation, milk production or exclusivity) or adverse infant growth outcomes among breastfeeding women using a Cu-IUD compared with breastfeeding women using a different non-hormonal method or no method. For further detailed information, see the GRADE tables in section 3.2 of this web annex.

Rationale

The GDG reviewed and discussed epidemiological evidence from an updated systematic review on the safety of initiating IUD use among breastfeeding women *(18)*. In addition, the GDG considered qualitative and quantitative evidence published in a systematic review of women's contraceptive values and preferences during their deliberations *(19)*.

In conjunction with the evidence presented in the systematic review on progestin-only method use among breastfeeding women *(20)*, the GDG determined that the recommendations remained consistent with the evidence and upheld the MEC Category 2 recommendation for use of LNG-IUDs and the MEC Category 1 recommendation for insertion of Cu-IUDs among breastfeeding women within the first 48 hours postpartum. The GDG noted that the purpose of the MEC guideline is to provide options for clients seeking contraceptive services and to enable them to make contraceptive choices that are consistent with their own values and preferences. The GDG further acknowledged that values and preferences regarding contraception may vary according to outcomes: optimizing available contraceptive choices allows clients to choose a contraceptive method that is more acceptable to them.

In making these recommendations, the GDG recognized that supportive policies for providing IUDs are essential for successful implementation of these recommendations. The feasibility of the

recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce.

The GDG also notes that IUDs do not protect against STIs, including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe but are not used as widely by national programmes as male condoms.

Evidence-to-Decision table W.2.2 Breastfeeding and intrauterine devices (IUDs)

Domain	Explanation/evidence		Judgement
Balance of benefits and harms	Cu-IUD	Contraception is a life-saving intervention with well recognized health, social and economic benefits. Cu-IUDs are highly effective at preventing pregnancy for women who breastfeed (effectiveness was not addressed in the systematic review). Use of a Cu-IUD may increase the risk of uterine perforation among women who are breastfeeding compared with those who are not breastfeeding at the time of IUD insertion; however, the absolute risk of perforation is low regardless of breastfeeding status. There is no consistent evidence for increased risk of other IUD-related adverse events for breastfeeding versus not breastfeeding. There is also no consistent evidence for increased risk of adverse breastfeeding or infant outcomes among Cu-IUD users versus those using other non-hormonal methods or no method.	Benefits may outweigh harms; there was no evidence of increased harms with Cu-IUDs.
	LNG-IUD	Contraception is a life-saving intervention with well recognized health, social and economic benefits. LNG-IUDs are highly effective at preventing pregnancy for women who breastfeed (effectiveness was not addressed in the systematic review). Use of an LNG-IUD may increase the risk of uterine perforation among women who are breastfeeding compared with those who are not breastfeeding at the time of IUD insertion; however, the absolute risk of uterine perforation is low regardless of breastfeeding status. There is no consistent	Benefits may outweigh harms; there was no evidence of increased harms with LNG-IUDs.

Domain	Explanation/evidence	Judgement
	evidence for an increased risk of other IUD-related adverse events for women who breastfeed versus women who do not breastfeed. No consistent evidence was identified for harms to either breastfeeding or infant health among LNG-IUD users.	
Quality of evidence	Evidence was considered very low quality for all outcomes (e.g. uterine perforation, IUD expulsion) among women using an IUD who breastfeed compared with IUD users who do not breastfeed. Evidence was assessed to be of very low quality for risk of adverse events among women who breastfeed and use an IUD compared with use of another contraceptive method. Evidence was considered to be very low quality for risk of adverse breastfeeding or infant outcomes among women who breastfeed and use a Cu-IUD compared with women who use a non-hormonal method or no contraceptive method.	Very low
Priority of the problem	Reproductive health and rights are key public health concerns globally. Promoting reproductive agency and ensuring contraceptive choice, while mitigating interaction with other medicines, treatments or physiologic conditions are important in reduction of mortality and morbidity, and to improve health and well-being.	Effective contraception and breastfeeding are both public health priorities.
Values and preferences	Contraceptive users have diverse values and preferences regarding outcomes. Generally, they value having a range of contraceptive methods from which to choose and prefer methods that are effective, easy to use, and have few side-effects. Differences in values and preferences regarding outcomes may impact contraceptive choices when the balance of benefits to harms is close; the purpose of the MEC is to provide options for clients so that they can make contraceptive choices that are consistent with their own values and preferences.	May vary; the MEC supports optimizing informed contraceptive choice – consistent with client values/preferences – from a range of contraceptive options.
Acceptability	The GDG noted that acceptability for different contraceptive methods will vary across and within populations. The purpose of the MEC is to provide a diverse range of contraceptive options that will allow clients to choose a contraceptive method that is more acceptable to them. The GDG underscored the importance of providing appropriate evidence-based,	May vary; the MEC supports selection of acceptable contraceptives from a range of contraceptive options.

Domain	Explanation/evidence	Judgement
	understandable information and counselling to support each client's decision-making.	
Costs/resources	As a preventive health service, contraception has repeatedly been shown to be a cost-saving intervention. Contraception prevents morbidity and mortality associated with unintended pregnancies and has been shown to reduce costs for the individual, the health system and society. However, costs for different contraceptive options vary. Costs were not formally assessed during the formulation of the recommendations; costs for a particular contraceptive may vary widely throughout different regions of the world and across different contexts within the same region. For a given condition, costs may inform choices among contraceptive alternatives with similar MEC ratings.	While costs may vary across settings, contraception overall is a cost-saving intervention. The MEC supports selection of contraceptives that are less costly from a range of contraceptive options, when cost is a relevant consideration.
Feasibility	The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce. The MEC provides diverse contraceptive options to support selection of contraceptives that are feasible/sustainable in the settings in which they will be used.	May vary; the MEC support selection of contraceptives that are more feasible in specific settings.
Equity	WHO's nine guiding human rights principles and standards for safeguarding a rights-based approach – which include non-discrimination, availability, accessibility, quality of contraception information and services, informed decision-making, privacy and confidentiality, participation and accountability – were followed by the GDG in its deliberations and formula. The MEC guideline promotes human rights principles and standards by supporting access to diverse contraceptive options across populations. The MEC supports equity and human rights by providing diverse contraceptive options for contraceptive users in different situations and settings. To maximize equity and human rights it is critical that recommended contraceptives be accessible for all persons in whom they are indicated and that their use not preferentially benefit certain groups or have negative impacts on certain groups.	Intervention supports human rights principles. Contraceptive accessibility for all persons is essential to maximize equity.

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2.3a Recommendations for the concomitant use of hormonal contraception and antiretroviral therapy (ART) among women living with HIV

Question 1: Among women of reproductive age living with HIV, does concomitant use of hormonal contraception and ART (a) reduce the effectiveness or (b) affect the safety of hormonal contraceptive use compared with hormonal contraceptive use and no ART?

PICO question for systematic review

Population	Women of reproductive age living with HIV
Intervention	Hormonal contraception and antiretroviral therapy (ART)
Comparator	Hormonal contraception and no ART
Outcomes	Contraceptive effectiveness (pregnancy, ovulation, ovarian activity, breakthrough bleeding), adverse effects

Question 2: Among women or reproductive age living with HIV, does concomitant use of hormonal contraception and ART (a) reduce effectiveness or (b) affect the safety of ART use compared with ART use and no contraceptive use?

PICO question for systematic review

Population	Women of reproductive age living with HIV
Intervention	Hormonal contraception and ART
Comparator	ART and no hormonal contraception
Outcomes	Antiretroviral (ARV) pharmacokinetics, ART effectiveness (HIV disease progression, viral load, CD4 count), adverse effects

Recommendations

- Women taking any nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) can use CHCs, POPs, injectables and implants without restriction (MEC Category 1).
- Women using any non-nucleoside/nucleotide reverse transcriptase inhibitor (NNRTIs) that do not contain efavirenz can use CHCs, POPs, injectables and implants without restriction (MEC Category 1).
- Women using NNRTIs containing efavirenz can generally use CHCs, POPs, NET-EN and implants (MEC Category 2). Women using efavirenz can use DMPA without restriction (MEC Category 1).
- Women using protease inhibitors (PIs) can use CHCs, POPs, injectables and implants without restriction (MEC Category 1).
- Women using integrase inhibitors (INIs) raltegravir and dolutegravir can use all hormonal contraceptive methods without restriction (MEC Category 1).
- Women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) who are using ART containing NRTIs, NNRTIs, PIs and INIs can generally have an LNG-IUD inserted (MEC

Category 2). There is no known interaction between ART and IUD use. Asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) is classified as Category 2 for both initiation and continuation.

- Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) who are using ART containing NRTIs, NNRTIs, PIs and INIs should generally not initiate use of the LNG-IUD (MEC Category 3). However, women who already have an LNG-IUD inserted and who develop severe, or advanced HIV clinical disease need not have their IUD removed (MEC Category 2 for continuation). LNG-IUD users with severe or advanced HIV clinical disease should be closely monitored for pelvic infection.

Quality of the evidence

Contraceptive effectiveness

Combined oral contraceptives

Outcome	Quality of the evidence
COCs and efavirenz (EFV) vs nevirapine (NVP), other ART or no ART	
Pregnancy	Very low
Ovulation	Very low
COCs and nevirapine vs other ART or no ART	
Pregnancy	Very low
Ovulation	Very low
Bleeding	Very low
COCs and rilpivirine vs no ART	
Ovulation	Very low
COCs and etravirine vs placebo	
Ovulation	Very low
COCs and ritonavir vs no Cytochrome P450 3A4 (CYP3A4)-inducing ARV or no ART	
Ovulation	Very low
COCs and darunavir vs no ART	
Ovulation	Very low
COCs and dolutegravir vs no ART	
Pregnancy	Very low
COCs and unspecified protease inhibitor (PI) vs NNRTI (EFV or NVP) or no NNRTI or no PI	
Pregnancy	Very low

Combined hormonal vaginal ring (CVR)

Outcome	Quality of the evidence
CVR and efavirenz vs ATV/r or no ART	
Ovulation	Very low

Combined hormonal contraceptive patch

Outcome	Quality of the evidence
Patch and lopinavir/r vs no ART	
Cervical mucus quality	Very low

Emergency contraceptive pills (ECPs)

Outcome	Quality of the evidence
LNG ECPs and efavirenz vs raltegravir (RPV) or dolutegravir (DTG)	
Pregnancy	Very low

Implants

Outcome	Quality of the evidence
LNG implant and efavirenz vs nevirapine, other ART or no ART	
Pregnancy	Very low
Ovulation	Very low
Bleeding	Very low
LNG implant and rilpivirine vs no ART	
Pregnancy	Very low
Ovulation	Very low
LNG or ETG implant and darunavir vs no ART	
Pregnancy	Very low
Ovulation	Very low
ETG implant and PI-based ART vs other ART or no ART	
Pregnancy	Very low

Injectables

Outcome	Quality of the evidence
Injectable and efavirenz vs nevirapine, other ART or no ART	
Pregnancy	Very low
Ovulation	Very low
Bleeding	Very low
Nevirapine vs no ART	
Pregnancy	Very low
Injectable and lopinavir/r vs no ART	
Pregnancy	Very low
Ovulation	Very low

Antiretroviral therapy (ART) effectiveness

ART unspecified

Outcome	Quality of the evidence
Oral contraceptive vs no hormonal contraception	
Viral suppression	Very low
Hormonal contraception vs no hormonal contraception	
Viral suppression	Very low
Implants vs no hormonal contraception	
Viral suppression	Low to very low
DMPA injectable vs no hormonal contraception	
Viral suppression	Low to very low
Injectable use vs no hormonal contraception	
Viral suppression	Very low

LNG-IUD vs Cu-IUD	
Viral suppression	Very low

Nevirapine

Outcome	Quality of the evidence
DMPA vs no hormonal contraception	
Viral suppression	Very low
Implant use vs no hormonal contraception	
Viral suppression	Very low

Darunavir/ritonavir

Outcome	Quality of the evidence
Implant use vs no hormonal contraception	
Viral suppression	Very low

Rilpivirine

Outcome	Quality of the evidence
Implant use vs no hormonal contraception	
Viral suppression	Very low

Oral contraceptives

Outcome	Quality of the evidence
COCs and nevirapine vs no ART or other ART	
Viral suppression	Very low

Combined hormonal vaginal ring (CVR)

Outcome	Quality of the evidence
CVR and efavirenz vs ATV/r or no ART	
Viral suppression	Very low

Combined hormonal contraceptive patch

Outcome	Quality of the evidence
Patch and lopinavir/r vs NRTI only or no ART	
Viral suppression	Very low

Implants

Outcome	Quality of the evidence
LNG or ETG implants and efavirenz vs NVP, other ART or no ART	
Viral suppression	Very low

Injectables

Outcome	Quality of the evidence
DMPA and efavirenz vs nevirapine, other ART or no ART	
Viral suppression	Very low

Evidence summary

Two systematic reviews *(1, 2)* examined the body of evidence on the safety of hormonal contraception for women living with HIV who are taking antiretroviral therapy. The earlier review by Nanda et al. published in 2017 informed recommendations presented in the fifth edition of the MEC guideline *(1)*. Fifty reports from 46 studies were included in the earlier review and subsequently the 2024 review, by Todd et al., identified 49 new studies. The updated review findings support and expand upon the earlier review's conclusions *(2)*.

In the 2024 review, three of four large retrospective cohort studies found higher pregnancy rates among implant users (LNG and ETG implant users analysed separately and together) who were also using efavirenz (EFV)-based ART compared with nevirapine (NVP)-based ART, other ART or no ART. In contrast, one retrospective Kenyan cohort found similar pregnancy rates for women using either ETG or LNG implants when comparing concomitant EFV-based ART to NVP-based ART. Additionally, among women using LNG or ETG implants with EFV-based ART, a greater proportion had evidence of presumptive ovulation (progesterone > 3 ng/ml) compared with women using other ART regimens. Doubling the LNG implant dose to 300 mg did not reduce presumed ovulation rates.

Among DMPA users, EFV-based ART users had similar pregnancy rates to HIV-negative women or NVP-based ART users. Additionally, one study found no evidence of presumed ovulation among those using DMPA with EFV-based ART and rifampicin-based tuberculosis (TB) treatment.

All studies assessing implant use with PI-based ART compared with no ART found no evidence of drug interactions resulting in higher pregnancy rates. Use of ritonavir-boosted PIs also did not increase the risk of presumptive ovulation in three studies that measured progesterone levels.

While no studies evaluated risk of pregnancy or ovulation with dolutegravir, one cross-sectional ETG pharmacokinetics assessment 3–12 months following implant insertion among dolutegravir-based ART users found ETG concentrations were 27% higher among dolutegravir users compared with HIV-negative controls.

One cohort study reported increased bone mineral density (BMD) loss among women using DMPA and taking TDF compared with those not using DMPA for contraception. No studies were identified observing drug–drug interactions that compromised ARV efficacy or safety. For further detailed information, see the GRADE table in section 3.3 of this web annex.

Rationale

The GDG reviewed and discussed epidemiological evidence from both the prior (published in 2017) and the updated systematic review (2024) on the safety and effectiveness of hormonal contraception among women living with HIV and taking antiretroviral therapy.

In the previous review, 50 reports from 46 studies were included. Prior evidence showed that most ARVs had limited interactions with hormonal contraceptive methods, except for EFV. Although DMPA was not affected, limited prior data on implants and COC pills suggested that EFV-containing combination ART could compromise contraceptive effectiveness of these methods.

Pharmacokinetic data also suggested potential drug interactions between ritonavir-boosted PIs and some hormonal contraceptives. Antiretroviral plasma concentrations and effectiveness were generally not affected by hormonal contraceptives.

The updated review presented evidence published within 49 articles since the 2017 review. In addition, the GDG considered qualitative and quantitative evidence published in a systematic review of the contraceptive values and preferences of women living with HIV during their deliberations *(3)*.

Overall, direct evidence for all outcomes was assessed to be of very low quality. Nevertheless, the GDG judged the lack of evidence showing harms to contraceptive effectiveness or ARV toxicity from concomitant ART and hormonal contraceptive use (except for EFV) as reassuring. Owing to the release of a WHO guidance statement in 2019 *(4, 5)*, evidence on dolutegravir was included in the systematic review shared with the GDG.

New evidence no longer supports previous concerns that NVP may reduce contraceptive effectiveness; thus, the GDG updated the MEC recommendations for NVP from a MEC Category 2 to a MEC Category 1 (no restrictions on use). The GDG considered the updated evidence on the impact of EFV on the effectiveness of contraceptive implants, noting that many studies suggest contraceptive effectiveness may decrease, particularly for progestin implants, while others do not report this finding.

New evidence also no longer supports any concerns with the use of hormonal contraceptives with ritonavir or ritonavir-boosted PIs. Thus, the GDG updated the MEC recommendations for PIs from a MEC Category 2 to a MEC Category 1 (no restrictions on use).

The GDG therefore determined that there should be no restrictions on the use of hormonal contraceptives by women living with HIV who use ARV drugs (other than EFV). For women living with HIV who are taking EFV-containing ART, the GDG upheld existing recommendations that CHCs and POCs can generally be used (MEC Category 2). The GDG upheld the existing recommendation for DMPA (IM and SC) as MEC Category 1. Further, the GDG pointed to the lack of evidence demonstrating an increased risk of these harms as justification for upholding the current recommendation for IUDs (Cu-IUD, LNG-IUD).

Throughout its deliberations, the GDG took note that the purpose of the MEC guideline is to provide options for clients seeking contraceptive services and to enable them to make contraceptive choices that are consistent with their own values and preferences. The GDG further acknowledged that values and preferences regarding contraception among women living with HIV and taking ART may vary according to outcomes: optimizing available contraceptive choices allows clients to choose a contraceptive method that is more acceptable to them.

In making these recommendations, the GDG recognizes that supportive policies for providing hormonal contraception and ART are essential for successful implementation of these recommendations. The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce.

The GDG also noted that hormonal contraceptives do not protect against STIs, including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used

correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe but are not as widely used by national programmes as male condoms.

Evidence-to-Decision table W.2.3a Antiretroviral drugs (ARVs) and hormonal contraceptives

Domain	Explanation/evidence		Judgement
Balance of benefits and harms	All ARVs (except efavirenz)	Contraception is a life-saving intervention with well recognized health, social and economic benefits. All CHCs and POCs are effective at preventing pregnancy with some variability in effectiveness according to ARV drug.	Benefits may outweigh harms; there was no evidence of increased harms with ARVs and hormonal contraceptives.
	Efavirenz	Contraception is a life-saving intervention with well recognized health, social and economic benefits. Except for contraceptive implants, hormonal contraceptives are effective at preventing pregnancy with no increased risk of ARV toxicity or reduction in ARV effectiveness. Limited and inconsistent evidence suggests contraceptive effectiveness may be decreased in those using contraceptive implants. Evidence does not show decreased contraceptive effectiveness for other methods (e.g. injectables, pills, rings or patches).	Benefits may outweigh harms; limited evidence suggests benefits may be decreased in those using contraceptive implants, otherwise there was no evidence of decreased benefits or harms.
Quality of evidence	Evidence was considered to be very low quality for all outcomes.		Very low
Priority of the problem	Reproductive health and rights are key public health concerns globally. Promoting reproductive agency and ensuring contraceptive choice, while mitigating interaction with other HIV drugs, HIV treatments or physiologic conditions are important in reduction of mortality and morbidity, and to improve health and well-being.		Effective contraception and high-quality treatment for women living with HIV are both public health priorities.
Values and preferences	Contraceptive users have diverse values and preferences regarding outcomes. Generally, they value having a range of contraceptive methods from which to choose and prefer methods that are effective, easy to use, and have few side-effects. Differences in values and preferences regarding outcomes may impact contraceptive choices when the balance of benefits to harms is close; the purpose of the MEC is to provide options for clients so that they can make		May vary; the MEC supports optimizing informed contraceptive choice – consistent with values/preferences – from a range of

Domain	Explanation/evidence	Judgement
	contraceptive choices that are consistent with their own values and preferences.	contraceptive options.
Acceptability	The GDG noted that acceptability for different contraceptive methods will vary across and within populations. The purpose of the MEC is to provide a diverse range of contraceptive options that will allow clients to choose a contraceptive method that is more acceptable to them. The GDG underscored the importance of providing appropriate, evidence-based, understandable information and counselling to support each client's decision-making.	May vary; the MEC supports selection of acceptable contraceptives from a range of contraceptive options.
Costs/resources	As a preventive health service, contraception has repeatedly been shown to be a cost-saving intervention. Contraception prevents morbidity and mortality associated with unintended pregnancies and has been shown to reduce costs for the individual, the health system and society. However, costs for different contraceptive options vary. Costs were not formally assessed during the formulation of the recommendations; costs for a particular contraceptive may vary widely throughout different regions of the world and across different contexts within the same region. For a given condition, costs may inform choices among contraceptive alternatives with similar MEC ratings.	While costs may vary across settings, contraception overall is a cost-saving intervention. The MEC supports selection of contraceptives that are less costly from a range of contraceptive options, when cost is a relevant consideration.
Feasibility	The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce. The MEC provides diverse contraceptive options to support selection of contraceptives that are feasible/sustainable in the settings in which they will be used.	May vary; the MEC supports selection of contraceptives that are more feasible in specific settings.
Equity	WHO's nine guiding human rights principles and standards for safeguarding a rights-based approach – which include non-discrimination, availability, accessibility, quality of contraception information and services, informed decision-making, privacy and confidentiality, participation and accountability – were followed by the GDG in its deliberations and formula. The MEC guideline promotes human rights principles and standards by supporting access to diverse contraceptive options across populations. The MEC supports equity and human rights by providing diverse contraceptive options for contraceptive users in different situations and settings. To maximize equity and human rights it is critical	Intervention supports human rights principles. Contraceptive accessibility for all persons is essential to maximize equity.

Domain	Explanation/evidence	Judgement
	that recommended contraceptives be accessible for all persons in whom they are indicated and that their use not preferentially benefit certain groups or have negative impacts on certain groups.	

2.3b Recommendations for the concomitant use of hormonal contraception among women taking HIV pre-exposure prophylaxis (PrEP)

Question 1: Among women of reproductive age at risk of HIV, does concomitant use of hormonal contraception and PrEP (a) reduce effectiveness, or (b) affect the safety of hormonal contraceptive use compared with hormonal contraceptive use and no PrEP?

PICO question for systematic review

Population	Women of reproductive age at risk of HIV
Intervention	Hormonal contraception and PrEP
Comparator	Hormonal contraception and no PrEP
Outcomes	Contraceptive effectiveness (pregnancy, ovulation, ovarian activity, breakthrough bleeding), adverse events

Question 2: Among women of reproductive age at risk of HIV, does concomitant use of hormonal contraception and PrEP (a) reduce the effectiveness or (b) affect the safety of PrEP use compared with PrEP use and no hormonal contractive use?

PICO question for systematic review

Population	Women of reproductive age at risk of HIV
Intervention	Hormonal contraception and PrEP
Comparator	PrEP and no hormonal contraception
Outcomes	PrEP effectiveness, adverse events

Recommendations

- Women using PrEP (whether containing NRTIs, NNRTIs or integrase inhibitors) can use all hormonal contraceptive methods (and also IUDs and barrier methods) without restriction (MEC Category 1).

Quality of the evidence

Contraceptive outcomes

Combined oral contraceptives (COCs)

Outcome	Quality of the evidence
COC and oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) vs COC and placebo	

Pregnancy	Low
COC and dapivirine (DPV) ring vs COC and placebo	
Pregnancy	Low
COC and injectable cabotegravir (CAB) vs placebo	
Ovulation	Very low

Implants

Outcome	Quality of the evidence
LNG implant and oral TDF/FTC vs LNG implant and placebo	
Pregnancy	Low
LNG implant and DPV ring vs LNG implant and placebo	
Pregnancy	Low

Injectables

Outcome	Quality of the evidence
DMPA and oral TDF/FTC vs DMPA and placebo	
Pregnancy	Low
Ovulation	Very low
DMPA and oral TDF/FTC vs no DMPA and oral TDF/FTC	
Bone mineral density	Very low
DMPA and oral TDF/FTC or OC and oral TDF/FTC vs no hormonal contraception and oral TDF/FTC	
Pregnancy	Very low
DMPA and DPV ring vs DMPA and placebo	
Pregnancy	Low
NET-EN and DPV ring vs NET-EN and placebo	
Pregnancy	Low

PrEP outcomes

Tenofovir (TDF) + emtricitabine (FTC): TDF/FTC

Outcome	Quality of the evidence
Oral TDF/FTC and DMPA vs oral TDF/FTC and no hormonal contraception	
PrEP efficacy	Very low

Evidence summary

A systematic review (2024) examined the body of evidence on drug–drug interactions between hormonal contraception and antiretroviral drugs (ARVs), including drugs used for HIV PrEP *(6)*. Of the 49 articles included in this review, six studies reported results on the concomitant use of hormonal contraception and PrEP (three evaluated oral tenofovir disoproxil fumarate/emtricitabine [TDF/FTC], one the dapivirine [DPV] ring, and two injectable cabotegravir [CAB]). Two studies were secondary analyses of data from RCTs *(7, 8)* and four were non-randomized trials focused on pharmacokinetic measures *(9–12)*. One additional cohort study evaluated bone mineral density among women taking oral TDF/FTC for ART *(13)*. Limited evidence found no significant differences for risk of pregnancy, PrEP effectiveness or adverse events for women using hormonal contraception and taking PrEP. Pharmacokinetic evidence also does not

suggest any potential drug–drug interactions between hormonal contraception and PrEP. For further detailed information, see the GRADE table in section 3.3 of this web annex.

Rationale

The GDG reviewed and discussed epidemiological evidence presented in a systematic review on the safety and effectiveness of hormonal contraception among women taking HIV PrEP *(2)*. In addition, the GDG considered qualitative and quantitative evidence published in a systematic review of the contraceptive values and preferences of women during their deliberations *(14)*.

The overall quality of the evidence was assessed as very low. Nevertheless, the GDG were reassured by the lack of evidence showing harms related to contraceptive effectiveness or PrEP effectiveness or toxicity from concomitant PrEP and hormonal contraceptive use. The GDG therefore determined there should be no restrictions on the use of hormonal or non-hormonal contraceptives for women using PrEP (MEC Category 1).

Throughout its deliberations, the GDG took note that the purpose of the MEC guideline is to provide options for clients seeking contraceptive services and to enable them to make contraceptive choices that are consistent with their own values and preferences. The GDG further acknowledged that values and preferences regarding contraception among women taking PrEP may vary according to outcomes: optimizing available contraceptive choices allows clients to choose a contraceptive method that is more acceptable to them.

In making these recommendations, the GDG recognizes that supportive policies for providing hormonal contraception and PrEP are essential for successful implementation of these recommendations. The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce.

The GDG also noted that hormonal contraceptives do not protect against STIs, including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe but are not used as widely by national programmes as male condoms.

Evidence-to-Decision table W.2.3b Pre-exposure prophylaxis (PrEP) and hormonal contraceptives

Domain	Explanation/evidence	Judgement
Balance of benefits and harms	Contraception is a life-saving intervention with well recognized health, social and economic benefits. All assessed hormonal contraceptives are effective at preventing pregnancy with some variability in effectiveness. Limited evidence suggests no impact of oral TDF/FTC, the dapivirine ring or injectable cabotegravir on the effectiveness of any hormonal contraceptive. Very limited evidence shows no impact of hormonal	Benefits may outweigh harms; there was no evidence of decreased benefits or increased harms with PrEP and hormonal contraceptives.

Domain	Explanation/evidence	Judgement
	contraception on the effectiveness of PrEP. No evidence of harms was identified.	
Quality of evidence	Overall, the evidence was considered very low quality for all outcomes.	Very low
Priority of the problem	Reproductive health and rights are key public health concerns globally. Promoting reproductive health agenda and ensuring contraceptive choice, while mitigating interaction with other HIV drugs, HIV treatments or physiologic conditions are important in reduction of mortality and morbidity, and to improve health and well-being.	Effective contraception and HIV prevention are both public health priorities.
Values and preferences	Contraceptive users have diverse values and preferences regarding outcomes. Generally, they value having a range of contraceptive methods from which to choose and prefer methods that are effective, easy to use, and have few side-effects. Differences in values and preferences regarding outcomes may impact contraceptive choices when the balance of benefits to harms is close; the purpose of the MEC is to provide options for clients so that they can make contraceptive choices that are consistent with their own values and preferences.	May vary; the MEC supports optimizing informed contraceptive choice – consistent with client values/preferences – from a range of contraceptive options.
Acceptability	The GDG noted that acceptability for different contraceptive methods will vary across and within populations. The purpose of the MEC is to provide a diverse range of contraceptive options that will allow clients to choose a contraceptive method that is more acceptable to them. The GDG underscored the importance of providing appropriate, evidence-based, understandable information and counselling to support each client's decision-making.	May vary; the MEC supports selection of acceptable contraceptives from a range of contraceptive options.
Costs/resources	As a preventive health service, contraception has repeatedly been shown to be a cost-saving intervention. Contraception prevents morbidity and mortality associated with unintended pregnancies and has been shown to reduce costs for the individual, the health system and society. However, costs for different contraceptive options vary. Costs were not formally assessed during the formulation of the recommendations; costs for a particular contraceptive may vary widely throughout different regions of the world and across different contexts within the same region. For a given condition, costs may inform choices	While costs may vary across settings, contraception overall is a cost-saving intervention. The MEC supports selection of contraceptives that are less costly from a range of contraceptive options, when cost is a relevant consideration.

Domain	Explanation/evidence	Judgement
	among contraceptive alternatives with similar MEC ratings.	
Feasibility	The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce. The MEC provides diverse contraceptive options to support selection of contraceptives that are feasible/sustainable in the settings in which they will be used.	May vary; the MEC supports selection of contraceptives that are more feasible in specific settings.
Equity	WHO's nine guiding human rights principles and standards for safeguarding a rights-based approach – which include non-discrimination, availability, accessibility, quality of contraception information and services, informed decision-making, privacy and confidentiality, participation and accountability – were followed by the GDG in its deliberations and formula. The MEC guideline promotes human rights principles and standards by supporting access to diverse contraceptive options across populations. The MEC supports equity and human rights by providing diverse contraceptive options for contraceptive users in different situations and settings. To maximize equity and human rights it is critical that recommended contraceptives be accessible for all persons in whom they are indicated and that their use not preferentially benefit certain groups or have negative impacts on certain groups.	Intervention supports human rights principles. Contraceptive accessibility for all persons is essential to maximize equity.

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Medical eligibility criteria for contraceptive use, sixth edition. Web Annex.

2.4 Recommendations for use of emergency contraceptive pills (ECPs) more than once in a menstrual cycle

Question 1: Among ECP users, does repeated use of ECP within a defined time frame increase the risk of adverse events, side-effects, or patient satisfaction compared with single use of ECP?

PICO question for systematic review

Population	Women of reproductive age taking ECP
Intervention	Repeated use of ECP within a defined time frame (ideally within one menstrual cycle)
Comparator	Single use of ECP
Outcomes	Adverse events (such as venous thromboembolism), side-effects (e.g. bleeding irregularities), patient satisfaction

Recommendations

- Women using ECPs more than once in a menstrual cycle can use ECPs (COC, LNG or UPA) without restriction (MEC Category 1).

Quality of the evidence

Levonorgestrel (LNG) (1.5 mg) ECP

Outcome	Quality of the evidence
Ectopic pregnancy	Very low
Adverse events	Very low
Adverse pregnancy/neonatal outcomes	Very low
Adverse infant/child outcomes	Very low

Ulipristal acetate (UPA) (30 mg) ECP

Outcome	Quality of the evidence
Adverse events (randomized controlled trial)	Very low
Adverse events (non-randomized trial without comparison group)	Very low

Evidence summary

A systematic review summarizing the evidence on the safety of repeated use of ECPs identified six studies *(1)*. Four studies of repeated LNG ECP use provided very-low-certainty evidence for all outcomes *(2–5)*. One study observed increased risk of ectopic pregnancy with repeated ECP use (1.5 mg LNG) compared with single use *(2)*; one study reported few (3%) serious adverse events with repeated pericoital use (1.5 mg LNG; mean 4–7 doses per month) *(3)*; and two analyses of overlapping study populations with ECP failure found no differences in pregnancy, fetal/neonatal, infant or child development outcomes comparing higher (2.25–9 mg LNG) and lower (0.75–1.5 mg LNG) doses *(4, 5)*. Two studies of repeated UPA ECP use provided very-low-certainty evidence for all outcomes *(6, 7)*. One study observed no serious adverse events, no abnormal laboratory results,

and normal endometrial biopsies with UPA (30 mg, 4–6 doses/month) *(6)*. One study observed no serious adverse events with UPA (10 mg, 20 mg or 50 mg for 10 days) compared with placebo *(7)*. For further detailed information, see the GRADE table in section 3.4 of this web annex.

Rationale

The GDG reviewed and discussed epidemiological evidence presented in the systematic review on the safety of repeated use of ECPs *(1)*. In addition, the GDG considered qualitative and quantitative evidence published in a systematic review of women's contraceptive values and preferences during their deliberations *(8)*.

The GDG considered the evidence showing lack of harms related to repeated ECP use as reassuring. While safety issues are not concerning, stakeholders frequently observe challenges interpreting, and ultimately implementing, the MEC condition currently labelled, "repeated ECP use". Stakeholders indicated the term "repeated" did not provide sufficient clarity on the quantity of ECPs used nor the timeframe of ECP intake. As a result, the GDG recommended the MEC condition name be changed to "ECPs taken more than once in a menstrual cycle". This name provides greater clarity and aligns with available evidence supporting the recommendations for ECP formulations.

The GDG therefore determined the current WHO recommendation for using ECPs more than once in a menstrual cycle (MEC Category 1) should be upheld as published in the previous/fifth edition of the MEC: there are no restrictions on the use of ECPs more than once in a menstrual cycle (MEC Category 1).

Throughout its deliberations, the GDG took note that the purpose of the MEC guideline is to provide options for clients seeking contraceptive services and to enable them to make contraceptive choices that are consistent with their own values and preferences. The GDG further acknowledged that values and preferences regarding contraception among people taking ECPs may vary according to outcomes: optimizing available contraceptive choices allows clients to choose a contraceptive method that is more acceptable to them.

In making these recommendations, the GDG recognized that supportive policies for offering ECPs are essential for successful implementation of these recommendations. The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce. Depending on the context, other programmatic approaches may be warranted depending upon the extent of repeated ECP use in a single menstrual cycle.

The GDG also noted that ECPs do not protect against STIs, including HIV. If there is a risk of STI/HIV, the correct and consistent use of condoms is recommended. When used correctly and consistently, male and female condoms offer one of the most effective methods of protection against STIs, including HIV. Female condoms are effective and safe but are not used as widely by national programmes as male condoms.

Evidence-to-Decision table W.2.4 Emergency contraceptive pills (ECPs) taken more than once in a menstrual cycle

Domain	Explanation/evidence	Judgement
Balance of benefits and harms	Contraception is a life-saving intervention with well recognized health, social and economic benefits. ECPs are effective at preventing pregnancy with some variability in effectiveness, including in relation to the timing of initiation (effectiveness of ECP use was not addressed in the systematic review). Overall, evidence from six studies suggested no increased risk in adverse events related to repeated ECP use with LNG or UPA ECPs, although one study with methodological limitations observed increased risk of ectopic pregnancy with repeated ECP use (1.5 mg LNG) compared with single use.	Benefits may outweigh harms; there was no clear evidence of increased harms with repeated ECP use.
Quality of evidence	Evidence was considered very low quality for all outcomes.	Very low
Priority of the problem	Reproductive health and rights are key public health concerns globally. Promoting reproductive agency and ensuring contraceptive choice are important in reduction of mortality and morbidity, and to improve health and well-being.	Effective contraception is a public health priority.
Values and preferences	Contraceptive users have diverse values and preferences regarding outcomes. Generally, they value having a range of contraceptive methods from which to choose and prefer methods that are effective, easy to use, and have few side-effects. Differences in values and preferences regarding outcomes may impact contraceptive choices when the balance of benefits to harms is close; the purpose of the MEC is to provide options for clients so that they can make contraceptive choices that are consistent with their own values and preferences.	May vary; the MEC supports optimizing informed contraceptive choice – consistent with client values/preferences – from a range of contraceptive options.
Acceptability	Taking ECPs more than once in a single menstrual cycle is likely to be acceptable among those who choose to use it. Any clinical consultation about the use of ECPs can be an opportunity to engage in a broader discussion about contraception with the client.	May vary; the MEC supports selection of acceptable contraceptives from a range of contraceptive options.
Costs/resources	As a preventive health service, contraception has repeatedly been shown to be a cost-saving intervention. Contraception prevents morbidity and mortality associated with unintended pregnancies and has been shown to reduce costs for the individual, the health	While costs may vary across settings, contraception is a cost-saving intervention. The MEC supports

Domain	Explanation/evidence	Judgement
	system and society. However, costs for different contraceptive options vary. Costs were not formally assessed during the formulation of the recommendations; costs for a particular contraceptive may vary widely throughout different regions of the world and across different contexts within the same region. For a given condition, costs may inform choices among contraceptive alternatives with similar MEC ratings.	selection of contraceptives that are less costly from a range of contraceptive options, when cost is a relevant consideration.
Feasibility	The feasibility of the recommendation is dependent on existing policies, regulatory considerations, availability of recommended contraceptive options, resources, existing service-delivery strategies, and the availability of an adequately trained health workforce. The MEC provides diverse contraceptive options to support selection of contraceptives that are feasible/sustainable in the settings in which they will be used.	May vary; the MEC supports selection of contraceptives that are more feasible in specific settings.
Equity	Taking ECPs more than once in a menstrual cycle may increase equity by providing an accessible option for users who wish to prevent pregnancy after intercourse. To maximize equity and human rights, it is critical that ECPs be accessible for all persons who wish to use them and that their use does not preferentially benefit certain groups or have negative impacts on certain groups.	Intervention supports human rights principles. Contraceptive accessibility for all persons is essential to maximize equity.

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2.5 Recommendations for contraception among women with inflammatory bowel disease (IBD)

Question 1: Among women with IBD, does use of a specific contraceptive method increase the risk of IBD relapse or other adverse health outcomes (e.g. thrombosis, osteopenia, osteoporosis) compared with no use of contraception or use of a different contraceptive method?

PICO question for systematic review

Population	Women with IBD (including ulcerative colitis and Crohn's disease)
Intervention	Use of contraception at or after IBD diagnosis
Comparator	Non-use of contraception or use of a different contraceptive method
Outcomes	IBD disease activity or relapse, or other adverse health outcomes/events (e.g. venous thromboembolism, osteoporosis, osteopenia)

Question 2: Among women using oral contraceptives, does having IBD modify contraceptive effectiveness (e.g. pregnancy or proxy measures of pregnancy risk, such as ovulation, exogenous [contraceptive] hormone levels) compared with not having IBD?

PICO question for systematic review

Population	Women using oral contraception
Intervention	Diagnosis of IBD (including ulcerative colitis, Crohn's disease)
Comparator	No diagnosis of IBD
Outcomes	Pregnancy, ovulation, changes in hormone plasma concentration

Recommendations

- The GDG judged the body of evidence was insufficient to make any recommendations considering the challenges in making an IBD diagnosis in many regions.

Quality of the evidence

Disease activity or relapse

Oral contraceptives

Outcome	Quality of the evidence
Oral contraceptives and ulcerative colitis	
Relapse of ulcerative colitis	Very low
Time to ulcerative colitis relapse	Very low
Number of ulcerative colitis relapses during follow-up period	Very low
1st ulcerative colitis-related surgery	Very low
1st prescription of oral steroids at least 90 days after start of follow-up	Very low
1st prescription for anti-tumor necrosis factor at least 90 days after start of follow-up	Very low
Oral contraceptives and Crohn's disease	
Relapse of Crohn's disease	Very low
Crohn's disease relapse with need for surgery	Very low

Time to Crohn's disease relapse	Very low
Median Crohn's disease Activity Index (CDAI) during relapse	Very low
1st Crohn's disease-related surgery	Very low
1st prescription for oral steroids after Crohn's disease diagnosis	Very low

LNG-releasing IUD (LNG-IUD)

Outcome	Quality of the evidence
LNG-IUD and Crohn's disease	
1st Crohn's disease-related surgery	Very low
1st prescription for oral steroids after Crohn's disease diagnosis	Very low

Hormonal contraception methods combined (COCs, POPs, LNG-IUD)

Outcome	Quality of the evidence
Hormonal contraception and IBD (ulcerative colitis and Crohn's disease)	
IBD symptoms	Very low
Flares	Very low
Inflammation	Very low

Adverse events

Oral contraceptives

Outcome	Quality of the evidence
Oral contraceptives and IBD	
Venous thromboembolism	Very low
Abnormal cervical smear results	Very low

Evidence summary

A systematic review identified 15 cohort studies reporting on contraceptive use and IBD *(1–16)*. The certainty of the evidence was very low for all outcomes assessed. Evidence from one study found a statistically significant association between hormonal contraceptive use and a decrease in the occurrence of IBD symptoms, and a non-statistically significant association between hormonal contraceptive use and a decrease in IBD flares. However, a statistically significant association between hormonal contraceptive use and an increase in IBD inflammation over one year was observed. Evidence from nine studies reported inconsistent results regarding oral contraceptive (OC) use and IBD disease activity or relapse (either ulcerative colitis or Crohn's disease), with OC use have associations with either increases or decreases in various measures of disease activity or relapse; most of the associations were not statistically significant. Evidence from two cohort studies did not demonstrate statistically significant associations between OC use and venous thromboembolism among IBD patients, although these studies may not have had sufficient statistical power to assess these outcomes. One study found no association between OC use and abnormal cervical smears. Evidence from two pharmacokinetic studies generally suggested no differences in plasma concentrations of steroid hormones after oral ingestion among participants

with and without IBD (evidence from pharmacokinetic studies was not assessed for quality of evidence). For further detailed information, see the GRADE tables in section 3.5 of this web annex.

Rationale

The GDG reviewed and discussed epidemiological evidence from a systematic review on contraceptive use among women diagnosed with IBD. Based upon their review of the quality of the body of evidence and thorough deliberations, the GDG decided not to develop any recommendations on contraceptive eligibility for women diagnosed with IBD.

More specifically, the GDG arrived at this decision based upon the following considerations.

- Data were only available for a few contraceptive methods and not for all identified outcomes.
- The GDG raised doubts as to the (current) feasibility of implementing screening and surveillance programmes to accurately diagnose the condition.
- The GDG questioned whether equitable application of recommendations on the topic was possible in all contexts and across all populations.
- The GDG highlighted knowledge gaps on this topic and therefore encourages the undertaking of research to address these knowledge gaps and to inform future guideline updates.

WHO will monitor the body of evidence on the safety and effectiveness of contraceptive use among women with IBD and will reconsider this topic if evidence becomes available that might enable WHO to issue recommendations in the future.

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3. GRADE tables

3.1 Progestogen-only contraception (POC) use during breastfeeding

GRADE table W.3.1a Systematic review question 1: Among women who breastfeed, does the use of POCs increase the risk of adverse breastfeeding or infant outcomes compared with those who do not use POCs or use a different method of POC?

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
POPs vs non-hormonal contraception, initiated < 6 week postpartum										
Breastfeeding (BF) outcomes										
Continuation	5 **(1 new)** *(1–5)*	Cohort	Very serious [a]	Not serious	Not serious	Not serious	1029 total **30**	**30**	None of 4 studies from the prior review *(6)* found various POPs associated with lower likelihood of BF continuation; 2 studies found POPs associated with higher likelihood of BF continuation. **At 3 months, lynestrenol POPs = 23, control (other contraception) = 24; at 6 months, POPs = 21, control = 24.**	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Supplementation	3 **(1 new)** *(2, 3, 7)*	Cohort	Very serious [a]	Serious [b]	Not serious	Not serious	530 **(30)**	530 **(30)**	1 poor-quality study found norgestrel vs non-hormonal associated with more frequent supplementary feeding but no difference in proportion of women supplementing; 1 poor-quality study found LNG associated with somewhat later initiation of supplementation (5.4 vs 4.6 months postpartum). **At 3 months, lynestrenol POP = 10, control (other contraception) = 11; at 6 months, POP = 13, control = 13.**	Very low
Initiation	1 *(8)*	RCT	Very serious [c]	Cannot assess	Very serious[d]	Not serious	12	8	1 RCT found no difference between norethisterone at ≤ 14 hours postpartum vs placebo in BF initiation.	Very low
Initiation	1 *(9)*	Cohort	Very serious [e]	Cannot assess	Very serious[d]	Not serious	10	10	1 non-randomized trial found lynestrenol at 2 days postpartum	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									associated with initiation of BF at 3 vs 5 days postpartum with placebo.	
Duration	2 *(10, 11)*	Cohort	Very serious [a]	Not serious	Not serious	Not serious	572 total		2 studies found POPs associated with somewhat longer duration of BF vs non-hormonal comparators.	Very low
Infant outcomes										
Growth	6 **(2 new)** *(1–3, 7, 9, 12)*	Cohort	Very serious [a]	Serious [b]	Not serious	Not serious	1103 105	 186	3 studies found no difference on measures of infant growth; 1 small, poor-quality, non-randomized study found greater increase with lynestrenol than placebo. **Higher or similar weights and lengths at months 1–6 in lynestrenol POP vs multiload IUD or control, no statistical testing.** **Average weight (lbs) at 3 months, lynestrenol POP = 13.8, control**	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									(other contraception) = 13.9; at 6 months, POP = 16.11, control = 16.8, no statistical testing.	
Growth	1 *(8)*	RCT	Very serious [c]	Cannot assess	Very serious[d]	Not serious	12	8	No difference between groups in weight gain.	Very low
POPs vs CHCs, initiated < 6 week postpartum										
Breastfeeding outcomes										
Continuation	1 *(13)*	RCT	Very serious [f]	Cannot assess	Serious [g]	Not serious	65	64	1 RCT compared norethindrone vs ethinyl estradiol COC: 64% vs 64%, RR 0.99 (95% CI: 0.76–1.3) at 8 weeks; 41% vs 44%, RR 0.94 (95% CI: 0.63–1.4) at 6 months.	Very low
Continuation	**1 new** *(2)*	**Cohort**	**Very serious** [a]	**Cannot assess**	**Very serious** [d]	**Not serious**	**30**	**30**	**At 3 months, lynestrenol POP = 23, COC = 17; at 6 months, POP = 21, COC = 14.**	**Very low**
Supplementation	1 *(13)*	RCT	Very serious [f]	Cannot assess	Serious [g]	Not serious	65	64	1 RCT compared norethindrone vs ethinyl estradiol COC: no difference at 8 weeks (data not provided).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Supplementation	**1 new** *(2)*	**Cohort**	**Very serious** [a]	**Cannot assess**	**Very serious** [d]	**Not serious**	**30**	**30**	**At 3 months, lynestrenol POP = 10, COC = 16; at 6 months, POP = 13, COC = 20.**	**Very low**
Infant outcomes										
Growth	1 *(13)*	RCT	Very serious [f]	Cannot assess	Serious [g]	Not serious	65	64	1 RCT compared norethindrone vs ethinyl estradiol COC: no difference in percent change in weight ($P = 0.56$), length ($P = 0.41$), or head circumference ($P = 0.79$) from weeks 2–8.	Very low
Growth	**1 new** *(2)*	**Cohort**	**Very serious** [a]	**Cannot assess**	**Very serious** [d]	**Not serious**	**30**	**30**	**Average weight (lbs) at 3 months, lynestrenol POP = 13.8, COC = 13.1, control = 13.9; at 6 months, POP = 16.11, COC = 16.13, control = 16.8.**	**Very low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Progestogen-only injectable (POI) vs unspecified, initiated < 6 week postpartum										
Breastfeeding (BF) outcomes										
Milk volume	**1 new** *(14)*	**Cohort**	**Very serious** [h]	**Cannot assess**	**Not serious**	**Not serious**	**29**	**141**	**No differences in milk volume between DMPA vs no DMPA at days 1–7, 14 and 21.**	**Very low**
Continuation	4 **(1 new)** *(14–17)*	Cohort	Very serious [h]	Not serious	Not serious	Not serious	617 total **29**	**141**	No clear differences in 2 studies; in a 3rd study weaning occurred later with DMPA or NET-EN. **Proportion of participants who continued lactation until hospital discharge: DMPA 37.5%, no DMPA 47.5% (*P* = 0.387).** **Mean days to hospital discharge: no DMPA = 70 days (SD: 34.6), DMPA = 83.5 days (SD: 30.8) (*P* = 0.026).**	Very low
Supplementation	5 *(15, 16, 18–20)*	Cohort	Very serious [i]	Not serious	Not serious	Not serious	1370 total		All 5 studies found DMPA and/or NET-EN associated with similar or lower likelihood of exclusive BF.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Duration	5 *(15, 16, 18–20)* [j]	Cohort	Very serious [k]	Not serious	Not serious	Not serious	1732 total		All 5 studies found DMPA associated with no difference or increased duration of BF vs non-hormonal methods.	Very low
Infant outcomes										
Infant growth	5 *(11, 15, 18, 21, 22)*	Cohort	Very serious [k]	Not serious	Not serious	Not serious	4403 total		None of 5 studies found DMPA or NET-EN associated with decreased infant growth; 1 study found POI associated with increased weight gain through 3 months.	Very low
Progestogen-only implant vs non-hormonal contraception, initiated < 6 week postpartum										
Breastfeeding outcomes										
Amount of milk ingested	**1 new** *(23)*	**RCT**	**Serious** [j]	**Cannot assess**	**Not serious**	**Serious** [m]	**12**	**12**	**At 29 days: ETG implant within 48 h postpartum (mean±SD) = 343.6±102.5 ml/day; control (no contraceptive): mean = 388.2±170.4 ml/day (*P* = 0.54). At 42 days: implant = 775±277.6 ml/days;**	**Very low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									control = 815.4±184.1 ml/day (*P* = 0.63).	
Continuation	**1 new** *(23)*	**RCT**	**Serious** [j]	**Cannot assess**	**Very serious** [d]	**Not serious**	**12**	**12**	**Through 6 weeks postpartum: ETG implant within 48 h postpartum, n = 11 (92%); control (no contraceptive), n= 8 (80%), no statistical testing.**	**Very low**
Continuation	3 *(15, 24)* [j]	Cohort	Very serious [a]	Serious [b]	Serious [n]	Not serious	520 total		3 studies (reported in 2 articles) reported conflicting findings regarding effects of progestogen-containing implants on measures of BF continuation; the 1 fair-quality study found no difference between nomegestrol implant in 2nd month postpartum vs Cu-IUD.	Very low
Duration	1 *(25)*	Cohort	Very serious [a]	Cannot assess	Very serious[d]	Not serious	42	38	1 fair-quality cohort study found no difference in duration of BF between ETG implant	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									at 28–56 days postpartum vs Cu-IUD.	
Supplementation	3 *(15, 24, 26)*	Cohort	Very serious [o]	Serious [b]	Serious [d]	Not serious	430 total		2 studies found no difference in use of supplementation; 1 study found norethindrone associated with increased likelihood of supplementation at 3 months.	Very low
Infant outcomes										
Growth	6 *(26–28)*[j]	Cohort	Very serious [e]	Not serious	Not serious	Not serious	870 total		2 fair-quality and 2 poor-quality studies found no difference in measures of infant growth; 1 poor-quality study found LNG associated with more weight gain than Cu-IUD; 1 poor-quality study found LNG associated with slower weight gain than Cu-IUD or barrier method/no method.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
LNG-IUD vs non-hormonal contraception, initiated at < 6 weeks postpartum										
Breastfeeding outcomes										
Continuation	1 *(29)*	RCT	Very serious [p]	Cannot assess	Serious [n]	Not serious	70	40	LNG-IUD (30 µg/day or 10 µg/day) vs Cu-IUD (1 RCT): 58% vs 79% at 8 months, RR 0.74 (95% CI: 0.57–0.95).	Very low
Duration	1 *(29)*	RCT	Very serious [p]	Cannot assess	Serious [n]	Not serious	70	40	LNG-IUD 30 µg/day vs LNG-IUD 10 µg/day vs Cu-IUD (1 RCT): 197 vs 182 vs 208 days ($P > 0.05$).	Very low
Infant outcomes										
Growth	1 *(29)*	RCT	Very serious [p]	Cannot assess	Serious [n]	Not serious	70	40	LNG-IUD (30 µg/day or 10 µg/day) vs Cu-IUD (1 RCT): no differences through 12 months.	Very low
Multiple POCs vs non-hormonal contraception, initiated at < 6 weeks postpartum										
Breastfeeding outcomes										
Continuation	1 *(16)*	Cohort	Very serious [i]	Cannot assess	Serious [n]	Not serious	181	138	1 study found no difference in BF continuation at 2–6 weeks postpartum between LNG implant or	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									POP prior to discharge vs non-hormonal contraception.	
Supplementation	1 *(16)*	Cohort	Very serious [i]	Cannot assess	Serious [n]	Not serious	181	138	1 study found no difference in use of supplementation at 2–6 weeks postpartum between LNG implant or POP prior to discharge vs non-hormonal contraception.	Very low
POP vs non-hormonal, initiated ≥ 6 week postpartum										
Breastfeeding outcomes										
Milk volume	**1 new** *(30)*	**Cohort**	**Very serious [o]**	**Cannot assess**	**Very serious [d]**	**Serious [m]**	**42**	**42**	**No differences in estimated 24-hour milk production between POP vs multiload Cu250 IUD at 10, 14, 18, 22, 26 and 30 weeks.**	**Very low**
Continuation	1[j]	RCT	Very serious	Cannot assess	Very serious	Not serious	144 total		1 RCT compared norgestrel at 6 weeks postpartum vs non-hormonal contraception: no difference in discontinuation of BF.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Duration	2 studies (3 articles) *(31–33)*	Cohort	Very serious [a]	Not serious	Not serious	Not serious	1709 total		2 studies found no difference in BF duration.	Very low
Supplementation	2 *(34)* [j]	RCT and cohort	Very serious [e]	Serious [b]	Serious [n]	Not serious	RCT, n = 144 total Cohort, n = 120 total		1 RCT found no difference in use of supplementation and 1 non-randomized trial found lower mean age at supplementation with lynestrenol vs IUD + placebo (11 vs 15 weeks, *P* not reported).	Very low
Infant outcomes										
Growth	2 **(1 new)** *(35)* [j]	**RCT**	**Very serious** [q]	**Not serious**	**Serious** [n]	**Not serious**	144 total		No differences in measures of infant growth.	**Very low**
							62	**53**	**Lynestrenol POP group with lower length at baseline vs multiload Cu250 IUD (*P* < 0.05), without differences in weight or biparietal head circumference; otherwise, no differences between groups in weight,**	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									length or biparietal head circumference at months 1, 3 and 6.	
Growth	5 **(2 new)** *(30–34, 36, 37)*	**Cohort**	**Very serious** [a]	**Not serious**	**Not serious**	**Not serious**	1829 total		3 studies from prior review found no difference in measures of infant growth.	**Very low**
							42	**42**	**Lower length in POP group vs multiload Cu250 IUD at 10 weeks (*P* = 0.01) and borderline at 14 weeks (*P* = 0.05); no other differences in weight, length or head circumference at 10, 14, 18, 22, 26 and 30 weeks.** **No differences in rates of normal, average or poor growth and development in desogestrel POP vs placebo (*P* = 0.314).**	
Illness	**1 new** *(35)*	**RCT**	**Very serious** [q]	**Cannot assess**	**Very serious** [d]	**Not serious**	**62**	**53**	**No differences in illness in the previous month in lynestrenol POP**	**Very low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									group vs multiload Cu250 IUD.	
Illness	**1 new** *(30)*	**Cohort**	**Very serious** [a]	**Cannot assess**	**Very serious** [d]	**Not serious**	**42**	**42**	**Lower infection rates in POP group vs multiload Cu250 IUD at 30 weeks (*P* = 0.01), otherwise no differences between groups at 10, 14, 18, 22 or 26 weeks.**	**Very low**
Progestogen-only injectable (POI) initiated at ≥ 6 weeks postpartum vs non-hormonal contraception										
Breastfeeding outcomes										
Continuation	1[j]	RCT	Very serious	Cannot assess	Serious	Not serious	170 total		1 RCT compared DMPA at 6 weeks postpartum vs non-hormonal contraception: no difference in rates of discontinuation.	Very low
Duration	1[j]	Cohort	Serious	Cannot assess	Not serious	Not serious	1538 total		1 cohort study compared DMPA or NET-EN at 6–8 weeks postpartum vs non-hormonal contraception: no difference in duration of BF.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Supplementation	2[j]	RCT and cohort	Very serious	Not serious	Serious	Not serious	RCT, n = 170 total Cohort, n = 212 total		2 studies found no differences in use of supplementation.	Very low
Infant outcomes										
Growth	3[j]	RCT and cohort	Very serious	Not serious	Not serious	Not serious	1920 total		None of the 3 studies found decreased infant growth with DMPA or NET-EN; 2 studies reported some findings suggesting greater weight gain.	Very low
Progestogen-only implant vs non-hormonal contraception, initiated ≥ 6 week postpartum										
Breastfeeding outcomes										
Supplementation	**1 new** *(38)*	**Cohort**	**Very serious [o]**	**Cannot assess**	**Very serious [d]**	**Not serious**	**100**	**100**	**Implants (6-rod LNG at 55±3 days) with higher frequency of supplementation due to poor infant growth compared with TCu380A IUD (no data provided).**	**Very low**
Exclusivity	**1 new** *(38)*	**Cohort**	**Very serious [o]**	**Cannot assess**	**Very serious [d]**	**Not serious**	**100**	**100**	**Implants (6-rod LNG at 55±3 days) with lower proportions of exclusive BF compared with TCu380A IUD (no**	**Very low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									numerical data provided); *P* < 0.02 at month 12.	
Infant outcomes										
Growth	**1 new** *(38)*	**Cohort**	**Very serious** [o]	**Cannot assess**	**Serious** [d]	**Not serious**	**100**	**100**	**Lower average weight in implant (6-rod LNG at 55±3 days) vs TCu380A IUD at 122, 153 and 183 days, otherwise no differences at delivery or at 31, 56, 92, 243, 305 or 366 days.**	**Very low**
LNG-IUD vs non-hormonal contraception, initiated ≥ 6 week postpartum										
Breastfeeding outcomes										
Duration	1 *(39)*	RCT	Serious [r]	Cannot assess	Not serious	Not serious	163	157	LNG-IUD at 6–8 weeks postpartum vs Cu-IUD (1 RCT): 149 vs 160 days.	Low
Supplementation	1 *(39)*	RCT	Serious [r]	Cannot assess	Not serious	Not serious	163	157	LNG-IUD at 6–8 weeks postpartum vs Cu-IUD (1 RCT): no difference in exclusive BF.	Low
Infant outcomes										
Growth	1 *(39)*	RCT	Not serious	Cannot assess	Not serious	Not serious	163	157	LNG-IUD at 6–8 weeks postpartum vs Cu-IUD (1	Medium

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									RCT): no difference in infant growth.	
Progestogen-only implant or LNG-IUD initiated at ≥ 6 weeks postpartum vs non-hormonal contraception										
Breastfeeding (BF) outcomes										
Continuation	2[j]	Cohort	Very serious	Not serious	Very serious	Not serious	57 total		2 studies found no difference in BF rates.	Very low
Duration	4[j]	Cohort	Serious	Not serious	Not serious	Not serious	2329 total		4 studies found no difference in BF duration.	Very low
Supplementation	3[j]	Cohort	Serious	Not serious	Serious	Not serious	549 total		3 studies found no difference in use of supplementation.	Very low
Infant outcomes										
Growth	6[j]	Cohort	Serious	Not serious	Not serious	Not serious	2386 total		6 studies found no difference in measures of infant growth.	Very low
Multiple POCs initiated at ≥ 6 weeks postpartum vs non-hormonal contraception										
Breastfeeding outcomes										
Duration	1 *(40)*	Cohort	Very serious [s]	Cannot assess	Very serious[d]	Not serious	28	54	DMPA, POP or LNG-IUD vs non-hormonal contraception (1 cohort study): 183 vs 183 days ($P = 0.38$).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Infant outcomes										
Growth	1 *(1)*	Cohort	Very serious [a]	Cannot assess	Very serious[d]	Not serious	51	89	DMPA at 6 weeks postpartum vs non-hormonal contraception (1 cohort study): no difference in weight through 26 weeks postpartum.	Very low
PVR vs IUD, progestogen-only implant or POP, timing of initiation not specified										
Breastfeeding outcomes										
Supplementation	4[j]	Cohort	Very serious [o]	Not serious	Not serious	Not serious	1129 total		No difference in proportion fully BF between PVR and IUD (3 studies), Norplant (2 studies) or POP (1 study); 1 study found PVR associated with fewer supplementation episodes and days than IUD at all follow-up periods ($P < 0.001$).	Very low
Duration	4[j]	Cohort	Very serious [o]	Not serious	Not serious	Not serious	1117 total		No difference between PVR and IUD (4 studies), Norplant (2 studies) or POP (1 study).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Infant outcomes										
Growth	8[j] (**1 new**) *(41)*	**Cohort**	**Very serious** [a]	**Not serious**	**Not serious**	**Not serious**	3397 total		No difference in weight gain between PVR vs IUD (7 studies), Norplant (2 studies) or POP (1 study).	**Very low**
							459	**330**	**No differences in mean weight between PVR vs Cu-IUD (either selected at 6–9 weeks postpartum) at months 1, 3, 6, 9 and 12.**	

Bold formatting indicates information from newly identified studies.

BF: breastfeeding; COC: combined oral contraceptive; CHC: combined hormonal contraception; CI: confidence interval; Cu: copper; DMPA: depo medroxyprogesterone acetate; ETG: etonogestrel; IUD: intrauterine device; LNG: levonorgestrel; NET-EN: norethisterone enanthate; NS: not significant; POI: progestogen-only injectable; POP: progestogen-only pill; PVR: progesterone vaginal ring; RCT: randomized controlled trial; RR: relative risk.

[a] Risk of bias considered very serious due to high risks of selection bias, information bias and confounding.

[b] Inconsistency considered serious due to some varying results among studies.

[c] Risk of bias considered very serious due to missing data, and high risks of poor measurement and reporting.

[d] Imprecision considered very serious due to no power calculations for outcomes of interest and/or small sample size.

[e] Risk of bias considered very serious due to high risk of confounding.

[f] Risk of bias considered very serious due to missing data and deviations.

[g] Imprecision considered serious due to small sample size and higher loss to follow-up than expected for power calculation.

[h] Risk of bias considered very serious due to high risk of selection and information biases.

[i] Risk of bias considered very serious due to high risk of information bias and confounding.

[j] Information included from prior GRADE table but unable to determine which individual studies were included for this outcome, and unable to specify further details for decisions to downgrade the evidence.

[k] Majority rated “poor” quality in prior review.

[l] Risk of bias considered serious due to moderate risk of deviations.

[m] Indirectness considered serious due to variable clinical significance of outcome.

[n] Imprecision considered serious due to lack of power calculation for outcomes of interest and/or relatively small sample size.
[o] Risk of bias considered very serious due to high risk of selection bias and confounding.
[p] Risk of bias considered very serious due to poor randomization, deviations and poor reporting.
[q] Risk of bias considered very serious due to poor randomizations and deviations.
[r] Risk of bias considered serious due to moderate outcome measurement.
[s] Risk of bias considered very serious due to high risk of selection bias.

GRADE table W.3.1b Systematic review question 2: Among women who breastfeed, does the initiation of POC before 6 weeks postpartum increase the risk of adverse breastfeeding or infant outcomes compared with the initiation of POC at 6 weeks postpartum or later?

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Progestogen-only implant (immediate postpartum vs delayed)										
Breastfeeding (BF) outcomes										
Continuation	**1 new** *(42)*	**RCT**	**Serious** [a]	**Cannot assess**	**Not serious**	**Not serious**	**96**	**87**	**Immediate implant (within 5 days postpartum) =74% BF, delayed implant (6–8 weeks postpartum) = 71% BF at 3 months follow-up (*P* = 0.74); immediate = 48% BF, delayed = 52% BF at 6 months follow-up (*P* = 0.58).**	**Low**
Continuation	1 *(24)*	Cohort	Very serious[b]	Cannot assess	Very serious [c]	Not serious	23	12	1 cohort study found norethindrone implant at 6 days vs 6 weeks postpartum was associated with lower rate of BF at 8 months follow-up (57% vs 67%).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Exclusivity	2 **(1 new)** *(43, 44)*	**RCT**	**Very serious** [d]	**Not serious**	**Not serious**	**Not serious**	**70**	**70**	No differences in rates of BF exclusivity between ETG implant insertion at 24–48 hours vs DMPA given at 6 weeks, at 6 or 12 weeks follow-up. **No differences in rates of BF exclusivity between ETG implant insertion within 48 hours vs 6 weeks, at 14, 40, 90 or 180 days follow-up.**	**Low**
Infant outcomes										
Growth	**3 (2 new)** *(42–44)*	**RCT**	**Very serious**[e]	**Not serious**	**Not serious**	**Not serious**	**176**	**157**	No differences in growth at 6 or 12 weeks follow-up between ETG implant insertion at 24–28 hours vs 6 weeks. **No differences between immediate (within 5 days postpartum) vs delayed (6–8 weeks postpartum)**	**Low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									insertion of 2-rod LNG implant in weight gain, head circumference increase, or length increase from birth to 6 months. **Sensitivity analysis in premature infants, immediate = 6033 g vs delayed = 4563 g (*P* = 0.006).** **Increase in head circumference in immediate (within 48 hours) vs 6 weeks insertion of ETG implant at 270 days postpartum follow-up (*P* = 0.02).** **No other differences in weight, head circumference, length or arm circumference at 14, 40, 90, 180, 270 or 360 days follow-up.**	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
LNG-IUD (immediate postpartum vs delayed)										
Breastfeeding (BF) outcomes										
Duration	1 *(45)*	RCT	Serious[a]	Cannot assess	Not serious	Not serious	50	46	1 RCT compared the duration of BF in groups that had immediate LNG-IUD insertion vs delayed insertion (6–8 weeks postpartum): 5 weeks vs 8.5 weeks (*P* = 0.06).	Very low
Continuation	1 *(45)*	RCTs	Serious[a]	Cannot assess	Not serious	Not serious	50	46	1 RCT found immediate LNG-IUD insertion was associated with lower BF rate at 6 months vs IUD initiation at 6–8 weeks postpartum (6% vs 24% BF, *P* = 0.02).	Very low
Earlier vs later initiation of POCs (prior review)										
Breastfeeding outcomes										
Supplementation	3[f]	RCTs	Serious	Serious	Not serious	Not serious	205 total		Inconsistent effects on use of supplementation among 3 studies.	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Supplementation	4[f]	Cohort	Very serious	Serious	Not serious	Not serious	660 total		Inconsistent effects on use of supplementation among 4 studies.	Very low
Infant outcomes										
Growth	3[f]	Cohort	Very serious	Not serious	Serious	Not serious	543 total		4 studies found no differences in measures of infant growth.	Very low

Bold formatting indicates information from newly identified studies.

ETG: etonogestrel; LNG: levonorgestrel; PP: postpartum; RCT: randomized controlled trial.

[a] Risk of bias considered serious due to moderate missing data.

[b] Risk of bias considered very serious due to high risk of selection bias, information bias and confounding.

[c] Imprecision considered very serious due to no power calculations for outcomes of interest and/or small sample size.

[d] Risk of bias considered very serious due to deviations.

[e] Risk of bias considered very serious due to deviations and missing data.

[f] Information included from prior GRADE table but unable to determine which individual studies were included for this outcome, and unable to specify further details for decisions to downgrade the evidence.

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3.2 Use of intrauterine devices (IUDs) during breastfeeding

GRADE table WA.3.2a Systematic review question 1: Among women using an IUD (either copper-bearing IUD [Cu-IUD] or levonorgestrel-releasing IUD [LNG-IUD]), does breastfeeding compared with not breastfeeding increase the risk of an IUD-related adverse event?

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Cu-IUD, breastfeeding (BF) vs not BF										
Immediate postpartum placement										
Expulsion	2 *(1, 2)*	Cohort	Very serious [a]	Serious [b]	Not serious	Not serious	1856	893	Rate at 3 months postpartum: 10.9% (BF) vs 7.3% (not-BF) (no *P*-value but reported no significant differences), no statistically significant differences at 6 months postpartum. Rate at 6 months postpartum: 11.9% (BF) vs 22.4% (not-BF) (*P* < 0.05).	Very low
Removal for pain or bleeding	1 *(1)*	Cohort	Very serious [a]	Cannot assess	Serious [c]	Not serious	1022	817	Rate at 3 months postpartum: 2.3% (BF) vs 0.7% (not-BF) (no *P*-value but reported no significant differences); no statistically significant differences at 6 months postpartum.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Interval postpartum placement										
Perforation	3 *(3–5)*	Cohort	Very serious [d]	Not serious	Not serious	Not serious	4634	5283	Immediate perforation: 0.06% in both groups ($P > 0.05$). Perforation: 0% in both groups in 2 studies.	Very low
Expulsion	6 *(1, 3, 5–8)*	Cohort	Very serious [a]	Not serious	Not serious	Not serious	6542	6045	No statistically significant differences at 3, 6, 12 or 24 months.	Very low
Removal for pain or bleeding	8 *(1, 3, 5–10)*	6 Cohort 2 Case–control	Very serious [a]	Serious [b]	Not serious	Not serious	Cohort, n = 6542 Case–control, n = 232	Cohort, n = 6045 Case–control, n = 22 559	Cohort: Rate at 3 months: no statistically significant differences. Rate at 6 months: 0.4 (BF) vs 3.2 (not-BF) ($P < 0.05$). Rate at 12 months: statistically significantly lower in BF group in 2 studies, not statistically significantly different in 1 study. Rate at 24 months: no statistically significant differences. Case–control: statistically significantly	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									lower in BF group in 2 studies.	
Mixed or unspecified timing of placement										
Expulsion	**1 new** *(11)*	**Cohort**	**Very serious** [a]	**Cannot assess**	**Not serious**	**Not serious**	**781**	**1801**	**Adjusted HR = 0.94 (95% CI: 0.72–1.22)**	**Very low**
Perforation	2 (3 articles, **2 new**) *(11–13)*	Cohort	Very serious [a]	Cannot assess	Not serious	Not serious	**3463 (1700 at 5 years)**	**17 489 (7983 at 5 years)**	1 year: RR 7.8 (95% CI: 2.8–21.4). Incidence/1000 women: 3.7 (BF) vs 0.5 (not-BF). **5-year incidence: 8/1700 (BF), 6/7893 (not BF)** **Perforation (proportion, %): BF (< 3 months postpartum) = 2/306, 0.65%; BF (≥ 3 months postpartum) = 1/475, 0.21%; not-BF = 4/1801, 0.22%.**	Very low
LNG-IUD, breastfeeding (BF) vs not BF										
Mixed or unspecified timing of placement										
Perforation	1 (2 articles, **1 new**) *(12, 13)*	Cohort	Very serious [e]	Not serious	Not serious	Not serious	3963 **(2660 at 5 years)**	39 115 **(22 677 at 5 years)**	1 year: RR 6.3 (95% CI: 3.8–10.5). Incidence/1000 women: 6.3 (BF) vs 1.0 (not-BF).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									5-year incidence: 21/2660 (BF),36/22 677 (not BF).	
IUD multiple types, breastfeeding (BF) vs not BF										
Immediate postpartum placement										
Expulsion	**2 new** *(14, 15)*	**Cohort**	**Very serious** [d]	**Serious** [b]	**Very serious** [f]	**Not serious**	**128**[g]	**69**[g]	**Adjusted HR for any BF vs exclusive bottle feeding = 1.4 (95% CI: 0.5–3.9).** **Adjusted OR for exclusive BF vs bottle only = 0.47 (95% CI: 0.28–0.79; *P* < 0.005).**	**Very low**
Interval placement										
Perforation	2 (**1 new**) *(12, 16)*	Cohort	Very serious [e]	Not serious	Not serious	Not serious	15 669 **(new, n = 9024)**	59 148 **(new, n = 4345)**	BF vs not-BF, RR 2.2 (95% CI: 0.3–16.3). Incidence/1000 women: 1.6 (BF) vs 0.7 (not-BF). **BF vs not-BF, aOR = 4.48 (95% CI: 1.95–10.33; *P* < 0.001).**	Very low
Expulsion	**1 new** *(16)*	**Cohort**	**Very serious** [e]	**Cannot assess**	**Serious** [h]	**Not serious**	**9024**	**4345**	**BF vs not-BF, aOR = 0.61 (95% CI: 0.36–1.01; *P* = 0.06).**	**Very low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Any insertion-related adverse event	1 *(4)*	Cohort	Very serious [i]	Cannot assess	Not serious	Not serious	3043	3450	RR 0.46 (95% CI: 0.38–0.56).	Very low
Mixed or unspecified timing of placement										
Perforation	4 studies, **1 new** (7 articles, **3 new**) *(12, 13, 17–21)*	3 Cohort 2 Case–control	Very serious [a]	Not serious	Not serious	Not serious	**Cohort, n = 70 831 (new, n = 64 186)** Case–control, n = 72	**Cohort, n = 85 434 (new, n = 30 631)** Case–control, n = 370	Cohort 1 year: RR 3.3 (95% CI: 1.6–6.7). Incidence/1000 women: 5.6 (BF) vs 1.7 (not-BF). **Perforation per 1000 insertions at 1 year: BF = 4.5 (95% CI: 3.0–6.4), not-BF = 0.6 (95% CI: 0.4–0.9), crude RR BF vs not-BF = 7.7 (95% CI: 4.6–12.9); relative perforation risk at 5 years: BF vs not-BF = 4.9 (95% CI: 3.0–7.8).** **Adjusted HR BF vs not-BF = 1.37 (95% CI: 1.12–1.66).** Case–control RR 10.1 (95% CI: 4.9–20.6).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									Percent 15.8% (BF) vs 3.2% (not-BF).	
Expulsion	**1 new** *(22)*	**Cohort**	**Serious** [j]	**Cannot assess**	**Not serious**	**Not serious**	**64 186**	**30 631**	**Adjusted HR in BF vs not-BF = 0.71 (95% CI: 0.64–0.78).**	**Very low**

Bold formatting indicates information from newly identified studies.

BF: breastfeeding; CI: confidence interval; Cu: copper; HR: hazard ratio; IUD: intrauterine device; OR: odds ratio; RR: relative risk.

[a] Risk of bias considered very serious due to high risks of selection bias, information bias and confounding.

[b] Inconsistency considered serious due to some varying results among studies.

[c] Imprecision considered serious due to no power calculations.

[d] Risk of bias considered very serious due to high risks of selection and information bias.

[e] Risk of bias considered very serious due to high risk of confounding.

[f] Imprecision considered very serious due to small samples and/or failure to meet power calculation.

[g] N for exposed vs unexposed unavailable for Hinz et al., 2019 *(15)*.

[h] Imprecision considered serious due to relatively wide confidence interval.

[i] Risk of bias considered very serious due to high risk of selection bias.

[j] Risk of bias considered serious due to moderate risk of selection and information biases.

GRADE table WA.3.2b Systematic review question 2: Among women who breastfeed, does the use of an IUD (either copper-bearing IUD [Cu-IUD] or LNG-releasing IUD [LNG-IUD]), as compared with the use of other contraceptive methods (either hormonal or nonhormonal) or no method, increase the risk of an adverse event?

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Cu-IUD vs implant, interval placement										
Removal for bleeding	2 *(23, 24)*	Cohort	Very serious [a]	Not serious	Serious [b]	Not serious	220	220	No significant differences between groups.	Very low
Haemoglobin levels	**1 new** *(25)*	**Cohort**	**Very serious[c]**	**Cannot assess**	**Very serious[d]**	**Not serious**	**60**	**60**	**No significant differences between groups (no numerical values reported).**	**Very low**
Adverse events	1 *(24)*	Cohort	Very serious [a]	Cannot assess	Very serious [d]	Not serious	100	100	No serious adverse events in either group.	Very low
Cu-IUD vs progesterone vaginal ring, interval placement										
Discontinuation or removals for bleeding	3 **(2 new)** *(26–28)*	**Cohort**	**Very serious[e]**	**Not serious**	**Serious [f]**	**Not serious**	486 **(new, n = 389)**	513 **(new, n = 413)**	0 (IUD) vs 3 (non-IUD) (*P* =0.048). **Cu-IUD (Cu T 200) = 1 in 794 woman-months of follow-up; PVR-6P = 0 in 301 woman-months of follow-up *(26)*; PVR-CHP = 1 in 438 woman-**	**Very low**

									months of follow-up *(26)*. **Cu-IUD (Cu T380A) = 1.8 per 100 woman-years; PVR = 0.4 per 100 at 1 year follow-up (NS).**	
Haemoglobin change	**1 new** *(29)*	**Cohort**	**Very serious** [g]	**Cannot assess**	**Serious** [h]	**Not serious**	**330**	**459**	**Haemoglobin change (mean): PVR = +0.3 g/dl; IUD = −0.3 g/dl (NS).**	**Very low**
Pelvic inflammatory disease (PID)	2 (**1 new)** *(28, 29)*	Cohort	Very serious [e]	Serious [i]	Serious [b, h]	Not serious	427 (new, n = 330)	559 (new, n = 459)	No PID among IUD users at 1 year follow-up. **PID (n, %): PVR = 2, 0.4%; IUD = 5, 1.5% at 1 year follow-up.**	Very low

Bold formatting indicates information from newly identified studies.

IUD: intrauterine device; NS: not significant; PID: pelvic inflammatory disease; PVR: progesterone vaginal ring.

[a] Risk of bias considered very serious due to high risk of confounding.

[b] Imprecision considered serious due to no power calculations.

[c] Risk of bias considered very serious due to high risks of selection bias and confounding.

[d] Imprecision considered very serious due to small samples and lack of power calculation.

[e] Risk of bias considered very serious due to high risks of selection bias, information bias and confounding.

[f] Imprecision considered serious due to smaller samples and/or lack of power calculation.

[g] Risk of bias considered very serious due to high risks of selection and information bias.

[h] Imprecision considered serious due to lack of power calculation for outcome.

[i] Inconsistency considered serious due to some varying results among studies.

GRADE table WA.3.2c Systematic review question 3: Among women who breastfeed, does the use of a copper-bearing IUD, as compared with the use of other nonhormonal methods or no method, increase the risk of adverse breastfeeding or infant outcomes?

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
Copper IUD vs non-hormonal contraception or no method, early postpartum placement or timing not specified										
Breastfeeding (BF) outcomes										
Continuation	1 (2 articles) *(30, 31)*	Cohort	Very serious [a]	Cannot assess	Serious [b]	Not serious	125	130	No significant differences at 3, 6 and 9 months. Discontinuation at 12 months: 34.7% (IUD) vs 40.7% (non-IUD); *P*-values not reported.	Very low
Duration	2 *(32, 33)*	Cohort	Very serious[c]	Not serious	Serious [b]	Not serious	190	2153	No significant differences in duration of any or exclusive BF; *P*-values not reported.	Very low
Supplementation	3 (**2 new)** *(34–36)*	Cohort	Very serious[c]	Not serious	Serious [d]	Not serious	322 **(new, n = 372)**	260 **(new, n = 210)**	No differences in number supplementing; *P*-values not reported. **No significant differences in number of supplementary**	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									feeds (data not shown). **Cu T inserted at 30 days postpartum: supplement (medical) = 29%; supplement (maternal) = 11%.** **Cu T inserted at 60 days postpartum: supplement (medical) = 36%; supplement (maternal) = 14%.** **Placebo: supplement (medical) = 26%; supplement (maternal) = 3%.**	
Exclusivity	**1 new** *(36)*	**Cohort**	**Very serious** [c]	**Cannot assess**	**Serious** [e]	**Not serious**	**256**	**130**	**Cu T inserted at 30 days postpartum, exclusive BF = 60%; Cu T inserted at 60 days postpartum, exclusive BF = 50%; Placebo,**	**Very low**

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									exclusive BF = 71%.	
Lack of milk secretion	**1 new** *(37)*	**Cohort**	**Very serious** [c]	**Cannot assess**	**Serious** [e]	**Not serious**	**109**	**143**	**IUD = 26 (24%); no contraception = 16 (11%).**	**Very low**
Infant outcomes										
Growth	5 studies (**2 new),** 6 articles (**2 new**) *(30–32, 34–36)*	Cohort	Very serious[c]	Not serious	Serious [e]	Not serious	619 **(new, n = 372)**	626 **(new, n = 210)**	No significant differences in weight at 2, 6 and 12 months or daily length; *P*-values not reported. **No significant differences in IUD vs control in weight or length at month 1, 2, 3, 4, 5 or 6.** **Average weight increase: Cu T at 30 days postpartum = 4801 g (SD 817); Cu T at 60 days postpartum = 4798 g (SD 546);**	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed or cases	No. patients: unexposed or controls	Effect	Certainty
									placebo = 4663 g (SD 529). **No significant differences in growth patterns of head circumference (data not shown).**	

Bold formatting indicates information from newly identified studies.

BF: breastfeeding; Cu: copper; IUD: intrauterine device; SD: standard deviation.

[a] Risk of bias considered very serious due to high risk of confounding.

[b] Imprecision considered very serious due to relatively small samples and lack of power calculation.

[c] Risk of bias considered very serious due to high risks of selection bias, information bias and confounding.

[d] Inconsistency considered serious due to some varying results among studies.

[e] Imprecision considered serious due to smaller samples and lack of power calculations.

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3.3 Concomitant use of hormonal contraceptives and antiretroviral drugs (ARVs): assessment of drug–drug interactions

Key questions:

1. Among women of reproductive age living with HIV, does concomitant use of hormonal contraception and antiretroviral therapy (ART) (a) reduce the effectiveness or (b) affect the safety of hormonal contraceptive use compared with hormonal contraceptive use and no ART?
2. Among women of reproductive age living with HIV, does concomitant use of hormonal contraception and ART (a) reduce the effectiveness or (b) affect the safety of ART use compared with ART use and no hormonal contraceptive use?
3. Among women of reproductive age at risk of HIV, does concomitant use of hormonal contraception and pre-exposure prophylaxis (PrEP) (a) reduce the effectiveness or (b) affect the safety of hormonal contraceptive use compared with hormonal contraceptive use and no PrEP?
4. Among women of reproductive age at risk of HIV, does concomitant use of hormonal contraception and PrEP (a) reduce the effectiveness or (b) affect the safety of PrEP use compared with PrEP use and no hormonal contraceptive use?

GRADE table WA.3.3 Systematic review questions 1–4

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Efavirenz (EFV)										
Implants: EFV vs NVP, other ART or no ART										
Pregnancy	**12 *(1–12)***	Observational	Very serious [a]	Serious	Not serious	Serious	13 666.2 person-years (py) 1114 subjects *Only person-years (py) presented for many studies* 290 subjects	824 subjects	ETG implant: EFV 6.8/100 py; no ART 5.6; NVP 3.1. LNG implant: EFV 9.2/100 py; no ART 4.6; NVP 2.86.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
							4451.6 py	9214.6 py	Unknown implant: EFV 0.4/100 py; no ART 5.2; NVP 4.4. Higher BMI/weight did not modify the relationship between EFV use and implant effectiveness. ETG implant: EFV vs NVP for EMR, chart review and phone: 2.1/100 py (95% CI: 1.6–2.8), 3.2 (1.4–7.3) and 4.3 (1.2–15.6). LNG implant: EFV vs NVP for EMR, chart review and phone: 3.3/100 py (95% CI: 1.6–6.9), 1.9 (0.9–	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									4.2) and 3.1 (1.6–5.9). aIRRs for protease inhibitors (PIs) and non-ART vs NVP not different. No significant interaction between pregnancy HR for EFV vs NVP and implant duration. Implant: EFV 6.4/100 py (95% CI: 5.1–8.1); NVP 6.4 (4.7–8.7); PI 0. ETG implant: EFV 10.0/100 py (95% CI: 7.2–13.8); NVP 8.7 (5.7–13.2). LNG implant: EFV 4.8/100 py (95% CI: 3.5–	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									6.6); NVP 4.8 (3.1–7.7). Implant: EFV 1/16.7 py (6.0/100 py); NVP 0/67.7 py (0); no ART 7/507.5 py (1.4). Implant: EFV 9/62 subjects (14.5%); non-EFV ART 0/86. Median duration between implant placement and pregnancy: 23 months (IQR: 16–29). LNG implant: EFV 1/8 subjects (12.5%); NVP 0/6; no ART 0/14. ETG implant: EFV 0/3 subjects; NVP	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									0/7; no ART 0/22. LNG implant: EFV 15/121 subjects (12.4%); NVP 0/208; LPV/r 0/18; no ART 1/223 (0.4%). LNG implant: EFV 0/30 subjects; no ART 0/12. LNG implant: EFV 1/26 subjects (3.8%) 16 weeks after implant insertion; LPV/r 0/26; ATV/r 0/22. LNG implant: EFV 3/20 subjects (15%) 1 at week 42 and 2 at week 48 visit; NVP 0/20; no ART 0/20.	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									9 potential hormonal contraceptive failures; 7 NVP and 1 EFV; no denominators.	
Ovulation	***3 (5, 13)***	Observational	Very serious [b]	Not serious	Serious	Very serious	151 53	98	300LNG implant + EFV: around week 48, 5/24 subjects (20.8%) had progesterone level at 4 weeks (P4) > 3 ng/ml (4 [16.7%] had P4 ≥ 5); 150LNG implant + no ART: around week 48, 0/9. 300LNG implant + EFV: around week 96, 4/12 subjects (33%) had elevated P4; all > 5; no comparison group.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									ETG implant: 2.8% of progestogen (P) samples in 15 EFV subjects had P4 > 4.7 ng/ml and 5% had P4 > 3 ng/ml (data not presented by subject); 0/15 in LPV/r or no ART groups had any P4 > 3 ng/ml. LNG implant: EFV: 2/14 (14%) samples had any P4 > 5 ng/ml; NVP: 1/20 (5%); no ART: 1/100 (1%). ETG implant: EFV: 3/8 (38%) samples; NVP: 0%; no ART: 1/100 (1%) had any P4 > 3 ng/ml;	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									2/8 EFV had P4 > 5 ng/ml.	
Bleeding	**1 *(14)***	Observational	Very serious [c]	Serious	Serious	Serious	15	45 30	ETG implant: EFV ↑ regular bleeding (71.5%, vs 21% non-ART vs 7% LPV/r, *P* = 0.001); LPV/r ↑ amenorrhoea (50% vs 36% non-ART vs 14.5% EFV, *P* = 0.001) and infrequent bleeding ↑ (36% vs 29% non-ART vs 7% EFV, *P* = 0.001); no differences in reported frequent or prolonged bleeding by ART groups.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Viral suppression	**3 *(9, 13, 15)***	Observational	Very serious [d]	Not serious	Serious	Serious *(CD4 count and viral RNA are surrogate markers for HIV progression/ death)*	159 62	97	LNG implant: no change in CD4 count between baseline and week 48 in EFV and NVP groups; 20/20 in EFV group had viral load (VL) < 400 copies/ml through final visit; 1/20 in NVP group had VL 17 935 copies/ml at week 48. LNG implant: 27 women in 300LNG+EFV group followed for 144 weeks; all had undetectable VLs from baseline throughout 144 weeks. ETG implant: EFV group:	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									14/15 had VL < 50 copies/ml at week 24; LPV/r group: 12/14 had VL < 50 at week 24.	
Injectables: EFV vs NVP, other ART, or no ART										
Pregnancy	4 *(3, 8, 16, 17)*	Observational	Very serious [e]	Not serious	Not serious	Serious [f]	108 *(23198.3 py)* *-0nly person years presented for some studies-*		DMPA: EFV 512/5001 py (10.2/100 py); NVP 940/10 827 (8.7/100); PI 142/1469 (9.7/100); no ART 553/5403 (10.2/100); EFV vs NVP not significant: IRR 1.1 (0.9–1.2), 1.0 (0.6–1.8) and 1.0 (0.3–2.9) for EMR, chart review, phone interview; aIRRs for pregnancy with PI and non-ART vs NVP also not	Very low
							44 *(5053.2 py)*	64 *(18145.1 py)*		

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									significantly different. Injectable: EFV 2/52.2 (3.8/100 py); NVP 8/245.6 (3.3/100); no ART 111/2100.5 (5.3/100). DMPA: EFV 0/27; NVP 0/1; no ART 0/10. DMPA: EFV 0/17; NVP 0/16; NFV 0/21; NRTI only or no ART 0/16.	
Ovulation	4 *(17, 18, 19)*	Observational	Very serious	Not serious	Not serious	Very serious	159 75	84	DMPA: EFV+ RIF: 0/42 P4 ≥ 1 ng/ml; NRTI only or no ART 0/16 (historical data from Cohn et al. *[17]*). DMPA: EFV 0/16 P4 > 3 ng/ml; no ART 1/17 at 12 weeks.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									DMPA: EFV 0/17 P4 > 1.6 ng/ml; NVP 0/16; NFV: 0/21; NRTI only or no ART: 0/16.	
Bleeding	2 *(17, 19)*	Observational	Very serious [g]	Not serious	Serious	Serious	103 33	70	DMPA: 16 EFV and 17 no ART subjects had no difference in number of bleeding/spotting episodes, average amount of bleeding, length of longest bleeding episode. DMPA: Abnormal bleeding occurred in EFV 3/17 (17.6%); NVP 3/16 (18.8%); NRTI or no ART 1/16 (6.3%); NFV 2/21 (9.5%) (*P* = 0.64).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Viral suppression	1 *(17)*	Observational	Very serious	Cannot assess	Serious	Serious (*CD4 count and viral RNA are surrogate markers for HIV progression/ death)*	70 17	53	DMPA: EFV (17 subjects), NVP (16); NFV (21); NRTI only or no ART (16). No significant changes in median CD4 count at weeks 4 and 12 when compared with baseline in all groups; most women in all groups had no changes in proportion with VL < 400 copies/ml.	Very low
OCs: EFV vs NVP, other ART or no ART										
Pregnancy	2 *(8, 20)*	Observational	Very serious	Serious	Not serious	Serious	1510.2 py 123.7 py	1386.5 py	OC: EFV 17/116 py (15.3/100 py; 95% CI: 8.2–22.5); NVP 45/451 (10.4; 7.4–13.4); no ART 29/268 (11.2; 7.0–15.3); LPV/r 4/32	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									(15.0; 0.45–29.6). OC: EFV 1/7.7 py (12.9/100 py); NVP 4/62.4 (6.4); no ART 63/573.1 (11.0).	
Ovulation	4 *(21–24)*	Observational	Very serious	Serious	Serious	Very serious [h]	78	139 61	COC: EFV 9/34 subjects (26.5%) P4 > 10.0 ng/ml ; no ART 3/15 (20%); OR 1.4 (95% CI: 0.33–6.31). COC: EFV 3/16 subjects (18.8%) P4 > 3.0 ng/ml; NVP 0/18 women P4 > 1.0 ng/ml. COC: 0/19 subjects had P4 > 1.25 ng/ml before or after use of EFV.	Very low
Combined contraceptive vaginal ring (CVR): EFV vs ATV/r or no ART										

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Ovulation	1 *(25)*	Observational	Very serious	Cannot assess	Serious	Very serious [i]	74 25	49	CVR: EFV 2/24 subjects (8.3%) P4 > 3 ng/ml on Day 14; 0/24 had P4 > limits of detection (LOD) on Day 21, and 0/24 had P4 > 3 ng/ml on Day 28; no ART 0/25 ever had P4 > LOD; ATV/r 0/24 ever had P4 > LOD at any time (ring used day 0–21).	Very low
Viral suppression	1 *(25)*	Observational	Very serious	Cannot assess	Serious	Serious [j]	56 28	28	CVR: EFV 1/28 subjects had VL > 1000 copies/ml on day 0 and detectable VL on day 21; ATV/r 1/28 had VL > 400 on day 21.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
EC (single and double dose): EFV vs RIF or DTG										
Pregnancy	1 *(26)*	Observational	Very serious	Cannot assess	Serious	Not serious	118 **52**	 **66**	EFV+LNG 1.5 mg 0/17; EFV+LNG 3 mg 0/35; DTG+LNG 1.5 mg 0/32; RIF+LNG 3 mg 0/34.	Very low
Nevirapine										
Implants vs non-hormonal contraception										
Viral suppression	1 *(27)*	Observational	Very serious	Cannot assess	Serious	Serious [j]	81 48	 33	CD4 counts for LNG implant and non-hormonal contraception rose slightly in both and did not differ between groups.	Very low
Injectables: NVP vs no ART										
Pregnancy	1 *(28)*	Observational	Very serious [k]	Cannot assess	Serious	Serious [l]	NA NA	 NA	90% started NVP; 589 pregnancies in 4531 women (7.8/100 py); higher pregnancy rate	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									in women taking ART (9.0/100 py) compared with women not on ART (6.5/100 py). Injectable users: pregnancy rates (per 100 py) 1.1 (95% CI: 0.6–1.9) before ART and 2.0 (1.3–3.0) after ART.	
DMPA vs non-hormonal contraception										
Viral suppression	1 *(29)*	Observational	Very serious [m]	Cannot assess	Serious	Serious [n]	845 *(visits not subjects)*		72 subjects completed ≥ 33 months follow-up; HIV RNA detectable at 113/671 (16.8%) visits without hormonal contraceptive exposure compared with 20/174 (11.5%) visits with	Very low
							174	671		

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									DMPA; no association between DMPA and HIV-1 RNA in multivariate analysis (OR 0.81, 95% CI: 0.47–1.39).	
OCs: NVP vs no ART or other ART										
Pregnancy	2 *(28, 30)*	Observational	Very serious [o]	Serious	Serious	Not serious	350 *(Sample sizes and denominators NA for Myer [28])*		COC: NVP group 10.0 per 100 py (95% CI: 4.6–19.1); no ART group 10.1 (4.6–12.1). 90% started NVP; 589 pregnancies in 4531 women (7.8/100 py); higher pregnancy rate in women taking ART (9.0/100 py) compared with women not on ART (6.5/100 py).	Very low
							172	178		

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									OC: pregnancy rates (per 100 py) 3.1 (95% CI: 1.5–6.2) before ART and 5.4 (95% CI: 2.9–10.0) after ART.	
Ovulation	2 *(30, 31)*	Observational	Very serious	Not serious	Not serious	Very serious [i]	345 171	174	COC: NVP group: 43/168 (26%) P4 > 3 ng/ml in cycle 1, 30/163 (18%) in cycle 2, 18/163 (11%) in both cycles; no ART group: 26/168 (15%) P4 > 3 ng/ml in cycle 1, 31/165 (19%) in cycle 2, 20/165 (12%) in both cycles; no significant difference in ovulation rates between groups. NVP 0 P4 > 3 ng/ml; no ART 0 P4 > 3 ng/ml.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Bleeding	1 *(30)*	Observational	Very serious	Cannot assess	Serious	Serious	350 172	178	COC: NVP group 12/172 (7.0%); no ART group 17/178 (9.6%) reported intermenstrual bleeding; NVP 2/172 (1.2%) and no ART: 2/178 (1.1%) reported menorrhagia.	Very low
Viral suppression	1 *(32)*	Observational	Very serious	Cannot assess	Very serious	Very serious [p]	10 10	10	NVP added to baseline ART; no change in VL or CD4 count on day 30 after NVP compared with baseline.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Darunavir (DRV)										
Implants: DRV vs no ART										
Pregnancy	1 *(33)*	Observational	Very serious	Cannot assess	Very serious [q]	Not serious	100 60	44	ETG DRV/r 0/30 pregnancies; no ART 0/20 pregnancies. LNG DRV/r 0/30 pregnancies; no ART 0/20 pregnancies.	Very low
Ovulation	1 *(33)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	104 58	33	ETG DRV/r 0/28 P4 > 3 ng/ml; no ART 0/17 P4 > 3 ng/ml. LNG DRV/r 1/28 P4 > 3 ng/ml at week 47; no ART 0/16 P4 > 3 ng/ml.	Very low
Viral suppression	1 *(33)*	Observational	Very serious	Cannot assess	Very serious	Serious [j]	60 (*Subjects served as own controls)* 60	60	No ART failures after starting ETG (N=30) or LNG implant (N=30).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
COCs: DRV vs no ART										
Ovulation	1 *(34)*	Randomized cross-over pharmacokinetics study	Very serious	Cannot assess	Very serious	Very serious [i]	22 (Own controls) 22	22	Measured only 17-OH progesterone at baseline and Day 14; all < 1 ng/ml.	Very low
Rilpivirine (RPV)										
Implants; RPV vs no ART										
Pregnancy	1 *(33)*	Observational	Very serious	Cannot assess	Very serious	Not serious	104 60	44	ETG RPV 0/30 pregnancies; no ART 0/20 pregnancies. LNG RPV 0/30 pregnancies; no ART 0/20 pregnancies.	Very low
Ovulation	1 *(33)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	104 30 LNG; 30 ETG	21 LNG, 23 ETG	ETG RPV 0/28 P4 > 3 ng/ml; no ART 0/17 P4 > 3 ng/ml. LNG RPV 1/26 P4 > 3 ng/ml at week 46; no ART 0/16 P4 > 3 ng/ml.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Viral suppression	1 *(33)*	Observational	Very serious	Cannot assess	Very serious	Serious [j]	60 (*Own controls*)		No ART failures after starting ETG (N=30) or LNG implant (N=30).	Very low
							60	60		
COCs: RPV vs no ART										
Ovulation	1 *(35)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	15		COC + RPV D14 P4 1.8 nmol/L (95% CI: 0.4–3.9); COC alone P4 1.7 nmol/L (95% CI: 0.5–4.1); no difference.	Very low
							15	15		
Ritonavir (RTV)										
COCs: RTV vs non-enzyme inducing ART or no ART										
Ovulation	1 *(36)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	15		COC RTV 5/5 P4 < 0.1 ng/ml; non-RTV or no ART 10/10 P4 < 0.1 ng/ml.	Very low
							5	10		

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Lopinavir/ritonavir (LPV/r)										
DMPA: LPV/r vs no ART										
Pregnancy	1 *(37)*	Observational	Very serious	Cannot assess	Very serious	Serious	24	38 14	DMPA: LPV/r 0/24 pregnancies; historical control 0/14 pregnancies.	Very low
Ovulation	1 *(37)*	Observational	Very serious	Cannot assess	Very serious	Very serious	24	38 14	DMPA: LPV/r 24/24 P4 ≤ 1.2 ng/ml; historical controls 14/14 P4 < 5 ng/ml.	Very low
Contraceptive patch: LPV/r vs no ART or NRTI only										
Ovulation	1 *(38)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	8	32 24	Patch: LPV/r median P4 0.39 ng/ml (n = 8), no ART median P4 0.47 ng/ml (n = 20); no difference.	Very low
Viral suppression	1 *(38)*	Observational	Very serious	Cannot assess	Very serious	Serious [j]	7	32 24	Patch: HIV-1 RNA in LPV/r (n = 7) were < 400 copies/ml at baseline and week 4;	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									NRTI/no ART 26% (6/23) and 30% (6/20) had baseline and week 4 HIV-1 RNA levels < 400 copies/ml, respectively; LPV/r median CD4 count increased by 15%; NRTI/no ART median CD4 count declined by 10%; change from baseline to week 4 significantly different between groups (*P* = 0.034).	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Cabotegravir (CAB)										
COCs: CAB vs no ART										
Ovulation	1 *(39)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	20 *(Subjects served as own controls.)*		COC+ CAB mean P4 < 6 ng/ml; COC alone mean P4 < 6 ng/ml.	Very low
							20	20		
Dolutegravir (DTG)										
COCs: DTG vs no ART										
Pregnancy	1 *(40)*	Randomized cross-over trial	Very serious	Cannot assess	Very serious	Serious	16 *(Subjects served as own controls)*		0 pregnancies before or after DTG.	Very low
							16	**16**		
Fostemsavir (FOS)										
COCs: FOS vs no ART										
Ovulation	1 *(41)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	20 *(Subjects served as own controls)*		COC + FOS 5% P4 > 3 ng/ml; COC alone (3.3–8.3%/cycle) P4 > 3 ng/ml.	Very low
							20	**20**		

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Tenofovir (TDF), tenofovir + emtricitabine (TDF-FTC)										
LNG implant: TDF/FTC vs placebo										
Pregnancy	2 *(42)*	RCT (secondary analysis)	Serious	Not serious	Serious	Not serious	29 (230.3 py) 17 (150.6 py)	12 (79.7 py)	LNG implant: TDF/FTC: 0/17; placebo 0/12 through 36 weeks. Implant: TDF/FTC: 1/150.6 py (0.7/100 py); placebo 0/79.7 py.	Low
Injectable: TDF/FTC vs placebo										
Pregnancy	2 *(42, 43)*	RCT (secondary analysis)	Serious	Not serious	Very serious	Serious	62 (884 py) 26 (564.3 py)	36 (319.7 py)	DMPA: TDF/FTC 7/26 (26.9%); placebo 5/36 (13.9%). Injectable: TDF/FTC: 29/564.3 py (5.1/100 py); placebo: 17/319.7 py (5.3/100 py).	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Ovulation	1 *(44)*	Observational	Very serious	Cannot assess	Very serious	Very serious [i]	12 (Subjects served as own controls) 12	12	DMPA+TDF/FTC: median progesterone 0.15 ng/ml (IQR: 0.09–0.27); DMPA alone: 0.14 ng/ml (IQR: 0.07–0.31); no difference.	Very low
PrEP efficacy	1 *(45)*	Observational	Serious [r]	Cannot assess	Not serious	Not serious	2323 901	1422	PrEP efficacy estimates for HIV-1 prevention, compared with placebo, were similar among women using DMPA and those using no hormonal contraception (64.7% and 75.5%, adjusted interaction $P = 0.65$).	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
TDF/FTC: DMPA vs no DMPA										
Bone mass density (BMD)	1 *(46)*	Observational	Very serious	Cannot assess	Serious	Serious	331 248	83	DMPA+TDF significantly ↑ BMD loss over 24 months vs TDF alone, with a decline of –2.677% for the lumbar spine, −2.518% for total hip, and –2.907% for femoral neck; $P < 0.0001$, after adjusting for age, BMI and baseline BMD.	Very low
OC: TDF, TDF/FTC vs placebo										
Pregnancy	2 *(42, 47)*	RCT (secondary analysis)	Serious	Not serious	Serious	Serious	643 py 380.4 py	262.6 py	COC: TDF/FTC 60/171.1 py (34.9, 95% CI: 26.7–45.0) vs placebo 43/153.9 py (incidence=27.9, 95% CI: 20.2–37.6), RR=1.3 (95% CI: 0.8–1.9).	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									OC: TDF/FTC 37/209.3 py (17.7/100 py); placebo 11/108.7 py (10.1).	
TDF, TDF/FTC: OC vs DMPA or no contraception										
Bone mass density (BMD)	1 *(48)*	Observational	Serious	Cannot assess	Very serious	Serious	73 71	2	Changes in BMD for women on either OCs (N=42) or injectables/implant (N=29) vs no contraception (N=2) not significant except for a positive effect of OCs on spine BMD for women on TDF/FTC.	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Dapivirine (DPV)										
Implants: DPV vs placebo										
Pregnancy	1 *(49)*	RCT (secondary analysis)	Not serious	Cannot assess	Serious	Not serious	893 458	435	Implant: DPV 1/458 py; placebo 3/435 py; adjusted HR 0.32 (95% CI: 0.03–3.10); 1/378 py with implant and DPV > 95 pg/ml vs 0/40 py for DPV < 95 pg/ml.	Low
DMPA: DPV vs placebo										
Pregnancy	1 *(49)*	RCT (secondary analysis)	Not serious	Cannot assess	Serious	Not serious	1066 512	554	DMPA: DPV 3 pregnancies/697 py; placebo 4/746 py; aHR 0.76 (95% CI: 0.16–3.52); 0 pregnancies with DMPA and DPV > 95 pg/ml vs 3 pregnancies/109 py with DPV < 95 pg/ml.	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
NET-EN: DPV vs placebo										
Pregnancy	1 *(49)*	RCT (secondary analysis)	Not serious	Cannot assess	Serious	Not serious	519 260	259	NET-EN: DPV 2/260 py; placebo 0/259 py; 1/178 py with NET-EN and DPV > 95 pg/ml vs 1/52 py with DPV < 95 pg/ml.	Low
OCs: DPV vs placebo										
Pregnancy	1 *(49)*	RCT (secondary analysis)	Not serious	Cannot assess	Serious	Not serious	276 136	140	OC: DPV 56/174 py; placebo 48/171 py; aHR 1.31 (95% CI: 0.87–1.99); 31/112 py with OC and DPV > 95 pg/ml vs 21/42 py with DPV < 95 pg/ml.	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
Etravirine (ETR)										
OCPs: ETR vs placebo										
Ovulation	1 *(50)*	Observational	Serious	Cannot assess	Very serious	Very serious [i]	24 (Subjects served as own controls)	24	COC+ETR P4 < 2.0 ng/ml; COC alone P4 < 2.0 ng/ml.	Very low
							24	24		
Combination ART (multiple ARVs within single study)										
ETG implant: PI-based ART vs other/non-ART										
Pregnancy	1 *(1)*	Observational	Serious	Cannot assess	Very serious	Not serious	56		NNRTI: 0/31; PI 0/25.	Very low
							31	25		
OC: PI vs NNRTI (EFV or NVP) or no NNRTI and no PI										
Pregnancy	1 *(51)*	Observational	Very serious	Cannot assess	Very serious	serious	88		OC: PI 8/33 (7/8 NFV); EFV 2/16; NVP 0/6; or other ART 0/33.	Very low
							33	55		
POP: Predominantly PIs vs non-ART										
Cervical mucus quality	3 *(52, 53, 54)*	Observational	Very serious	Not serious	Very serious	Very serious [s]	33		Cervical mucus scores in PI and non-PI groups similar after POPs: median score 3.5 for PI group and 4 for controls; score < 10	Very low
							16	17		

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									(unfavourable to sperm penetration): 81% of PI; 60% of controls.	
ART: LNG-IUD vs copper IUD										
Viral suppression	1 *(55)*	RCT	Not serious	Cannot assess	Serious	Serious	134 65	67	Detectable VL not significantly different between LNG-IUD and Cu-IUD at 6 months (aOR = 0.83, 95% CI: 0.37–1.86, *P* = 0.65) and 24 months (aOR = 0.94, 95% CI: 0.49–1.81, *P* = 0.85).	Very low
ART: Hormonal contraception (pooled or not specified) vs no hormonal contraception										
Viral suppression	2 *(56, 57)*	Observational	Very serious [t]	Not serious	Not serious	Serious	2416 254	2162	58% hormonal contraceptive users (n=38) and 64% of non-users (n=44) achieved undetectable VL after ART initiation	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									(*P* =0.529); duration of hormonal contraceptive use did not predict viral suppression (*P* = 0.765). Hormonal contraception not associated with VL change over time (*P* = 0.526, py not reported).	
ART: implants vs no hormonal contraception										
Viral suppression	1 *(58)*	Observational	Serious	Cannot assess	Serious	Serious	69	818 749	Implant use did not alter time to plasma viral suppression; aHR: implants vs no hormonal contraception 0.91 (95% CI: 0.68–1.23).	Very low
Viral suppression	1 *(59)*	RCT	Not serious	Cannot assess	Serious	Serious	114	259 135	In "as-randomized" analysis: time to reach viral	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									suppression did not differ between implant and Cu-IUD: HR 1.0 (95% CI: 0.6–1.4) for LNG implant versus the Cu-IUD group; findings similar in continuous use analysis.	
ART use: injectables vs no hormonal contraception										
Viral suppression	2 *(58, 60)*	Observational	Serious	Not serious	Not serious	Serious	262	1378 1116	No significant difference in time to viral suppression among ART initiators between injectables and non-hormonal contraception, aHR = 0.89 (95% CI: 0.75–1.09). No difference between injectables and	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									no use of injectables in composite virologic failure, failure to achieve virologic suppression, switch to second-line therapy, or death within 12 months, at 12 months follow-up (11% vs 12%, *P* =0.99).	
ART: DMPA vs no hormonal contraception										
Viral suppression	3 *(29, 46, 61)*	Observational	Very serious	Not serious	Not serious	Serious [u]	283 / 466	183	VL detectable at 20/174 (11.5%) visits exposed to DMPA vs 113/671 (16.8%) visits without hormonal contraception exposure; no association between DMPA and VL detection in	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									either univariate (OR 0.64, 95% CI: 0.39–1.03) or multivariate analysis adjusted for baseline VL, CD4 and ART adherence (AOR 0.81, 95% CI: 0.47–1.39). Among participants choosing DMPA at enrolment, 12 virally suppressed at enrolment of whom 10 (83%) remained suppressed with median 23 months follow-up; no significant change in CD4 cell count or viral suppression between DMPA	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									and non-hormonal contraception users. High proportions of virologic suppression were achieved in both groups on TDF (on DMPA-IM [90%] or non-hormonal contraceptives [94%]) at 12- and 24-month time points.	
Viral suppression	1 *(59)*	RCT (secondary analysis)	Not serious	Cannot assess	Not serious	Serious	268 133	135	Time to viral suppression faster among DMPA users vs Cu-IUD in "as-randomized" analysis (HR = 1.3, 95% CI: 0.9–2.0) and "as-treated" analysis	Low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									(HR=1.5, 95% CI: 1.0–2.3).	
ART: OC vs no hormonal contraception										
Viral suppression	2 *(58, 61)*	Observational	Very serious [v]	Not serious	Serious	serious	74	859 785	Women using OCs achieved viral suppression (aHR 1.33, 95% CI: 1.06–1.66) faster than comparators; 47 achieved suppression/13 py. Associations between hormonal contraception use and viral suppression did not differ by ART regimen. Among participants choosing COCs at enrolment, 23 were virally suppressed at enrolment of whom 20 (87%) remained	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. subjects exposed	No. subjects comparison	Effect	Certainty
									suppressed during follow-up.	

aHR: adjusted hazard ratio; ART: antiretroviral therapy; ATV/r: atazanavir/ritonavir; BMD: bone mass density; BMI: body mass index; CAB: cabotegravir; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; DPV: dapivirine; DRV: darunavir; DTG: dolutegravir; EFV: efavirenz; EMR: electronic medical record; ETG: etonogestrel; FTC: emtricitabine; IM: intramuscular; IQR: interquartile range; LNG: levonorgestrel; LPV/r: lopinavir/ritonavir; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; NVP: nevirapine; OCP: oral contraceptive pill; PI: protease inhibitors; py: person years; RCT: randomized clinical trial; RPV: rilpivirine; TDF: tenofovir disaproxil fumarate; VL: viral load.

[a] Very serious due to retrospective nature of electronic medical record (EMR) data for most studies, timing of implant initiation and adherence to implant or ART often not assessed, pregnancy outcome by self-report in participant chart, may have missed pregnancies from women seeking care elsewhere or misclassified pregnancies.

[b] Two thirds of the studies did not analyse data by participant; unclear if samples were equally collected in all groups; in 1 study, the comparator group was women without HIV using LNG implant; only 74% of double LNG dose completed 144 weeks, proportionately higher number of controls did not reach primary outcome point; study underpowered to compare P4.

[c] EFV group significantly older; women chose to use implant; 3 women removed (1/group) due to ART changes possible under-reporting in bleeding change; bleeding somewhat subjective, relies on participant report, some reported bleeding change may stem from knowing they were using implant; selected result reporting: report full cohort from parent pharmacokinetics study, this is sub-analysis.

[d] In 1 study, eligible women were those intending to initiate LNG implant anyway so they may be significantly different from the overall population of women living with HIV; in another study, only 74% of those in the double LNG dose group completed 144 weeks; ART use was self-reported.

[e] Very serious due to retrospective nature of EMR data for the largest study, adherence to contraceptive or ART often not assessed, pregnancy outcome by self-report in participant chart, may have missed pregnancies from women seeking care elsewhere.

[f] Pregnancy by self-report in the largest study; other studies too small to assess pregnancy.

[g] Studies too small to adequately assess bleeding, no bleeding diaries collected.

[h] Proxy of progesterone/presumed ovulation and healthy population in 1 study; infrequent progesterone measurement.

[i] Ovulation is a surrogate for pregnancy, and all studies evaluated presumed ovulation serum progesterone levels, which is a surrogate for ovulation itself.

[j] CD4 count and viral RNA are surrogate markers/measures for HIV progression/death.

[k] Unclear whether women were actually using contraceptives when pregnancy occurred; study not designed to look at pregnancy; self-reported pregnancy and contraceptive use.

[l] Self-reported pregnancy.

[m] Self-reported contraceptive and ART use; large loss to follow-up; 14% changed ART regimen; small number of women using DMPA.

[n] Viral load is a surrogate marker.

[o] For the Myer et al. study (2010), it is unclear whether women were actually using contraceptives when pregnancy occurred; study not designed to look at pregnancy; self-reported pregnancy and contraceptive use *(28)*.

[p] Viral load is a surrogate for HIV disease progression; follow-up too short to assess disease progression.

[q] Too small to adequately assess risk of pregnancy.

[r] DMPA provided at study site but unclear whether women all received at study site and contraception not required as part of trial, so DMPA and no hormonal contraception relied predominantly on participant self-report. TDF and TDF/FTC pooled together due to similar effect; no demographics provided between groups with or without DMPA stratification. Analysis in w-y so no clear reflection on retention. ARV levels not assessed for adherence.

[s] Mucus is a surrogate for risk of pregnancy that is even more remotely associated than ovulation.

[t] Chu et al. (2005): 65% of hormonal contraception users had discontinued method by 4th follow-up visit *(57)*.

[u] One population with established ART use, one of new initiates.

[v] Prospective cohort with women self-selecting contraceptive method; adherence is inconsistent based on pregnancy rate, though primary outcome was HIV progression. Less than 80% provided any follow-up data, especially in the ART-using arm.

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3.4 Use of emergency contraceptive pills (ECPs) more than once in a menstrual cycle

GRADE table WA.3.4 Key question 1: Does taking ECPs repeatedly, compared with taking a single dose of ECPs in a single cycle increase the risk of pregnancy and/or adverse events?

Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Certainty
Levonorgestrel (LNG) ECPs										
Ectopic pregnancy (EP)	1 *(1)*	Case–control	Serious [a]	Cannot assess[d]	Serious [i]	Not serious	EP: 2411	Intrauterine pregnancy (IUP): 2416; no pregnancy: 2419.	aOR (95% CI): EP vs IUP: 2.5 (1.0–6.2), 14% vs 5%*; EP vs no pregnancy: 3.1 (1.1–8.7), 14% vs 5%*.	Very low
Adverse events	1 *(2)*	NRT, single arm	Very serious [c,f,g]	Cannot assess[d]	Very serious[e]	Not serious	330	NA	SAE: 3 (2.9%)	Very low
Adverse pregnancy/ neonatal outcomes	1 *(3)*	Cohort	Very serious [a,b,c]	Cannot assess[d]	Very serious[e]	Serious [f]	33	268	No differences in outcomes.[+]	Very low
Adverse infant/child outcomes	1 *(4)*	Cohort	Very serious [a,b,c]	Cannot assess[d]	Very serious[e]	Serious [f]	19	172	No differences in outcomes.[+]	Very low
Ulipristal acetate (UPA) ECPs										

Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Certainty
Adverse events	1 *(5)*	RCT	Very serious [j]	Cannot assess[d]	Very serious[e,k]	Serious [h]	8 (10 mg) 8 (20 mg) 8 (50 mg)	8	SAE: 0 (0%) Mild/moderate adverse events: UPA 10 mg: 37.5%; 20 mg: 50.0%; 50 mg: 62.5%; placebo: 62.5%.	Very low
Adverse events	1 *(6)*	NRT, non-comparative	Very serious [c,g]	Cannot assess[d]	Very serious[e,k]	Not serious	11 (q5d arm) 12 (q7d arm)	NA	SAE: 0 Abnormal labs: 0; Abnormal EMB: 0.	Very low

aOR: adjusted odds ratio; CI: confidence interval; EMB: endometrial biopsy; NA: not applicable; NRT: non-randomized trial; RCT: randomized controlled trial; SAE: severe adverse effect.

* Event rates (ectopic pregnancy, intrauterine pregnancy, no pregnancy) among those with repeated LNG ECP use.

+ No statistical testing reported for comparisons by LNG dose; no statistically significant difference in outcomes in LNG-exposed vs non-exposed groups.

[a] Unclear or inadequate assessment/definition of the exposure.

[b] Unclear or inadequate comparison group.

[c] Crude estimates only in at least 1 study or important confounders not included in multivariable analysis.

[d] Inconsistency cannot be assessed because there is only 1 study; overall certainty was rated down 1 level for inconsistency.

[e] No CIs or other measures of precision reported.

[f] Indirect outcome; pregnancy and infant/child outcomes among ECP users with contraceptive failure.

[g] Response rate < 80% or inadequate information about participant recruitment.

[h] Indirect exposure; not a standard dose or regimen of ECP.

[i] Wide CIs, some of which contain both beneficial and harmful effects, or other measures of precision.

[j] Inadequate information about allocation, randomization, blinding.

[k] Small total sample size, or sample size not reported.

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3.5 Inflammatory bowel disease (IBD)

GRADE table WA.3.5a IBD: disease activity or relapse

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
Ulcerative colitis (UC)											
Oral contraceptives (OCs)											
UC relapse (increase in symptoms leading to changes in medical treatment or surgery)	1 *(1)*	Cohort	Very serious[a,b,c,d]	Cannot assess[e]	Not serious	Not serious	74	173	Current OC use vs never use: cHR = 1.9, 95% CI: 1.4–2.7. Findings were no longer statistically significant in the multi-variable model (numeric results not reported).	Not reported	Very low
Time to UC relapse	2 *(1, 2)*	Cohort	Very serious[a,b,c,d,f]	Not serious	Very serious[g,h]	Not serious	Study 1 (S1): 74 Study 2 (S2): Not reported	S1: 173 S2: Not reported	S1: % with relapse (95% CI) Before 2 years: OC users: 55% (48–61%);	S1: see Effect column S2: Not reported	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									never users: 36% (27–45%). Before 5 years: OC users: 77% (67–86%); never users: 51% (41–60%). Before 10 years: OC users: 86% (79–94%); never users: 59% (50–69%). S2: Current OC use vs never OC use: cHR = 2.1, CIs not reported, *P* > 0.05.		
Number of UC relapses during follow-up period	1 *(1)*	Cohort	Very serious[a,b,c,d,f]	Cannot assess[e]	Not serious	Not serious	74	173	Current OC use vs never use: cHR = 1.5, 95% CI: 1.2–1.8.	Not reported	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
First UC-related surgery	1 *(3)*	Cohort	Serious[d,f]	Cannot assess[e]	Serious [g]	Not serious	572	2628	Current OC use vs never use: aHR = 0.79, 95% CI: 0.52–1.18. The risk of UC-related surgery did not appear to increase with longer duration of OC use (*P*-value for trend = 0.28) or higher number of DDDs of OC use (*P*-value for trend = 0.70).	Incident rates per 100 000 person-years: Current OC users: 495; never users: 527.	Very low
First prescription for oral steroids at least 90 days after start of follow-up	1 *(3)*	Cohort	Serious[d,f]	Cannot assess[e]	Serious [g]	Not serious	572	2628	Current OC use vs never use: aHR = 0.94, 95% CI: 0.71–1.26. The risk of receiving an	Incident rates per 100 000 person-years: Current OC users: 1039; never	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									oral steroid prescription did not increase with longer duration of OC use (*P*-value for trend = 0.68) or with higher number of DDDs of OC use (*P*-value for trend = 0.63).	users: 1347.	
First prescription for anti-TNF at least 90 days after start of follow-up	1 *(3)*	Cohort	Serious [d,f]	Cannot assess[e]	Serious [g]	Not serious	572	2628	Current OC use vs never use: aHR = 0.83, 95% CI: 0.59–1.18. The risk of receiving anti-TNF therapy did not increase with longer duration of OC use (*P*-value for trend = 0.97)	Not reported	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									or with higher number of DDDs of OC use (*P*-value for trend = 0.98).		
Crohn's disease											
Oral contraceptives (OCs)											
CD relapse (increase of CDAI, development of new abscess or fistula, or need for corticosteroids or hospitalization)	2 *(4, 5)*	Cohort	Very serious[a, c,d,f]	Not serious	Very serious[g]	Not serious	162	244	S1: OC use vs non-users: cHR = 1.11, 95% CI: 0.80–1.55. S2: Current OC use vs never use: aHR = 1.7, 95% CI: 0.7–3.4.	S1: CD relapse: OC use: 46%; non-use: 43%. S2: CD relapse: OC use: 43%; never use: 27%.	Very low
CD relapse (need for surgery)	2 *(6, 7)*	Cohort	Very serious[a, b,c,d,f,j]	Not serious	Very serious[h,i]	Not serious	42	81	S1: No statistically significant differences in CD relapse comparing OC use with non-use in bivariate S2: CD relapse rates: Overall (*P* > 0.05): OC users: 34%; non-	S1: Not reported	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									analysis (data not shown).	users: 53%.	
									S2: OC use was not associated with CD relapse compared with non-use in multi-variable Cox proportional hazard modelling (data not shown).	5 years ($P > 0.05$): OC users: 25% (95% CI: 7–43%); non-users: 28% (95% CI: 7–43%). 10 years ($P > 0.05$): OC users: 41% (95% CI: 2–80%); non-users: 64% (95% CI: 41–88%).	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
Time to CD relapse	2 *(4, 8)*	Cohort	Very serious[a, b,c,d,f]	Not serious	Serious[g]	Not serious	185	197	S1: Median time to relapse: OC users: 484 days (SD = 30 days); non-users: 504 days (SD = 41 days). S2: Mean time to first relapse: OC users: 24.2 months (SD = 26.7); non-users: 32.9 months (SD = 38.0).	S1: See Effect column S2: See Effect column	Very low
Median CDAI during relapse	1 *(4)*	Cohort	Very serious[c, d,f]	Cannot assess[e]	Very serious[h]	Not serious	134	197	Median CDAI during relapse did not differ between OC users (246) and non-OC users (241).	See Effect column	Very low
First CD-related surgery	1 *(9)*	Cohort	Serious[d ,f]	Cannot assess[e]	Serious[g]	Not serious	28/12 382 person-months	420/230 491 person-months	Current OC use vs never use: aHR = 1.30,	Incident rates per 100 000 person-	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									95% CI: 0.89–1.92. The risk of CD-related surgery increased with longer duration of OC use (*P*-value for trend = 0.036) and higher number of DDDs of OC use (*P*-value for trend = 0.016). The risk of CD-related surgery increased with longer duration of COC use (*P* = 0.041) and POP use (*P* > 0.50). For every 1 year of COC use, the risk of CD-related	months: Current OC users: 22.6; never users: 18.2.	

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									surgery increased by nearly 30% (aHR = 1.29, 95% CI: 1.05–1.57).		
First prescription for oral steroids after CD diagnosis	1 *(9)*	Cohort	Serious[d,f]	Cannot assess[e]	Serious[g]	Not serious	25/14 225 person-months	405/268 059 person-months	Current OC use vs non-use: aHR = 1.09, 95% CI: 0.73–1.64. The risk of receiving an oral steroid prescription did not increase with longer duration of OC use (*P*-value for trend = 0.88) or with higher number of DDDs of OC use (*P*-value for trend = 0.20).	Incident rates per 100 000 person-months: Current OC users: 17.6; never users: 15.1.	Very low
Progestin-containing IUDs											

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
First CD-related surgery	1 *(9)*	Cohort	Serious[d,f]	Cannot assess[e]	Serious[i,g]	Not serious	Not reported	Not reported	Progestin-containing IUD use vs never use: aHR = 0.98, 95% CI: 0.69–1.40.	Not reported	Very low
First prescription for oral steroids after CD diagnosis	1 *(9)*	Cohort	Serious[d,f]	Cannot assess[e]	Serious[i,g]	Not serious	Not reported	Not reported	Progestin-containing IUD vs never use: aHR = 1.03, 95% CI: 0.71–1.60.	Not reported	Very low
IBD (CD and UC combined)											
Hormonal contraceptives											
IBD symptoms	1 *(10)*	Cohort	Serious[c]	Cannot assess[e]	Serious[g,i]	Not serious	17	54	Hormonal contraceptive use vs no use: aOR = 0.16, 95% CI: 0.02–0.90.	% with IBD symptoms over 1 year: Hormonal contraceptive use: 71%; no use: 94%.	Very low
Flares	1 *(10)*	Cohort	Serious[c]	Cannot assess[e]	Very serious[g,i]	Not serious	17	54	Hormonal contraceptive use vs no use:	% with flare over 1 year:	Very low

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
									aOR = 0.53, 95% CI: 0.14–1.93.	Hormonal contraceptive use: 59%; no use: 65%.	
Inflammation	1 *(10)*	Cohort	Serious[c]	Cannot assess[e]	Serious[g,i]	Not serious	17	54	Hormonal contraceptive use vs no use: aOR = 5.71, 95% CI: 1.23–43.63.	% with inflam-mation over 1 year: Hormonal contraceptive use: 88%; No use: 63%.	Very low

aHR: adjusted hazard ratio; cHR: crude hazard ratio; CD: Crohn's disease; CDAI: Crohn's disease activity index; CI: confidence interval; COC: combined oral contraceptive pill; DDD: defined daily dose; HR: hazard ratio; IUD: intrauterine device; NS: not significant; OC: oral contraceptive; POP: progestin-only pill; S1: Study 1; S2: Study 2; SD: standard deviation; TNF: tumor necrosis factor; UC: ulcerative colitis.

[a] Response rate < 80%.

[b] High loss to follow-up (> 20%).

[c] Unclear or inadequate assessment/definition of the exposure.

[d] Unclear or inadequate comparison group.

[e] Inconsistency cannot be assessed because there is only 1 study; overall certainty was rated down 1 level for inconsistency.

[f] Crude estimates only in at least 1 study or important confounders not included in multivariable analysis.

[g] Wide CIs, some of which contain both beneficial and harmful effects, or other measures of precision.

[h] No CIs or other measures of precision reported.

[i] Small total sample size, or sample size not reported.

[j] Unequal follow-up periods for groups.

GRADE table WA.3.5b IBD: other adverse health outcomes

Outcome	No. studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	No. patients: exposed	No. patients: comparison	Effect	Absolute event rates	Certainty
Oral contraceptives (OCs)											
Venous thrombo-embolism (VTE)	2 *(11, 12)*	Cohort	Very serious[a, b,c,d]	Not serious	Very serious[e]	Not serious	Study 1 (S1): Not reported (total sample 627) Study 2 (S2): 372	S1: Not reported (total sample 627) S2: 8664	S1: OC and VTE: cOR = 1.53, 95% CI: 0.38–6.2. Ulcerative colitis: 0 VTEs in OC users (VTE in non-users not reported). S2: DVT during 90 days since hospital admission for IBD: aOR = 0.57, 95% CI: 0.21–1.53; *P* = 0.26 for OC use vs non-use. Pulmonary embolism during 90 days since hospital	S1: Not reported S2: Not reported	Very low

									admission for IBD: aOR = 2.56, 95% CI: 0.75–8.75; *P* = 0.14 for OC use vs non-use.		
Abnormal cervical smear results	1 *(13)*	Cohort	Very serious[b,c,d,f]	Cannot assess[g]	Very serious[h]	Not serious	77	262	No statistically significant differences in abnormal cervical smear results in IBD patients by OC use *(P* = 0.106).[i]	See effect column	Very low

aOR: adjusted odds ratio; cOR: crude odd ratio; CI: confidence interval; DVT: deep vein thrombosis; OR: odds ratio.

[a] No information on response/recruitment rate.

[b] No information on loss to follow-up.

[c] Unclear or inadequate assessment/definition of the exposure.

[d] Unclear or inadequate comparison group.

[e] Wide CIs that contain both beneficial and harmful effects.

[f] Low response rate.

[g] Inconsistency cannot be assessed because there is only 1 study; overall certainty was rated down 1 level for inconsistency.

[h] No CIs or other measures of precision reported.

[i] See supplementary data table for this effect:

OC use	**Normal**	**Low grade dysplasia**	**High grade dysplasia**
Current	66/77 (85.7%)	4/77 (5.2%)	7/77 (9.1%)
Never	38/47 (80.9%)	8/47 (17.0%)	1/47 (2.1%)
Previous	184/215 (85.6%)	16/215 (7.4%)	15/215 (7.0%)

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