Part I

Development of the
Medical eligibility criteria for contraceptive use,
fifth edition

1.1 Background

1.1.1 Overview and scope of the guidelines

Over the past 40 years, there have been significant advances in the development of new contraceptive technologies, including changes in formulations and dosing, schedules for administration and novel delivery systems. However, current policies and health-care practices in some countries are based on scientific studies of contraceptive products that are no longer in wide use, on long-standing theoretical concerns that have never been substantiated or on the personal preference or bias of service providers. These outdated policies or practices often result in limitations to both the quality of, and the access to, family planning services for clients.

The goal of this document is to improve access to, and quality of, family planning services by providing policy-makers, decision-makers and the scientific community with recommendations that can be used for developing or revising national guidelines on medical eligibility criteria used in the provision of all hormonal contraceptives, intrauterine devices, barrier methods, fertility awareness-based methods, coitus interruptus, lactational amenorrhoea method, male and female sterilization, and emergency contraception. These evidence-based recommendations do not indicate a "best" method that *should* be used given 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 characteristics (e.g. age).

Because country situations and programme environments vary so greatly, it is inappropriate to set firm international guidelines on criteria for contraceptive use. However, it is expected that national programmes will use these recommendations for updating or developing their own contraceptive eligibility guidelines according to national health policies, needs, priorities and resources, while reflecting upon local values and preferences.

There are a total of four WHO guidance documents (cornerstones) pertaining to contraception; two that focus on evidence-based recommendations (primarily targeted towards policy-makers and programme managers) and two that focus on application of the recommendations (primarily targeted towards health-care providers). All four cornerstones are best interpreted and used in a broader context of reproductive and sexual health care. These four documents, listed below, are updated periodically to reflect changes in the medical and scientific knowledge.

Evidence-based recommendations for provision of contraception:

1. *Medical eligibility criteria for contraceptive use* (MEC) – provides guidance regarding "who" can use contraceptive methods safely; and

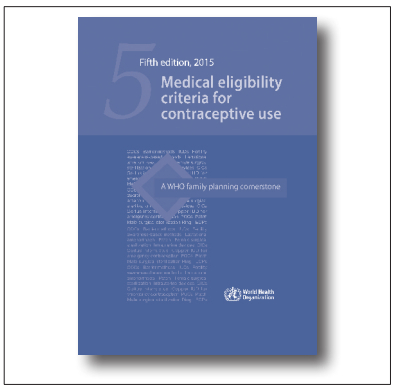
2. *Selected practice recommendations for contraceptive use* (SPR) – provides guidance regarding "how" to use contraceptive methods safely and effectively.

Practical tools for front-line providers of contraceptive counselling and services:

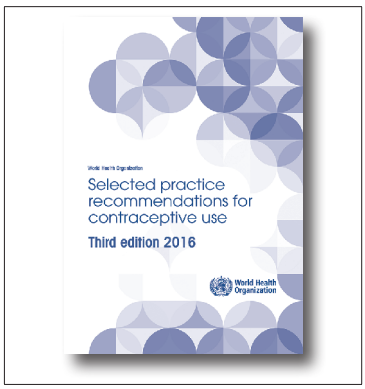
3. *Decision-making tool for family planning clients and providers* – counselling tool that supports both provider and client in the process of choosing a contraceptive method; and

4. *Family planning: a global handbook for providers* – offers evidence-based information on service delivery, method by method.

Figure 1. The four cornerstones of family planning guidance



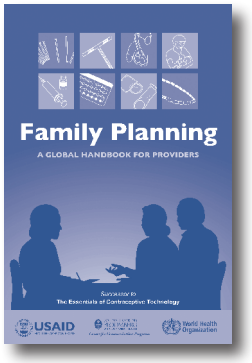
Medical eligibility criteria for contraceptive use



Selected practice recommendations for contraceptive use

These are evidence-based guidance and consensus-driven guidelines. They provide recommendations made by expert working groups based on an appraisal of relevant evidence. They are reviewed and updated in a timely manner.

Decision-making tool for family planning clients and providers



Family planning: a global handbook for providers

These are tools that incorporate the *Medical eligibility criteria*, the *Selected practice recommendations* and other consensus recommendations on how to meet the needs of the family planning client. They will be updated as the guidelines are updated or as other evidence warrants.

Process for assuring that the guidelines remain current:

1. Identify new, relevant evidence as soon as it becomes available through an ongoing comprehensive bibliographic search.
2. Critically appraise the new evidence.
3. Evaluate the new evidence in light of prior evidence.
4. Determine whether the newly synthesized evidence is sufficient to warrant an update of existing recommendations.
5. Provide electronic updates on WHO's reproductive health web site (www.who.int/reproductivehealth) as appropriate and determine the need to convene an expert working group to reassess guidelines formally.

1.2 Methods

1.2.1 Development of earlier editions of the *Medical eligibility criteria for contraceptive use*

This document builds on a process initiated in 1994 to develop the first edition. The initial process involved comparing the eligibility criteria used by different agencies for various contraceptives, preparing summaries of published medical and epidemiological literature relevant to medical eligibility criteria, and preparing a draft classification for review by a larger group of experts and agencies. Two expert Working Group meetings were organized by WHO, in March 1994 and May 1995, to review the background classifications and to formulate recommendations; publication of the document followed in 1996.

Since the publication of the first edition of the MEC, the guideline has been revised and updated three times. With each revision, a Working Group of multidisciplinary experts was assembled to review newly published evidence pertaining to the topics addressed in the guideline. Moreover, with each revision, the Working Group used the opportunity to consider inclusion of new medical conditions and new contraceptive methods, as appropriate.

The second edition of the MEC was based on the recommendations of an expert Working Group meeting held at WHO on 8–10 March 2000, which brought together 32 participants from 17 countries, including representatives of many agencies and organizations. The Working Group reviewed new evidence since the last meetings in 1994 and 1995, primarily obtained from systematic reviews of the most recent literature.

The third edition of the MEC, was based on the recommendations of an expert Working Group meeting held at WHO on 21–24 October 2003, which gathered 36 participants from 18 countries, including representatives of many agencies and organizations. Systematic reviews of the evidence were prepared on topics with newly published evidence since the meeting in 2000; they were presented to the Working Group and provided the basis for their decision-making. A Guideline Steering Group (GSG), comprising seven external members, was established for this edition. The GSG was formed to advise WHO on behalf of the larger expert Working Group on matters related to emerging published evidence on topics covered by the guideline during interim periods between expert Working Group meetings.

The fourth edition of the MEC was based on the recommendations of an expert Working Group meeting held at WHO on 1–4 April 2008, which brought together 43 participants from 23 countries, including nine agency representatives. Eighty-six new recommendations were developed and 165 recommendations were revised for the fourth edition. All members of the expert Working Group were asked to declare any conflict of interest and three of the experts declared conflicts of interest relevant to the subject matter of the meeting. These conflicts of interest were determined not to be sufficient to preclude the experts from participating in the deliberations and development of recommendations and thus they were not asked to withdraw from this process.

The Guidelines Review Committee (GRC) was established by the Director-General of WHO in 2007 to ensure that WHO guidelines are of a high methodological quality and are developed through a transparent, evidence-based decision-making process. The fourth edition of the MEC was reviewed by the newly established GRC and was approved on 16 September 2009.

To assure that the guidelines remain current between guideline meetings, new evidence is identified through an ongoing comprehensive bibiliographic search (the Continuous Identification of Research Evidence, or CIRE system)[1]. This evidence is synthesized and reviewed. In circumstances where new evidence warrants further evaluation, the GSG is tasked with evaluating such evidence and issuing interim guidance if necessary. Since the release of the fourth edition of the MEC, interim guidance has been issued twice. At the request of the GSG, WHO first convened a technical consultation on 26 January 2010 via teleconference to review new evidence regarding the risk of venous thromboembolism (VTE) in postpartum women. The teleconference brought together members of the GSG and three experts on VTE during the postpartum period. All participants in the consultation were asked to declare any conflict of interest; two participants declared a conflict of interest relevant to the subject matter, but they were not asked to withdraw from the process of recommendation formulation because the WHO Secretariat and GSG did not find these conflicts of interest sufficient to preclude them from participating in the deliberations and development of recommendations. The GRC approved the updated recommendations on 21 April 2010.

1 Mohllajee AP, Curtis KM, Flanagan RG, Rinehart W, Gaffield ML, Peterson HB. Keeping up with evidence: a new system for WHO's evidence-based family planning guidance. Am J Prev Med. 2005;28(5):483–90.

Following new findings of epidemiological studies regarding the use of hormonal contraception and HIV acquisition, progression and transmission, a second technical consultation was convened by WHO during 31 January – 1 February 2012. The meeting involved 75 individuals representing a wide range of stakeholders. Through a consensus-driven process, the group considered whether recommendations in the MEC pertaining to hormonal contraceptive use among women at high risk of HIV or women living with HIV should be changed in light of the accumulating evidence. All participants in the consultation were asked to declare any conflict of interest; 13 participants declared an academic conflict of interest relevant to the subject matter of the meeting. These conflicts of interest were determined not to be sufficient to preclude them from participating in the deliberations and development of recommendations and so they were not asked to withdraw from this process. The GRC approved the technical statement presenting the conclusions and updated recommendations of the meeting on 15 February 2012.

1.2.2 Development of the *Medical eligibility for criteria for contraceptive use, fifth edition*

In preparation for the fifth edition of the document, both approval for the planning and ultimately the final document were obtained from the GRC. Several key aspects of the updating process were adjusted to be in closer alignment with requirements set forth in the *WHO handbook for guideline development,* authored by the GRC Secretariat.[2] Specifically, these alterations included:

- creation of groups with varying roles to undertake the revision;
- convening an additional consultation to define the scope of the revision, giving priority to controversial topics and those for which new evidence had emerged, including topics addressed in interim guidance, clarifying recommendations with a Category 2/3 classification, and drafting questions relating to population, intervention, comparator and outcome (PICO questions) to guide the preparation of systematic reviews; and
- applying the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach to evidence review and recommendation formulation.[3]

The groups responsible for the development of the fifth edition of the MEC included: a WHO Secretariat; an Evidence Secretariat including a GRADE methodologist; a Guideline Steering Group (GSG); and a Guideline Development Group (GDG), which was formerly called the expert Working Group for the earlier MEC editions. The GSG, which has served as an external advisory group to WHO on family planning guidelines since 2003, was part of the larger GDG, to be compliant with WHO requirements for guideline development and to gain input from a larger advisory group. For a summary of the members of the WHO Secretariat, the Evidence Secretariat and the GDG, see the Acknowledgements at the beginning of this document.

1.2.3 Prioritization of topics for the revision process

On 14–15 May 2013, the first GDG meeting convened in Ferney Voltaire, France, to initiate the revision process for the development of the fifth edition of the MEC. Prior to the meeting, the CIRE system[1] was used to identify recommendations from the fourth edition of the MEC for which new evidence was available.

To further inform decision-making with respect to clinical questions and priorities, the WHO Secretariat reached out to a broad group of stakeholders with expertise in family planning and familiarity with the guideline, including individuals from a number of implementing agencies, professional societies, and WHO regional and country offices, as well as the Ministry of Health in each of the Member States. They were asked to voluntarily complete an electronic 24-question anonymous survey available in English, French and Spanish, and to forward the link for the survey to others in their professional communities familiar with family planning and the MEC during the period 2 March – 2 May 2013. The respondents were asked to rank the importance of various outcomes pertaining to topics that had been identified as priority questions for the current revision, as well as to suggest other outcomes and clinical questions of importance, and to give input regarding the format of the guidance. More than 250 individuals submitted completed surveys; these results were presented to the GDG during the meeting to inform the prioritization process.

At the meeting, the WHO Secretariat presented brief summaries of new evidence to the GDG to determine whether the existing recommendation remained consistent or had become inconsistent with the updated body of evidence. Recommendations considered to be possibly inconsistent with the updated body of evidence were selected for presentation and discussion at a larger meeting convened in March 2014. Recommendations considered to be consistent with the updated body of evidence, and recommendations for which no new evidence had been identified through CIRE were

2 The first edition was published in 2012, the second edition in 2014.

3 For further information on GRADE, see: www.gradeworkinggroup.org/index.htm

determined by the GDG to need no further review during the revision process.

Also at this first GDG meeting, the members were asked to consider whether WHO should include several new conditions, contraceptive methods and/or formulations of methods, based upon their global relevance and availability in multiple countries. Participants were also asked to review the two interim guidance documents released since the fourth edition. Further, during this meeting the GDG was asked to address current recommendations which were classified as category "2/3" in the fourth edition, as earlier reviews by the GRC noted that these recommendations may be confusing to users of the document.

Thus, topics were prioritized for review and consideration by the GDG at the second meeting in March 2014 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; topics with interim guidance issued by WHO since the MEC fourth edition; newly introduced contraceptive methods; or recommendations from the MEC fourth edition that were determined to lack clarity by the GRC. All existing recommendations that did not fall into one of these categories were reaffirmed by the GRC and thus were not reviewed.

Table 1.1 Medical eligibility criteria for contraceptive use, fifth edition: selection of topics for 2014 revision

Prioritized topics reviewed by the Guideline Development Group (GDG) using the GRADE process in 2014:
1. **Topics identified as important to the field and/or topics with new, potentially inconsistent evidence identified (6 topics):** • progesterone-only contraceptive (POC) use among breastfeeding women • combined hormonal contraceptive (CHC) use among breastfeeding women • CHC use among women with superficial venous disorders • CHC use by age group • hormonal contraceptive use among women using antiretroviral therapy • emergency contraceptive pill (ECP) use among women with obesity (new condition added to ECP recommendations).
2. **Interim guidance issued by WHO since the MEC fourth edition (2 topics):** • CHC use during the postpartum period (guidance updated in 2010) • hormonal contraceptive use among women at high risk of HIV acquisition and women living with HIV (guidance reaffirmed in 2012).
3. **New contraceptive methods added to the MEC for the fifth edition (4 methods):** • subcutaneously-administered depot medroxyprogesterone acetate (DMPA) 104 mg • 2-rod levonorgestrel (LNG)-containing implant with 75 mg LNG/rod, approved for 4 years of use, i.e. Sino-implant (II) • progesterone-releasing vaginal ring (PVR) • ulipristal acetate (UPA) for emergency contraception.
4. **Recommendations reviewed by the GDG for clarity, as required by the Guidelines Review Committee (GRC) (2 topics):** • intrauterine device (IUD) use among women with increased risk of sexually transmitted infections (STIs) (no new evidence identified since 2008 systematic review) • CHC use among women with known dyslipidaemias.
All other existing recommendations from the MEC fourth edition (approximately 2000 recommendations):[a] • reaffirmed by the GDG in March 2014.

CIRE: Continuous Identification of Research Evidence; GRADE: Grading Recommendations, Assessment, Development and Evaluation.

[a] Evidence continuously monitored using CIRE system. Topics not prioritized for 2014 update.

For the topics outlined in Table 1.1, the GDG developed questions using the PICO format (i.e. questions with specified populations, interventions, comparators and outcomes) to serve as the framework for the systematic reviews and GRADE evidence tables. In order to inform the MEC recommendations, PICO questions generally guide the systematic review to focus on studies of populations with the condition or characteristic of interest using a specific contraceptive method compared with the same population not using the method, reporting on critical safety outcomes. PICO questions were also crafted to also identify relevant indirect evidence that may have included comparator populations without the condition or characteristic of interest using the same method, or reporting on surrogate outcomes. These systematic reviews, therefore, assessed the safety risks of using a given method among women with a particular medical condition or characteristic. The remainder of the existing recommendations were determined to be consistent with the body of published evidence and did not need to be formally reviewed for this revision.

1.2.4 Evidence identification and synthesis

For each of the priority topics listed in Table 1.1, systematic reviews were conducted in accordance with PRISMA guidelines to answer PICO-formatted questions regarding safety outcomes.[4] The systematic reviews may be accessed in Annex 2. In general, the PubMed and Cochrane databases were searched for studies published in any language in a peer-reviewed journal up to 15 January 2014, to inform the systematic reviews. Reference lists and direct contact with experts in the field were also used to identify other studies, including those in press; neither grey literature nor conference abstracts were included in these reviews. Due to heterogeneity of study designs, contraceptive formulations and outcome measures, meta-analyses were generally not performed. The quality of evidence presented in individual studies within a systematic review was assessed by review authors using the United States Preventive Services Task Force system.[5] GRADE evidence profiles were then prepared by a GRADE methodologist to assess the quality of the summarized evidence and include the range of the estimates of effect for each clinical outcome assessed. GRADE evidence profiles were prepared for each PICO question for which evidence was found and clinical outcomes were reported. The systematic reviews that resulted from this process were peer-reviewed by selected members of the GDG, and final drafts were made electronically available to all GDG members prior to the consultations. Printed copies of GRADE evidence profiles for each topic were also given to each GDG member during the March 2014 GDG meeting. The written and orally presented systematic reviews and GRADE evidence profiles served as the basis for the GDG's deliberations.

1.2.5 Decision-making during the Guideline Development Group meetings

During 9–12 March 2014 and 24–25 September 2014, WHO convened a series of GDG meetings to review the evidence for the priority topics and, where appropriate, revise specific recommendations in the MEC. Members of the GDG and members of the External Peer Review Group (who did not participate in the GDG meeting) submitted Declaration of Interest forms to the WHO Secretariat: 14 individuals declared an academic conflict of interest relevant to the MEC guidance. The WHO Secretariat and the GDG reviewed all declarations of interest and, with the exception of two members (Dr Glasier and Dr Sitruk-Ware), found no conflicts of interest sufficient to preclude anyone from participating in the deliberations or development of recommendations. In the case of the two exceptions, the WHO Secretariat and the GDG agreed that their disclosed academic conflicts of interest were sufficient to preclude them from participating in the deliberations and development of recommendations relevant to ulipristal acetate (Dr Glasier) and the progesterone-releasing vaginal ring (Dr Sitruk-Ware). For details of the declared academic interests see Annex 1.

The GDG considered the overall quality of the safety evidence, paying particular attention to the strength and consistency of the data, according to the GRADE approach to evidence review. 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. To arrive at a category designation, within the range 1–4, the GDG considered these potential harms, the GRADE evidence profiles, the benefits of preventing unintended pregnancy, as well as the other GRADE constructs of values and preferences.

The GDG endorsed an approach to patient preferences and values that prioritized the availability of a wide range of contraceptive options, as women vary in their preferences regarding contraceptive selection and in the value they place

4 Moher D, Liberati A, Tetzlaff J, Altman DG; The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med. 2009;6(6):e1000097.

5 Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21–35.

on different beneficial and harmful outcomes.[6 7] In addition, the availability of a range of contraceptive options is critical because a woman's contraceptive choices are made at a particular time and in a particular societal and cultural context, and these choices are complex, multifactorial and subject to change.[8 9] Decision-making for contraceptive methods usually requires making trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Owing to the focus of this guidance on the safety of specific contraceptive methods for women with medical conditions or personal characteristics, opportunity costs were not formally assessed during the formulation of these recommendations since costs may vary widely throughout different regions.[10]

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. These categories are well known by health-care providers, professional organizations, training institutions and ministries of health as the basis for determining contraceptive eligibility for women with medical conditions or characteristics. As a result, to avoid confusion and retain consistency, it was determined that recommendations would not be defined as "strong" or "weak" 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 the majority of the existing recommendations using the categories 1–4. For the topics they reviewed in 2014 (see Box 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.

Owing to the public health importance of recommendations on hormonal contraceptive use for women at risk of HIV and women living with HIV, and based on encouragement from the GDG, WHO issued its contraceptive eligibility guidance for women living with HIV or at high risk of acquiring the infection in advance of the entire guideline revision. The document, *Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statement* was approved by the WHO Guidelines Review Committee (GRC) on 7 July 2014. The statement was released on 24 July 2014, at the 20th International AIDS Conference.

A draft version of the entire MEC document was sent to the External Peer Review Group, comprising eight experts who did not participate in the GDG meeting. Comments received from these reviewers were addressed and incorporated into this guidance by the WHO Secretariat as appropriate. The final version of this document was approved by the GRC on 18 March 2015.

1.3 Dissemination and evaluation of the *Medical eligibility criteria for contraceptive use, fifth edition*

The recommendations in the *Medical eligibility criteria for contraceptive use, fifth edition* guidance were released during a global live Facebook Chat on 1 June 2015. A comprehensive dissemination and evaluation plan will be implemented, which will include widespread dissemination through the WHO regional and country offices, WHO Member States, the United Nations (UN) agency cosponsors of the Special Programme of Research, Development and Research Training in Human Reproduction (HRP) within the WHO Department of Reproductive Health and Research (i.e. UNDP, UNFPA, UNICEF, WHO and the World Bank), WHO collaborating centres, professional organizations, governmental and nongovernmental partner organizations working in the area of sexual and reproductive health, and civil society groups engaged in sexual and reproductive health projects The WHO Secretariat will work closely with sexual and reproductive health points of contact in the WHO regional offices to conduct a series of regional events during 2015–2016. In addition, special panel sessions will be organized during the summer and autumn of 2015 at international conferences convened by the International Society of Obstetricians and Gynaecologists (FIGO), the International Council of Nurses (ICN) and the International

6 Madden T, Secura GM, Nease RF, Politi MC, Peipert JF. The role of contraceptive attributes in women's contraceptive decision making. Am J Obstet Gynecol. 2015;pii: S0002-9378(15)00107–6. [Epub ahead of print]

7 Hooper DJ. Attitudes, awareness, compliance and preferences among hormonal contraception users: a global, cross-sectional, self-administered, online survey. Clin Drug Investig. 2010;30(11):749–63.

8 d'Arcangues CM, Ba-Thike K, Say L. Expanding contraceptive choice in the developing world: lessons from the Lao People's Republic and the Republic of Zambia. Eur J Contracept Reprod Health Care. 2013;18:421–34.

9 Blanc A, Tsui AO, Croft TN, Trevitt JL. Patterns and trends in adolescents' contraceptive use and discontinuation in developing countries and comparisons with adult women. Int Perspect Sex Reprod Health. 2009;35(2):63–71.

10 Singh S, Darroch JE. Adding it up: costs and benefits of contraceptive services – estimates for 2012. New York (NY): Guttmacher Institute and United Nations Population Fund (UNFPA); 2012 (https://www.guttmacher.org/pubs/AIU-2012-estimates.pdf, accessed 24 March 2015).

Confederation of Midwives (ICM) to update the membership of these societies about the revised recommendations. Once translations of the document in other official languages of the UN become available, opportunities to ensure effective dissemination will be actively sought. An evaluation survey targeting ministries of health, WHO offices and partners, professional organizations and civil society will be fielded to assess the extent and effectiveness of the dissemination, evaluate the level of implementation of the guidance into national policies, and identify areas for further refinement and research gaps in contraceptive eligibility criteria.

1.4 Reviewed recommendations

The Guideline Development Group (GDG) determined priority topics to be addressed as part of the revision process for the fifth edition (see Table 1.1).

Information on using the recommendations in practice, as well as recommendations in the fifth edition (new, revised and confirmed) are presented in Part II, sections 2.3 and 2.7, starting on p. 91. A summary of changes between the fourth edition of the MEC and the updated fifth edition is available in Part II (see section 2.6 and Tables 2.4–2.6, pp. 93–96).

1. Recommendations for combined hormonal contraceptives by age group

Question 1: Are women who use combined hormonal contraceptives (CHCs) at increased risk for fracture compared with women who do not use CHCs? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women of reproductive age
Intervention	CHC use
Comparator	Non-use of CHCs
Outcome	Fracture
Databases searched	PubMed and Cochrane Library

Question 2: Are women who use combined hormonal contraceptives (CHCs) at increased risk for decreased bone mineral density compared with women who do not use CHCs, with a specific focus on adolescents? (Indirect evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women of reproductive age (with a specific focus on adolescents)
Intervention	CHC use
Comparator	Non-use of CHCs
Outcome	Decreased bone mineral density
Databases searched	PubMed and Cochrane Library

Recommendations

- Women from menarche to < 40 years of age can use combined hormonal contraceptives (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) without restriction (MEC Category 1).
- Women 40 years and older can generally use combined hormonal contraceptive methods (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 2).

Remarks

- In 2014, the GDG focused specifically on the evidence pertaining to fracture risk among women of all ages, and the evidence for combined hormonal contraceptives (CHCs) and potential for decreased bone mineral density (BMD) among adolescents. BMD is a surrogate marker for fracture risk that may not be valid for premenopausal women, and therefore may not accurately predict current or future (postmenopausal) fracture risk *(1–3)*. The risk of cardiovascular disease increases with age and may also increase with CHC use. In the absence of other adverse clinical conditions, CHC can be used until menopause.
- Due to heterogeneity of study designs, contraceptive formulations and outcome measures a meta-analysis was not performed.
- CHCs 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, male or female, is recommended.

- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

Evidence is inconsistent on the question of whether CHC use affects fracture risk *(4–15)*, although three recent studies show no effect *(4, 5, 15)*. CHC use may decrease BMD in adolescents, especially in those choosing very-low-dose formulations (< 30 µg ethinylestradiol-containing combined oral contraceptives) (16–29). CHC use has little to no effect on BMD in premenopausal women *(30–44)*, and may preserve bone mass in those who are perimenopausal *(45-54)*.

Quality of the evidence

(intervention versus comparator; outcome)

CHC use versus non-use of CHC; fracture risk (direct):	low
COC use versus non-use in adolescents; bone mineral density (indirect):	low
Combined contraceptive patch use versus non-use in adolescents; bone mineral density (indirect):	very low

GRADE table 1 (Question 1): Are women who use combined hormonal contraceptives (CHCs) at increased risk for fracture compared with women who do not use CHCs? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Oral combined hormonal contraceptive use vs non-use								
Fracture	3 cohort studies (n=128 255); 7 case-control studies (n=84 695 cases)	Serious limitations (1 good, 6 fair, 3 poor)	Serious inconsistency	No serious imprecision	Serious indirectness (no study specifically evaluated CHC use during adolescence)	No duration-response effect observed	Low	7 studies showed no association between CHC use and fracture risk, including 1 good-quality study (OR 1.05, 95% CI 0.86–1.29); 3 studies found a statistically significant but weak association (risk estimate range 1.07–1.3)[a]

CI: confidence interval; OR: odds ratio.
a Six studies evaluated any fracture, two studies hip fracture, two studies forearm fracture.

GRADE table 2 (Question 2): Are women who use combined hormonal contraceptives (CHCs) at increased risk for decreased bone mineral density compared with women who do not use CHCs, with a specific focus on adolescents? (Indirect evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Oral combined hormonal contraceptive use vs non-use in adolescent women								
Bone mass density (BMD)	1 RCT (n=83), 1 non-randomized trial (n=84); 11 cohort studies (n=3242)	Serious limitations (2 good, 5 fair, 6 poor)	Serious inconsistency	No serious imprecision	Serious indirectness (intermediate outcome)	1 study showed duration-response effect; variability in duration of follow-up	Low	9 studies showed oral CHC use associated with less BMD gain (or greater loss) than non-use, including the 2 good-quality studies; 4 studies showed no difference[a]
Patch use vs non-use in adolescent women								
BMD	1 non-randomized trial (n=10)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	Serious indirectness (intermediate outcome)	None	Very low	1 study found no effect of patch on BMD vs non-use

RCT: randomized controlled trial.
a Eight studies evaluated 30–35mcg ethinyl estradiol (EE) formulation (one 30–40mcg EE), six studies 15–20mcg EE, two not specified.

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2. Recommendations for combined hormonal contraceptives among breastfeeding women

Question 1: Among breastfeeding women, does initiation of combined hormonal contraceptives (CHCs) at < 6 weeks postpartum have negative effects on breastfeeding outcomes or infant outcomes, compared with no contraception or non-hormonal contraception? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Breastfeeding women
Intervention	Use of CHCs
Comparator	No contraception or use of non-hormonal contraception
Outcome	Breastfeeding outcomes (duration, exclusivity, supplementation) Infant outcomes (growth, health, development)
Databases searched	PubMed and Cochrane Library

Question 2: Among breastfeeding women, does initiation of combined hormonal contraceptives (CHCs) at ≥ 6 weeks postpartum have negative effects on breastfeeding outcomes or infant outcomes, compared with no contraception or non-hormonal contraception? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Breastfeeding women
Intervention	Use of CHCs
Comparator	No contraception or non-hormonal contraception
Outcome	Breastfeeding outcomes (duration, exclusivity, supplementation) Infant outcomes (growth, health, development)
Databases searched	PubMed and Cochrane Library

Recommendations

- Breastfeeding women < 6 weeks postpartum should not use combined hormonal contraceptives (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 4).
- Breastfeeding women ≥ 6 weeks to < 6 months postpartum (primarily breastfeeding) generally should not use CHCs (MEC Category 3).
- Breastfeeding women ≥ 6 months postpartum can generally use CHCs (MEC Category 2).

Remarks

- Due to heterogeneity of study designs, contraceptive formulations and outcome measures, a meta-analysis was not performed.
- Combined hormonal contraceptives (CHCs) 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

Clinical studies demonstrate conflicting results regarding effects on breastfeeding continuation or exclusivity in women exposed to combined oral contraceptives (COCs) during lactation. No consistent effects on infant growth or illness have been reported *(1–6)*. Adverse health outcomes or manifestations of exogenous estrogen in infants exposed to CHCs through breast-milk have not been demonstrated; however, studies have been inadequately designed to determine whether a risk of either serious or subtle long-term effects exists.

Quality of the evidence
< 6 weeks postpartum:
(method; outcome)

For COCs compared with progestogen-only pills (POPs), breastfeeding and infant outcomes:	low
For COCs compared with non-hormonal or non-use, breastfeeding continuation:	very low
For COCs compared with non-hormonal or non-use, breastfeeding duration:	very low
For COCs compared with non-hormonal or non-use, supplementation:	low
For COCs compared with non-hormonal or non-use, infant outcomes:	very low
For patch, ring, combined injectable contraceptives (CICs):	no evidence

≥ 6 weeks postpartum:
(method; outcome)

For COCs, breastfeeding continuation:	low
For COCs, breastfeeding duration:	very low
For COCs, breastfeeding episodes:	very low
For COCs, supplementation:	low
For COCs, infant outcomes:	low
For patch, ring, CICs:	no evidence

GRADE table 1 (Question 1): Among breastfeeding women, does initiation of combined hormonal contraceptives (CHCs) at < 6 weeks postpartum have negative effects on breastfeeding outcomes or infant outcomes, compared with no contraception or non-hormonal contraception? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Combined oral contraceptives (COCs) vs progestogen-only pills initiated at < 6 weeks postpartum								
Breastfeeding continuation	1 RCT (n=127)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	Not applicable	Low	Ethinyl estradiol (EE) vs POP (1 RCT): 64% vs 64%, RR 1.0 (95% CI 0.78–1.3) at 8 weeks; 44% vs 41%, RR 1.1 (95% CI 0.71–1.6) at 6 months
Use of supplementation	1 RCT (n=127)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	Not applicable	Low	EE vs POP (1 RCT): no difference at 8 weeks (data not provided)
Infant growth	1 RCT (n=127)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	Not applicable	Low	EE vs POP (1 RCT): no difference in percent change in weight ($P = 0.56$), length ($P = 0.41$), or head circumference ($P = 0.79$) from weeks 2–8
COCs initiated at < 6 weeks postpartum vs non-hormonal or non-use								
Breastfeeding continuation	1 RCT; 2 non-randomized studies (n=550)	Very serious limitations (1 fair-quality RCT; 2 poor-quality studies)	Serious inconsistency	No serious imprecision	Serious indirectness (older COC formulations with mestranol)	Variability in outcomes assessed and duration of follow-up	Very low	1 RCT found EE COC associated with lower likelihood of breastfeeding continuation vs placebo or Cu-IUD at 6 months (84% vs 91% vs 95%, RR 0.92 [95% CI 0.82–1.0] vs placebo and 0.88 [95% CI 0.79–0.97] vs IUD) but no difference at 12 months (61% vs 59% vs 65%); 1 poor-quality study of various COCs found no difference in breastfeeding continuation at 6 weeks; 1 poor-quality study found initiation of mestranol at 2 weeks associated with lower likelihood vs initiation at 6 weeks (RR 0.40, 95% CI 0.17–0.96) or non-use (RR 0.29, 95% CI 0.13–0.64)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Breastfeeding duration	1 cohort study (n=696)	Very serious limitations (1 poor)	Cannot determine (1 study)	No serious imprecision	Serious indirectness (older estrogen component of COC formulations)	None	Very low	Various COCs (quinestrol, EE or mestranol) vs no COC (1 study): 2.5 to 4.6 vs 5.3 months, $P = 0.01$ for quinestrol and mestranol vs no COC
Use of supplementation	2 RCTs (n=727)	Serious limitations (1 fair, 1 poor)	No serious inconsistency	Serious imprecision	Serious indirectness (largest study [n=451] evaluated mestranol COC)	Variability in duration of follow-up	Low	1 fair-quality RCT found EE COC associated with increased likelihood of supplementation vs injectable placebo (19.4% vs 7.8%, RR 2.5 [95% CI 1.1–5.4]) or oral placebo (19.4% vs 8.0%, RR 2.4 [95% CI 1.0–5.8]) at day 91; 1 poor-quality RCT found mestranol COC associated with increased likelihood (12.3% vs 3.4%, RR 3.6 [95% CI 1.7–8.1]) at day 8
Infant growth	3 RCTs (n=712); 3 observational studies (n=100)	Very serious limitations (1 fair-quality RCT; 5 poor-quality studies)	Serious inconsistency	No serious imprecision	Serious indirectness (most studies evaluated mestranol COC)	Variability in outcomes assessed and duration of follow-up	Very low	1 fair-quality RCT found EE COC associated with lower infant weight at 6 months (7864 vs 8333) and 1 year (9938 vs 10 746) vs placebo; 4 poor-quality studies of mestranol COC reported conflicting results vs placebo or no COC (1 study no difference, 1 study growth greater with COC, and 2 studies less weight gain with COC)

CI: confidence interval; COC: combined oral contraceptive; EE: ethinyl estradiol; IUD: intrauterine device; POP: progestogen-only pill; RCT: randomized, controlled trial; RR: relative risk.

GRADE table 2 (Questions 2): Among breastfeeding women, does initiation of combined hormonal contraceptives (CHCs) at > 6 weeks postpartum have negative effects on breastfeeding outcomes or infant outcomes, compared with no contraception or non-hormonal contraception? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Combined oral contraceptive (COC) initiated at ≥ 6 weeks postpartum vs non-hormonal or non-use								
Breastfeeding continuation	2 non-randomized studies (n=339)	Serious limitations (2 fair)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	2 non-randomized studies found no difference between ethinyl estradiol (EE) COC vs non-COC (various) in breastfeeding continuation rates at 6 or 12 months (RR 0.96–0.99 in both studies)
Duration of breastfeeding	1 cohort study (n=96)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	1 cohort study found no difference between EE COC vs no oral contraceptives in duration of breastfeeding (3.7 vs 4.6 months, $P < 0.05$)
Breastfeeding episodes	1 cohort study (n=20)	Serious limitations (1 fair)	Cannot determine (1 study)	Very serious imprecision	No indirectness	None	Very low	1 small study found EE COC associated with more breastfeeding episodes than IUD on 7 of 21 days from postpartum day 42 to day 63 with no differences on other days
Use of supplementation	3 non-randomized studies; 1 cohort study (n=359 plus 1 study with < 50 women)	Serious limitations (3 fair, 1 poor)	Serious inconsistency	Serious imprecision	No indirectness	None	Low	2 fair-quality non-randomized studies found EE COC associated with increased likelihood of use of supplementation vs non-COC (various) at 3–12 months (differences ranged from 10–25% at various time points); 1 cohort study found no difference; 1 study found no difference between mestranol COC and IUD in age at supplementation
Infant growth	2 non-randomized studies; 3 cohort studies (n=455 plus 1 study with < 50 women)	Serious limitations (3 fair, 1 poor)	Serious inconsistency	Serious imprecision	No indirectness	None	Low	1 cohort study found EE COC associated with lower infant growth vs non-COC (various) from 3–4 months (599 vs 708 g) but not at 5–6 months and no difference in mean weight at 1 year; 1 non-randomized study found no difference in change in weight at 12–16 or 20–24 weeks; 1 non-randomized study found mestranol COC 0.1 mg with more infant growth than 0.075 mg or IUD; 1 cohort study found no difference in infant growth through 8 years; 1 cohort study showed no difference between EE COC and IUD from day 42 to 63

COC: combined oral contraceptive; EE: ethinyl estradiol; IUD: intrauterine device; RR: relative risk.

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3. Recommendations for combined hormonal contraceptives among postpartum women

Question 1: Among postpartum women, does combined hormonal contraceptive (CHC) use increase risk of venous thromboembolism (VTE) compared with no CHC use? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Postpartum women
Intervention	CHC use
Comparator	Non-use of CHCs
Outcome	VTE
Databases searched	PubMed and Cochrane Library

Question 2: Among women of reproductive age, do postpartum women have increased risk of venous thromboembolism (VTE) compared with non-postpartum, non-pregnant women? (Indirect evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women of reproductive age
Intervention	Postpartum
Comparator	Non-postpartum, non-pregnant
Outcome	VTE
Databases searched	PubMed and Cochrane Library

Recommendations

- Women who are < 21 days postpartum and do not have other risk factors for venous thromboembolism (VTE) generally should not use combined hormonal contraceptives (CHCs) (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 3).
- Women who are < 21 days postpartum with other risk factors for VTE should not use CHCs (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 4). For women ≤ 42 days postpartum with other risk factors for VTE, such as immobility, transfusion at delivery, BMI > 30 kg/m^2, postpartum haemorrhage, immediately post-caesarean delivery, pre-eclampsia or smoking, use of CHCs may pose an additional increased risk for VTE.
- Women who are 21–42 days postpartum and do not have other risk factors for VTE can generally use CHCs (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 2). Women who are 21–42 days postpartum with other risk factors for VTE generally should not use CHC methods (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 3). For women ≤ 42 days postpartum with other risk factors for VTE, such as immobility, transfusion at delivery, BMI > 30 kg/m^2, postpartum haemorrhage, immediately post-caesarean delivery, pre-eclampsia or smoking, use of CHCs may pose an additional increased risk for VTE.
- Women who are > 42 days postpartum can use CHC methods (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) without restriction (MEC Category 1).

Remarks

- The Guideline Development Group (GDG) considered the balance of benefits and harms for CHC use among postpartum women, at different time points postpartum, and with and without other risk factors for VTE, including the risk of VTE in the postpartum period, the risks associated with rapid repeat pregnancy, the benefits of preventing rapid repeat pregnancy, and the availability of other contraceptive methods that are safe for use by postpartum women. The GDG also considered that risk of pregnancy during the first 21 days postpartum is very low, but increases after that time in non-breastfeeding women; ovulation before first menses is common *(1).*
- Due to heterogeneity of study designs, contraceptive formulations and outcome measures, a meta-analysis was not performed.
- CHCs 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the

right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

One study examined use of CHCs during the postpartum period and found that VTE rates were higher for CHC users compared with non-users at all time points postpartum. Rates were significantly different only after 13 weeks postpartum, but the numbers needed to harm were lowest in the first 6 weeks postpartum *(2)*. VTE risk is elevated during pregnancy and the postpartum period; this risk is most pronounced in the first 3 weeks after delivery, declining to near baseline levels by 42 days postpartum *(3–7)*.

Quality of the evidence
(intervention versus comparator; outcome)

CHC use versus non-CHC use postpartum; VTE (direct):	very low
First 6 weeks postpartum versus non-pregnant, non-postpartum; VTE (indirect):	low

GRADE table 1 (Question 1): Among postpartum women, does combined hormonal contraceptive (CHC) use increase risk of venous thromboembolism (VTE) compared with no CHC use? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
CHC use vs non-use in postpartum period								
Venous thromboembolism (VTE)	1 cohort study (773 017 person-years)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	VTE (1 study): rate ratio 1.3 (95% CI 0.3–5.2) in weeks 0–6 for CHC use vs non-use; incidence 4.9 (95% CI 0.6–18) vs 3.5 (95% CI 3.1–3.9) per 1000 person-years in weeks 0–6 and 0.7 (95% CI 0.3–1.6) vs 0.3 (95% CI 0.2–0.5) per 1000 person-years in weeks 7–13

CI: confidence interval.

GRADE table 2 (Question 2): Among women of reproductive age, do postpartum women have increased risk of venous thromboembolism (VTE) compared with non-postpartum, non-pregnant women? (Indirect evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
First 6 weeks postpartum vs non-pregnant, non-postpartum								
Venous thromboembolism (VTE)	4 cohort studies (n=3 365 650); 1 case-control study (285 cases)	Serious limitations (1 good, 4 fair)	No serious inconsistency (direction consistent; variability in magnitude)	No serious imprecision	Serious indirectness (not women using CHC vs not using CHC)	Duration-response effect in first 6 weeks, first 1–3 weeks associated with highest risk;[a] weeks 0–6 associated with higher risk than after week 7[b]	Low	Any VTE (2 studies): rate ratio 21.5 (CI not available) and 22 (95% CI 18–27) and OR 84 (95% CI 32–223) and 12 (95% CI 7.9–18.6) DVT (1 study): incidence ratio 15 (95% CI 13–18) Pulmonary embolism (1 study): incidence ratio 9.2 (95% CI 6.5–13)

CI: confidence interval; OR: odds ratio.
a Based on 5 studies, 4 of which reported incidence by week and 1 of which reported the proportion of VTE events by week.
b Based on 6 studies.

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4. Recommendations for combined hormonal contraceptives among women with superficial venous disorders

The disease nomenclature has been updated to reflect current recognized standard terminology and more accurately describe the condition and sub-conditions. The overall name of the condition has been changed to "superficial venous disorders". The subcondition "superficial thrombophlebitis" has been changed to "superficial venous thrombosis" (SVT).

Question 1: Among women with varicose veins, does use of combined hormonal contraceptives (CHCs) increase the risk of venous thromboembolism (VTE) or superficial venous thrombosis (SVT) compared with non-use of CHCs? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women with varicose veins
Intervention	Use of CHCs
Comparator	Non-use of CHCs
Outcome	VTE or SVT
Databases searched	PubMed and Cochrane Library

Question 2: Among women with superficial venous thrombosis (SVT), does use of combined hormonal contraceptives (CHCs) increase the risk of venous thromboembolism (VTE) compared with non-use of CHCs? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women with SVT
Intervention	Use of CHCs
Comparator	Non-use of CHCs
Outcome	VTE
Databases searched	PubMed and Cochrane Library

Recommendations

- Women with varicose veins can use combined hormonal contraceptives (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) without restriction (MEC Category 1).
- Women with superficial venous thrombosis (SVT) can generally use combined hormonal contraceptives (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 2). SVT may be associated with an increased risk of venous thromboembolism (VTE).

Remarks

- Due to heterogeneity of study designs, contraceptive formulations and outcome measures, a meta-analysis was not performed.
- CHCs 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

One study suggested that among women with varicose veins, the rate of VTE and SVT was higher in oral contraceptive users compared with non-users; however, statistical significance was not reported and the number of events was small *(1)*. One study demonstrated that among women with SVT, the risk of VTE was higher in oral contraceptive users compared with non-users *(2)*.

Quality of the evidence

Women with varicose veins:
(intervention versus comparator; outcome)

Use of CHCs versus non-use of CHCs; risk of VTE:	very low
Use of CHCs versus non-use of CHCs; risk of SVT:	very low

Women with superficial venous thrombosis:
(intervention versus comparator; outcome)

Use of CHCs versus non-use of CHCs; risk of VTE:	very low

GRADE table 1 (Question 1): Among women with varicose veins, does use of combined hormonal contraceptives (CHCs) increase the risk of venous thromboembolism (VTE) or superficial venous thrombosis (SVT) compared with non-use of CHCs? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Use of oral contraceptives vs non-use in women with varicose veins								
Deep vein thrombosis (DVT)	1 cohort study (96 335 women-years)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	IRR 5.97 in women with history of varicose veins; 4.42 in women with no history of varicose veins
Superficial venous thrombosis (SVT)	1 cohort (96 335 women-years)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	IRR 1.40 in women with history of varicose veins; 2.45 in women with no history of varicose veins

IRR: incidence rate ratio.

GRADE table 2 (Question 2): Among women with superficial venous thrombosis (SVT), does use of combined hormonal contraceptives (CHCs) increase the risk of venous thromboembolism (VTE) compared with non-use of CHCs? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Use of oral contraceptives vs non-use in women with superficial venous thrombosis								
Venous thromboembolism (VTE)	1 case-control study (1445 cases)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	OR 4.0 (95% CI 3.3–4.7) for OC use vs non-use with no history of SVT; OR 8.4 for OC use vs non-use with history of SVT (based on OR of 5.1 (95% CI 2.8–9.5) for no OC use and 43.0 (95% CI 15.5–119.3) OC use, reference no SVT history/no OC use)[a]

CI: confidence interval; OC: oral contraceptive; OR: odds ratio.
a Adjusted for age, BMI, smoking and family history of VTE; similar pattern observed for DVT, DVT + PE, and PE.

References

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5. Recommendations for combined hormonal contraceptives among women with dyslipidaemias

Question 1: Among women with known dyslipidaemias, without other known cardiovascular risk factors, does combined hormonal contraceptive (CHC) use increase risk of arterial thromboembolism (ATE), venous thromboembolism (VTE) or pancreatitis compared with no CHC use? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort and case-control studies
Population	Women of reproductive age with dyslipidaemia
Intervention	CHC use
Comparator	Non-use of CHCs
Outcome	Arterial thrombotic events (e.g. myocardial infarction or thrombotic stroke), VTE or pancreatitis
Databases searched	PubMed and Cochrane Library

Question 2: Among women of reproductive age using combined hormonal contraception (CHC), are women with known dyslipidaemias without other known cardiovascular risk factors at increased risk for ATE, VTE or pancreatitis compared to women without known dyslipidaemias? (Indirect evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort and case-control studies
Population	Women of reproductive age using CHCs
Intervention	Known dyslipidaemia without other known cardiovascular risk factors
Comparator	No known dyslipidaemia
Outcome	ATE or VTE or pancreatitis
Databases searched	PubMed and Cochrane Library

Question 3: Among women with known dyslipidaemias without other known cardiovascular risk factors, does combined hormonal contraceptive (CHC) use increase risk for worsening of lipid abnormalities compared with no CHC use? (Indirect evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort and case-control studies
Population	Women of reproductive age with dyslipidaemia
Intervention	CHC use
Comparator	Non-use of CHCs
Outcome	Worsening of lipid abnormalities (e.g. increase in total cholesterol, LDL or triglycerides; decrease in HDL)
Databases searched	PubMed and Cochrane Library

Recommendations

- Women with known dyslipidaemias without other known cardiovascular risk factors can generally use combined hormonal contraceptive methods (combined oral contraceptives, combined contraceptive patch, combined contraceptive vaginal ring, combined injectable contraceptives) (MEC Category 2). Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. Increased levels of total cholesterol, low-density lipoprotein (LDL) and triglycerides, as well as decreased levels of high-density lipoprotein (HDL), are known risk factors for cardiovascular disease. Women with known severe genetic lipid disorders at much higher lifetime risk for cardiovascular disease may warrant further clinical consideration.

Remarks

- The Guideline Development Group (GDG) determined that the existing condition name, “known hyperlipidaemias”, should be changed to “known dyslipidaemias” to better describe the spectrum of clinically important lipid abnormalities. They also specified that the condition should include only women “without other known cardiovascular risk factors” for better clarity.
- The GDG noted that the baseline absolute risk for cardiovascular disease among women of reproductive age is very low. Using available cardiovascular risk prediction

models, even among healthy perimenopausal women with high total cholesterol and normal HDL, 10-year risks for cardiovascular disease remain low. The most recent guidelines from the Fifth Joint Task Force of the European Society of Cardiology, published in 2012, predict that a healthy woman aged 45–49 years with total cholesterol levels greater than 280 mg/dL has < 1% 10-year risk for fatal myocardial infarction (MI) or stroke; similarly, recent guidelines released by the American College of Cardiology and the American Heart Association predict a 1.9% 10-year risk for a non-fatal or fatal first MI or stroke. Further, it was concluded that even if combined oral contraceptive (COC) use increases risk for MI or stroke among women of reproductive age with known dyslipidaemias and no other risk factors for cardiovascular disease, the absolute risk for these serious adverse events remains low.

- Use of combined hormonal contraception (CHC) among women with severe genetic lipid disorders may warrant further clinical consideration given that these women are at much higher lifetime risk for cardiovascular disease.
- The GDG determined that risk for arterial thrombotic events was the main safety concern for women with known dyslipidaemias without other cardiovascular risk factors. Independent of COC use, there does not appear to be a clear association between dyslipidaemia and risk for VTE among women of reproductive age, and indirect evidence from one study identified in our systematic review noted only a slight increased risk for VTE among COC users with the condition compared to users without the condition. No comparative data were available to assess the risk of pancreatitis among women with known dyslipidaemias, and while it is well established that elevated triglyceride levels are associated with acute pancreatitis, severe hypertriglyceridemia is a very rare condition with a risk for pancreatitis associated with triglyceride levels ≥ 1000 mg/dL estimated at approximately 5%.
- Due to heterogeneity of study designs, contraceptive formulations and outcome measures, a meta-analysis was not performed.
- CHCs 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

One case-control study suggested an increased risk for MI among COC users with hypercholesterolemia compared to non-users without hypercholesterolemia *(1)*. One retrospective cohort study suggested an increased risk for stroke and VTE among COC users with dyslipidaemia compared to COC users without dyslipidaemia *(2)*. One prospective cohort study suggested no worsening of lipid abnormalities among CHC users with dyslipidaemia compared to non-users with dyslipidaemia *(3)*.

Quality of the evidence

CHC use versus non-use of CHCs; ATE, VTE or pancreatitis (direct):	very low
Know dyslipidaemia versus no known dylipidaemia; ATE, VTE or pancreatitis (indirect):	very low
CHC use versus non-use of CHC; risk of lipid abnormalities (indirect):	very low

GRADE table 1 (Question 1): Among women with known dyslipidaemias without other known cardiovascular risk factors, does combined hormonal contraceptive (CHC) use increase risk of arterial thromboembolism (ATE), venous thromboembolism (VTE) or pancreatitis compared with no CHC use? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Use of combined oral contraceptives (COCs) vs non-use in women with hyperlipidaemia								
Myocardial infarction	1 case-control study (248 cases)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	OR 7.5 for COC use vs no COC use, based on OR 24.7 (95% CI 5.6–108.5) for COC use/ hyperlipidemia and 3.3 (95% CI 1.6–6.8) for no COC use/hyperlipidaemia, reference no COC use/no hyperlipidaemia

CI: confidence interval; OR: odds ratio.

GRADE table 2 (Question 2): Among women of reproductive age using combined hormonal contraception (CHC), are women with known dyslipidaemias without other known cardiovascular risk factors at increased risk for ATE, VTE or pancreatitis compared to women without known dyslipidaemias? (Indirect evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Women with hyperlipidaemia vs no hyperlipidaemia prescribed combined oral contraceptives								
Deep vein thrombosis (DVT) and pulmonary embolism (PE)	1 cohort study (n=329 995)	Very serious limitations (1 poor)	Cannot determine (1 study)	No serious imprecision	Serious indirectness (not COC use vs non-use)	None	Very low	8.51 vs 6.14 per 10 000 woman-years, IRR 1.39 (95% CI 1.04–1.85)

CI: confidence interval; IRR: incidence rate ratio.

GRADE table 3 (Question 3): Among women with known dyslipidaemias without other known cardiovascular risk factors, does combined hormonal contraception (CHC) use increase risk of worsening lipid abnormalities compared with no CHC use? (Indirect evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Worsening hyperlipidemia in users of combined oral contraceptives vs non-users								
Transient ischemic attacks and cerebrovascular accidents	1 cohort study (n=329 995)	Very serious limitations (1 poor)	Cannot determine (1 study)	No serious imprecision	Serious indirectness (not COC use vs non-use)	None	Very low	10.14 vs 5.76 per 10 000 woman years, IRR 1.76 (95% CI 1.51–2.06)

CI: confidence interval; IRR: incidence rate ratio.

References

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6. Recommendations for progestogen-only contraceptives and levonorgestrel-releasing intrauterine devices among breastfeeding women

Question 1: Among breastfeeding women (and their infants), does the use of progestogen-only contraceptives (POCs) and levonorgestrel-releasing intrauterine devices (LNG-IUDs) have an impact on breastfeeding or infant health outcomes compared with those not using POCs? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Breastfeeding women and their infants
Intervention	Use of POCs or LNG-IUDs
Comparator	Non-use of POCs
Outcome	Breastfeeding continuation and exclusivity/ supplementation; infant growth (as measured by weight, length, head circumference, arm circumference or skin-fold thickness); infant health (as measured by illness and mortality); infant development
Databases searched	PubMed and Cochrane Library

Question 2: Among breastfeeding women (and their infants), does the use of progestogen-only contraceptives (POCs) and levonorgestrel-releasing intrauterine devices (LNG-IUDs) initiated up to 6 weeks postpartum have an impact on breastfeeding or infant health outcomes compared with initiation after 6 weeks postpartum? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Breastfeeding women and their infants
Intervention	Use of POCs or LNG-IUDs initiated ≤ 6 weeks postpartum
Comparator	Use of POCs or LNG-IUDs initiated > 6 weeks postpartum
Outcome	Breastfeeding continuation and exclusivity/ supplementation; infant growth (as measured by weight, length, head circumference, arm circumference or skin-fold thickness); infant health (as measured by illness and mortality); infant development
Databases searched	PubMed and Cochrane Library

6a. Recommendations for use of progestogen-only contraceptives (pills, injectables, implants)

< 6 weeks postpartum

- Breastfeeding women who are < 6 weeks postpartum can generally use progestogen-only pills (POPs), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC Category 2).
- Breastfeeding women who are < 6 weeks postpartum generally should not use progestogen-only injectables (DMPA/NET-EN) (MEC Category 3). There is theoretical concern about the potential exposure of the neonate to DMPA/NET-EN during the first 6 weeks postpartum. However, in many settings pregnancy-related morbidity and mortality risks are high, and access to services is limited. In such settings, DMPA/NET-EN may be one of the few types of methods widely available and accessible to breastfeeding women immediately postpartum.

≥ 6 weeks to < 6 months postpartum

- Breastfeeding women who are 6 weeks to < 6 months postpartum can use without restriction the following contraceptive methods: POPs, progestogen-only injectables (DMPA and NET-EN), and LNG and ETG implants (MEC Category 1).

≥ 6 months postpartum

- Breastfeeding women who are ≥ 6 months postpartum can use without restriction the following contraceptive methods: POPs, progestogen-only injectables (DMPA and NET-EN), and LNG and ETG implants (MEC Category 1).

6b. Recommendations for use of levonorgestrel-releasing intrauterine devices (LNG-IUDs)

< 48 hours postpartum

- Breastfeeding women who are < 48 hours postpartum can generally use LNG-IUDs (MEC Category 2).

≥ 48 hours to < 4 weeks postpartum

- Breastfeeding (and non-breastfeeding) women generally should not have an LNG-IUD inserted from 48 hours to < 4 weeks postpartum (MEC Category 3).

≥ 4 weeks postpartum

- Breastfeeding (and non-breastfeeding) women can use an LNG-IUD without restriction at ≥ 4 weeks postpartum (MEC Category 1).

Puerperal sepsis

- Breastfeeding (and non-breastfeeding) women with puerperal sepsis should not have an LNG-IUD inserted (MEC Category 4).

Remarks

- Animal data suggest an effect of progesterone on the developing brain; whether similar effects occur following progestogen exposure in humans is unclear *(1–3)*. Available data from clinical and observational trials do not suggest an increased risk for either breastfeeding performance or infant health outcomes with use of progestogen-only injectables compared to outcomes in studies using other progestogen-only methods *(4–8)*. However, the Guideline Development Group felt that, as infants in the first 6 weeks of life may be exposed to higher hormone levels with use of progestogen-only injectables, as compared to the exposure using other methods of progestogen-only contraceptives (POCs), the theoretical risks of progestogen-only injectables may outweigh the benefits, particularly in settings with access to a wide variety of contraceptive methods.
- Due to heterogeneity of study designs, contraceptive methods/formulations and outcome measures, a meta-analysis was not performed.
- 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

Forty-seven articles reporting on 45 different studies were identified in the systematic review that investigated the use of POCs in breastfeeding women and reported clinically relevant outcomes of infant growth, health or breastfeeding performance. Direct evidence demonstrates no effect of POCs on breastfeeding performance *(4–51)*, and generally demonstrates no harmful effects on infant growth, health or development *(6, 7, 28, 42)*. However, these studies have been inadequately designed to determine whether a risk of long-term effects exists.

One randomized trial found that immediate insertion of the LNG-IUD was associated with decreased breastfeeding duration compared with delayed insertion *(5)*. Two other randomized controlled trials assessing early versus delayed initiation of POCs failed to show a difference in breastfeeding outcomes *(4, 16)*. In other studies, initiation of LNG-IUD after 4 weeks postpartum demonstrated no detrimental effect on breastfeeding outcomes *(11, 13, 45)*.

Quality of the evidence
< 6 weeks postpartum:

Breastfeeding outcomes

Progestogen-only pills (POPs):

Breastfeeding continuation, breastfeeding duration:	low
Use of supplementation:	very low

Progestogen-only injectables (DMPA/NET-EN):

Breastfeeding duration and use of supplementation:	low
Breastfeeding continuation:	very low

Progestogen-containing implants:

Breastfeeding continuation, breastfeeding episodes, breastfeeding duration, and use of supplementation:	very low

LNG-IUD:

Breastfeeding continuation anxd breastfeeding duration:	very low

Infant outcomes

POPs:

Infant growth:	very low

Progestogen-only injectables (DMPA/NET-EN):

Infant growth:	low

Progestogen-containing implants:

Infant growth:	low

LNG-IUD:

Infant growth:	very low

Progestogen-only injectables (DMPA/NET-EN):

Infant growth:	low

Progestogen-containing implants:

Infant growth:	low

LNG-IUD:

Infant growth:	very low

≥ 6 weeks postpartum:

Breastfeeding outcomes

POPs:

Breastfeeding duration:	low
Breastfeeding continuation and use of supplementation:	very low

Progestogen-only injectables (DMPA/NET-EN):

Breastfeeding duration:	low
Breastfeeding continuation and use of supplementation:	very low

Progestogen-containing implants:

Breastfeeding duration and use of supplementation:	low
Breastfeeding continuation:	very low

LNG-IUD:

Breastfeeding duration and use of supplementation:	very low

Infant outcomes

POPs:

Infant growth:	low

GRADE table 1 (Question 1): Among breastfeeding women (and their infants), does the use of progestogen-only contraceptives (POCs) and levonorgestrel-releasing intrauterine devices (IUDs) have an impact on breastfeeding or infant health outcomes compared with those not using POCs? (Direct evidence)

Question 2: Among breastfeeding women (and their infants), does the use of progestogen-only contraceptives (POCs) and levonorgestrel-releasing intrauterine devices (LNG-IUDs) initiated up to 6 weeks postpartum have an impact on breastfeeding or infant health outcomes compared with initiation after 6 weeks postpartum? (Direct evidence)

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Progestogen-only pill (POP) vs combined oral contraceptive (COC) initiated at < 6 weeks postpartum								
Breastfeeding continuation	1 RCT (n=127)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	NA	Low	Norethindrone vs ethinyl estradiol (EE) COC (1 RCT): 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
Use of supplementation	1 RCT (n=127)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	NA	Low	Norethindrone vs EE COC (1 RCT): no difference at 8 weeks (data not provided)
Infant growth	1 RCT (n=127)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	NA	Low	Norethindrone vs EE COC (1 RCT): no difference in percent change in weight ($P = 0.56$), length ($P = 0.41$), or head circumference ($P = 0.79$) from weeks 2–8
LNG-IUD initiated at < 6 weeks postpartum vs non-hormonal contraception								
Breastfeeding continuation	1 RCT (n=110)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	NA	Very low	LNG-UD (30 mcg/d or 10 mcg/d) vs Cu-IUD (1 RCT): 58% vs 79% at 8 months, RR 0.74 (95% CI 0.57–0.95)
Breastfeeding duration	1 RCT (n=110)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	NA	Very low	LNG-IUD 30 mcg/d vs LNG IUD 10 mcg/d vs Cu-IUD (1 RCT): 197 vs 182 vs 208 days ($P > 0.05$)
Infant growth	1 RCT (n=110)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	NA	Very low	LNG-IUD (30 mcg/d or 10 mcg/d) vs Cu-IUD (1 RCT): no differences through 12 months

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Progestogen-only injectable initiated at < 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	3 cohort studies (n=617)	Very serious limitations (1 fair, 2 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	No clear differences in 2 studies; in a 3rd study weaning occurred later with DMPA or NET-EN
Use of supplementation	5 cohort studies (n=1370)	Very serious limitations (1 fair, 4 poor)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	All 5 studies found DMPA or NET-EN associated with similar or lower likelihood of exclusive breastfeeding
Duration of breastfeeding	5 cohort studies (n=1732)	Very serious limitations (1 fair, 4 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	All 5 studies found DMPA associated with no difference or increased duration of breastfeeding vs non-hormonal methods
Infant growth	6 cohort studies (n=4403)	Very serious limitations (5 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	None of 5 studies found DMPA or NET-EN associated with decreased infant growth; 1 study found progestogen-only injectable associated with increased weight gain through 3 months
POPs initiated at < 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	1 non-randomized trial (n=273); 3 cohort studies (n=756)	Serious limitations (1 fair-quality cohort study, 3 poor-quality studies)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	None of 4 studies found various POPs associated with lower likelihood of breastfeeding continuation; 2 studies found POPs associated with higher likelihood of breastfeeding continuation
Breastfeeding initiation	1 RCT (n=20) and 1 non-randomized trial (n=20)	Very serious limitations (2 poor)	No serious inconsistency	Very serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	1 RCT found no difference between norethisterone at ≤ 14 hours postpartum (PP) vs placebo in breastfeeding initiation; 1 non-randomized trial found lynestrenol at 2 days PP associated with initiation of breastfeeding at 3 vs 5 days PP with placebo

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Duration of breastfeeding	2 cohort studies (n=572)	Very serious limitations (2 poor)	No serious inconsistency	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	2 studies found POPs associated with somewhat longer duration of breastfeeding vs non-hormonal comparators
Use of supplementation	2 cohort studies (n=1000)	Very serious limitations (1 fair, 1 poor)	Serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	1 fair-quality study found norgestrel 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 PP)
Infant growth	1 RCT (n=20), 1 non-randomized trial (n=20); 3 cohort studies (n=1083)	Serious limitations (2 fair-quality cohort studies, 3 poor-quality studies)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	4 studies found no difference on measures of infant growth; 1 small, poor-quality, non-randomized study found greater increase with lynestrenol than placebo
Progestogen-containing implants initiated at < 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	3 cohort studies (n=520)	Very serious limitations (1 fair, 2 poor)	Serious inconsistency	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	3 studies reported conflicting findings regarding effects of progestogen-containing implants on measures of breastfeeding continuation; the 1 fair-quality study found no difference between nomegestrol implant in 2nd month PP vs Cu-IUD
Breastfeeding episodes	2 cohort studies (n=392)	Very serious limitations (1 fair, 1 poor)	No serious inconsistency	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	2 studies found no differences in breastfeeding frequency
Duration of breastfeeding	1 cohort study (n=80)	Serious limitations (1 fair)	Cannot determine (1 study)	Very serious imprecision	No indirectness	None	Very low	1 fair-quality cohort study found no difference between etonogestrel (ETG) implant at 28–56 days PP vs Cu-IUD in duration of breastfeeding

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Use of supplementation	3 cohort studies (n=430)	Very serious limitations (1 fair, 2 poor)	Serious inconsistency	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	2 studies found no difference in use of supplementation; 1 study found norethindrone associated with increased likelihood of supplementation at 3 months
Infant growth	6 cohort studies (n=870)	Serious limitations (2 fair, 4 poor)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and assessment of outcomes[a]	Low	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/no method
Multiple progestogen-only methods initiated at < 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	1 cohort study (n=319)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	1 study found no difference between LNG implant or POP prior to discharge vs non-hormonal contraception in breastfeeding continuation at 2–6 weeks PP
Use of supplementation	1 cohort study (n=319)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	1 study found no difference between LNG implant or POP prior to discharge vs non-hormonal contraception in use of supplementation at 2–6 weeks PP
Non-orally available progesterone initiated at < 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	2 cohort studies (n=1092)	Very serious limitations (1 fair, 1 poor)	Serious inconsistency	Serious imprecision	No indirectness	None	Very low	1 fair-quality study found progesterone pellets at 30–35 days PP associated with decreased likelihood of breastfeeding at 6 months (51% vs 58%) and 12 months (11% vs 18%); 1 poor-quality study found no difference between progesterone pellets at 30 or 60 days vs Cu-IUD or placebo injection in breastfeeding rates
Use of supplementation	2 cohort studies (n=1092)	Very serious limitations (1 fair, 1 poor)	No serious inconsistency	Serious imprecision	No indirectness	None	Very low	2 studies found no differences in use of supplementation

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Infant growth	2 cohort studies (n=1092)	Very serious limitations (1 fair, 1 poor)	No serious inconsistency	Serious imprecision	No indirectness	None	Very low	2 studies found no differences in infant growth
LNG-IUD initiated at > 6 weeks postpartum vs non-hormonal								
Duration of breastfeeding	1 RCT (n=320)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	LNG-IUD at 6–8 weeks PP vs Cu-IUD (1 RCT): 149 vs 160 days
Use of supplementation	1 RCT (n=320)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	LNG-IUD at 6–8 weeks PP vs Cu-IUD (1 RCT): no difference in exclusive breastfeeding
Infant growth	1 RCT (n=320)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	LNG-IUD at 6–8 weeks PP vs Cu-IUD (1 RCT): no difference in infant growth
Progestogen-only injectable initiated at > 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	1 RCT (n=170)	Very serious limitations (1 poor)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	DMPA at 6 weeks PP vs non-hormonal (1 RCT): no difference in rates of discontinuation
Duration of breastfeeding	1 cohort study (n=1538)	Serious limitations (1 fair)	Cannot determine (1 study)	No serious imprecision	No indirectness	None	Low	DMPA or NET-EN at 6–8 weeks PP vs non-hormonal contraception (1 cohort study): no difference in duration of breastfeeding
Use of supplementation	1 RCT (n=170); 1 cohort study (n=212)	Very serious limitations (2 poor)	No serious inconsistency	Serious imprecision	No indirectness	None	Very low	2 studies found no differences in use of supplementation
Infant growth	1 RCT (n=170); 2 cohort studies (n=1750)	Very serious limitations (1 fair-quality cohort study, 2 poor-quality studies)	No serious inconsistency	No serious imprecision	No indirectness	Variability in outcomes[a]	Low	None of 3 studies found decreased infant growth with DMPA or NET-EN; 2 studies reported some findings suggesting greater weight gain

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
POP initiated at > 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	1 RCT (n=144)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	No indirectness	None	Very low	Norgestrel at 6 weeks PP vs non-hormonal contraception (1 RCT): no difference in discontinuation of breastfeeding
Duration of breastfeeding	2 cohort studies (n=1709)	Serious limitations (2 fair)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions[a]	Low	2 studies found no difference in breastfeeding duration
Use of supplementation	1 RCT (n=144); 1 non-randomized trial (n=120)	Very serious limitations (2 poor)	Serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	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)
Infant growth	1 RCT (n=144); 3 non-randomized studies (n=1829)	Serious limitations (2 fair-quality cohort studies, 2 poor-quality studies)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	4 studies found no difference in measures of infant growth
Progestogen-only implant or progestogen-containing IUD initiated at > 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	2 cohort studies (n=57)	Very serious limitations (2 poor)	No serious inconsistency	Very serious imprecision	No indirectness	None	Very low	2 studies found no difference in breastfeeding rates
Breastfeeding duration	4 cohort studies (n=2329)	Serious limitations (4 fair)	No serious inconsistency	No serious imprecision	No indirectness	Variability in outcomes[a]	Low	4 studies found no difference in breastfeeding duration

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Use of supplementation	3 cohort studies (n=549)	Serious limitations (2 fair, 1 poor)	No serious inconsistency	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	3 studies found no difference in use of supplementation
Infant growth	6 cohort studies (n=2386)	Serious limitations (4 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	6 studies found no difference in measures of infant growth
Multiple progestogen-only methods initiated at > 6 weeks postpartum vs non-hormonal								
Breastfeeding duration	1 cohort study (n=34)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	No indirectness	None	Very low	DMPA, POP or LNG-IUD vs non-hormonal contraception (1 cohort study): 183 vs 183 days (P =0.38)
Infant growth	1 cohort study (n=140)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	No indirectness	None	Very low	DMPA at 6 weeks PP vs non-hormonal contraception (1 cohort study): no difference in weight through 26 weeks PP
Non-orally available progesterone initiated at > 6 weeks postpartum vs non-hormonal								
Breastfeeding continuation	2 cohort studies (n=788)	Very serious limitations (1 fair, 1 poor)	No serious inconsistency	No serious imprecision	No indirectness	Variability in interventions[a]	Very low	1 fair-quality study found elcometrine implant associated with higher breastfeeding rate at 3 and 5 months (but not at 9 and 12 months); 1 poor-quality study found no difference between progesterone pellets vs Cu-IUD or placebo at 6 or 13 months PP
Breastfeeding duration	1 cohort study (n=200)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	Nesterone implant at 55–60 days PP vs Cu-IUD (1 cohort study): 273 vs 263 days (NS)
Infant growth	3 cohort studies (n=988)	Serious limitations (2 fair, 1 poor)	No serious inconsistency	No serious imprecision	No indirectness	Variabilty in interventions and outcomes[a]	Low	3 studies found no differences in measures of infant growth

Factor	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Earlier vs later initiation of progestogen-only methods								
Breastfeeding continuation	2 RCTs (n=165) and 1 cohort study (n=35)	Serious limitations (2 fair-quality RCTs, 1 poor-quality cohort study)	No serious inconsistency	Serious imprecision	No indirectness	Variabilty in interventions and outcomes[a]	Low	1 RCT found immediate LNG-IUD associated with lower breastfeeding rate at 6 months vs initiation at 6–8 weeks PP (6% vs 24%, $P = 0.02$); 1 cohort study found norethindrone implant at 6 days PP associated with lower rate at 8 months (57% vs 67%); 1 RCT found no difference in rate of lactation failure
Breastfeeding duration	1 RCT (n=96)	Serious limitations (1 fair)	Not applicable 1 study)	Very serious imprecision	No indirectness	None	Very low	Immediate LNG-IUD vs 6–8 weeks PP (1 RCT): 5 vs 8.5 weeks (P=0.06)
Use of supplementation	3 RCTs (n=205) and 4 cohort studies (n=660)	Serious limitations (3 fair-quality RCTs, 1 fair- and 3 poor-quality cohort studies)	Serious inconsistency	No serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Very low	Inconsistent effects on use of supplementation among 7 studies
Infant growth	1 RCT (n=40) and 3 cohort studies (n=543)	Very serious limitations (1 fair-quality RCT, 3 poor-quality cohort studies)	No serious inconsistency	Serious imprecision	No indirectness	Variability in interventions and outcomes[a]	Low	4 studies found no differences in measures of infant growth

CI: confidence interval; COC: combined oral contraceptive; Cu-IUD: copper-bearing intrauterine device; EE: ethinyl estradiol; LNG-IUD: levonorgestrel intrauterine device; NA: not applicable; NS: not significant; POP: progestogen-only pill; PP: postpartum; RCT: randomized controlled trial; RR: relative risk.

[a] Refers to variability in the progestogen evaluated, timing of initiation of POC, outcome measures assessed, and/or timing of outcome assessment.

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7. Recommendations for safety of depot medroxyprogesterone acetate delivered subcutaneously

Question 1: What is the safety of depot medroxyprogesterone acetate (104 mg/0.65 mL) delivered subcutaneously (DMPA-SC) for women with medical conditions or other specific characteristics established within the World Health Organization's eligibility criteria for contraceptive use? (Direct evidence)

A. Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women of reproductive age with medical conditions or other specific characteristics
Intervention	Use of DMPA-SC
Comparator	Users of DMPA-intramuscular (DMPA-IM); for endometriosis included non-comparative prospective data
Outcome	Serious adverse events (i.e. ectopic pregnancy or method discontinuation due to a medical condition) or outcomes related to medical conditions (i.e. changes in weight, contraceptive efficacy, changes in bone mineral density)
Databases searched	PubMed and Cochrane Library

B. Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women of reproductive age using DMPA-SC
Intervention	Presence of medical condition or specific characteristics
Comparator	No medical condition or specific characteristic
Outcome	Serious adverse events (i.e. changes in weight, contraceptive efficacy, changes in bone mineral density)
Databases searched	PubMed and Cochrane Library

Question 2: Among healthy women or among a general population of women of reproductive age, do those who use depot medroxyprogesterone acetate (104 mg/0.65 mL) delivered subcutaneously (DMPA-SC) have an increased risk for serious adverse events or other relevant outcomes compared with those who use DMPA delivered intramuscularly (DMPA-IM)? (Indirect evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Healthy women or general population of reproductive-age women
Intervention	Use of DMPA-SC
Comparator	Users of DMPA-IM
Outcome	Serious adverse events or outcomes relevant to medical conditions (i.e. changes in weight, blood pressure, vaginal bleeding)
Databases searched	PubMed and Cochrane Library

Recommendations

Age:

- Young women (menarche to < 18 years) can generally use DMPA (MEC Category 2).
- Women between the ages of 18 and 45 years can use DMPA without restriction (MEC Category 1)
- Women > 45 years old can generally use DMPA (MEC Category 2).

Endometriosis:

- Women with endometriosis can use DMPA without restriction (MEC Category 1).

HIV:

- Women living with HIV who have asymptomatic or mild clinical disease (WHO stage 1 or 2) can use DMPA without restriction (MEC Category 1).
- Women living with HIV who have severe or advanced HIV clinical disease (WHO stage 3 or 4) can use DMPA without restriction (MEC Category 1).

Obesity:

- Women with a body mass index (BMI) ≥ 30 kg/m^2 can use DMPA without restriction (MEC Category 1).

- Young women (menarche to < 18 years) with a BMI ≥ 30 kg/m^2 can generally use DMPA (MEC Category 2).
- There is evidence for differential weight gain among normal-weight and obese adolescents who use DMPA, but not those using norethisterone enanthate (NET-EN). However, NET-EN is MEC Category 2 due to evidence regarding potential effects of NET-EN on bone mineral density among adolescents.

Remarks

- The Guideline Development Group determined that no change to the existing recommendations for DMPA was warranted with inclusion of DMPA-SC as a new method.
- The body of evidence evaluating use of DMPA-SC and DMPA-IM among healthy women of reproductive age suggests a similar safety profile. Due to heterogeneity of study designs and outcome measures, a meta-analysis was not performed.
- DMPA-SC does 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

A randomized trial evaluating changes in bone mineral density (BMD) among adult DMPA-SC and IM users demonstrated no differences at two years of follow-up *(1)*. Limited evidence from three Phase 3 contraceptive trials reported no consistent differences in weight change or bleeding patterns according to age; adolescents aged < 18 years were not included in any studies *(1–3)*. Two prospective, non-comparative studies demonstrated that women with endometriosis treated with DMPA-SC for six months experienced minimal weight gain and decreases in BMD; serious adverse events were rare and DMPA-SC improved pain symptoms associated with the condition *(4, 5)*. A randomized cross-over study reported that women living with HIV tolerated injection of DMPA-SC and that experiences of serious adverse events were rare and occurred at similar rates as in users of DMPA-IM *(6)*. Evidence from three Phase 3 contraceptive trials and four reports from a small prospective cohort study reported similar contraceptive efficacy, weight change, bleeding patterns and other adverse effects, including variations in a number of biomarkers, among obese and non-obese DMPA-SC users *(1, 3, 7–12)*.

DMPA-IM and DMPA-SC appear to be therapeutically equivalent; the two formulations demonstrate similar pharmacokinetics, effects on serum estradiol levels and high contraceptive efficacy *(1)*. In addition, similar effects on weight change, bleeding patterns and experience of other adverse effects have been reported among healthy reproductive age users *(1, 3, 13)*.

Quality of the evidence

DMPA-SC and age:	very low
DMPA-SC and endometriosis:	very low
DMPA-SC and HIV:	very low
DMPA-SC and obesity:	very low
DMPA-SC versus DMPA; contraceptive efficacy (indirect):	very low
DMPA-SC versus DMPA; weight gain (indirect):	very low
DMPA-SC versus DMPA; changes in bleeding pattern (indirect):	very low.

GRADE table 1 (Question 1): What is the safety of depot medroxyprogesterone acetate (104 mg/0.65 mL) delivered subcutaneously (DMPA-SC) for women with medical conditions or other specific characteristics established within the World Health Organization's eligibility criteria for contraceptive use? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
DMPA-SC use in women in different BMI categories								
Contraceptive efficacy	1 RCT and 1 cohort from an RCT (n=2321)	Serious limitations (2 fair)	No serious inconsistency	No serious imprecision	No indirectness	None	Very low	No pregnancies in women in all BMI categories
Weight gain	2 non-randomized studies (n=2336)	Serious limitations (1 fair-quality and 1 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Very low	No differences in weight gain across BMI categories
Changes in bleeding patterns	1 study with pooled data from 3 studies (n=2321)	Serious limitations (1 fair)	Cannot determine (1 study)	No serious imprecision	No indirectness	None	Very low	No differences in bleeding patterns across BMI categories
Change in bone mineral density	1 cohort study (n=15)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	No indirectness	None	Very low	No differences in BMD changes across BMI categories
DMPA-SC use in women in different age groups								
Weight gain	1 study with pooled data from 3 studies (n=2321)	Serious limitations (1 fair)	Cannot determine (1 study)	No serious imprecision	No indirectness	None	Very low	No differences in weight gain across age categories
Changes in bleeding patterns	1 study with pooled data from 3 studies (n=2321)	Serious limitations (1 fair)	Cannot determine (1 study)	No serious imprecision	No indirectness	None	Very low	No differences in bleeding patterns across age categories

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Changes in bone mineral density	1 RCT (n=534)	No serious limitations (1 good)	Cannot determine (1 study)	Serious imprecision	No indirectness	BMD changes not reported by age category, enrolled women aged 18–35 years	Very low	Smaller decrease in median BMD with DMPA-SC vs DMPA-IM
DMPA-SC in women with endometriosis								
Weight gain	2 uncontrolled studies (n=289)	Very serious limitations (1 fair)	No serious inconsistency	Serious imprecision	No indirectness	No comparison group of women without endometriosis	Very low	Weight gain 0.70–0.95 kg at 6 months and 0.90–1.35 kg at 18 months
Change in bleeding pattern	2 uncontrolled studies (n=289)	Very serious limitations (1 fair)	No serious inconsistency	Serious imprecision	No indirectness	No comparison group of women without endometriosis	Very low	Increase in amenorrhoea 20% at 3 months and 24% at 6 months in 1 study; 1 study reported 35 bleeding or spotting days in 1st 90 days and 24 in 2nd 90 days
DMPA-SC vs DMPA-IM in women with HIV								
Contraceptive efficacy	1 RCT (n=357)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	Pregnancy rate 1.1% with both DMPA-SC and DMPA-IM
Change in bleeding pattern	1 RCT (n=357)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	No differences in menstrual irregularity, heavier bleeding

BMD: bone mass density; BMI: body mass index; DMPA: depot medroxyprogesterone acetate; IM: intramuscular; RCT: randomized controlled trial; SC: subcutaneous.

GRADE table 2 (Question 2): Among healthy women or among a general population of women of reproductive age, do those who use depot medroxyprogesterone acetate (104 mg/0.65 mL) delivered subcutaneously (DMPA-SC) have an increased risk for serious adverse events or other relevant outcomes compared with those who use DMPA delivered intramuscularly (DMPA-IM)? (Indirect evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
DMPA-SC vs DMPA-IM use in healthy women								
Contraceptive efficacy	1 RCT (n=534)	No serious limitations (1 good)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	Low rates of pregnancy with DMPA-SC and DMPA-IM
Weight gain	1 study with pooled data from 3 studies (n=2321)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	Median weight gain 4.5 kg with DMPA-SC vs 5.8 kg with DMPA-IM at 36 months
Change in bleeding pattern	1 RCT (n=534)	No serious limitations (1 good)	Cannot determine (1 study)	Serious imprecision	No indirectness	None	Very low	No differences in rates of intermenstrual bleeding or amenorrhoea between DMPA-SC vs DMPA-IM

DMPA: depot medroxyprogesterone acetate; IM: intramuscular; RCT: randomized controlled trial; SC: subcutaneous.

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8. Recommendations for safety of Sino-implant (II)

Question 1: What is the safety of the contraceptive implant Sino-implant (II) for women with medical conditions established within the World Health Organization's eligibility criteria for contraceptive use? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women with medical conditions or other specific characteristics
Intervention	Use of Sino-implant (II)
Comparator	Non-use of a hormonal contraceptive (i.e. either use of no contraceptive method or use of a non-hormonal method such as barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.) or users of other implants (Norplant, Jadelle, Implanon/Nexplanon)
Outcome	Serious adverse events (i.e. ectopic pregnancy or method discontinuation due to a medical condition) or outcomes related to medical conditions (i.e. changes in weight, blood pressure, vaginal bleeding)
Databases searched	PubMed and Cochrane Library

Question 2: Among healthy women or among a general population of women of reproductive age, do those who use Sino-implant (II) have an increased risk for serious adverse events or other relevant outcomes compared with those who do not use Sino-implant (II)? (Indirect evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Healthy women or general population of reproductive-age women
Intervention	Use of Sino-implant (II)
Comparator	Users of non-hormonal contraceptive methods (i.e. either use of no contraceptive method or use of a non-hormonal method such as barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/ vasectomy, etc.) or users of other implants (Norplant, Jadelle, Implanon/Nexplanon)
Outcome	Serious adverse events (i.e. ectopic pregnancy or method discontinuation due to a medical condition) or outcomes related to medical conditions (i.e. changes in weight, blood pressure, vaginal bleeding)
Databases searched	PubMed and Cochrane Library

Recommendations

- Recommendations for Sino-implant (II) will be the same recommendations as for other levonorgestrel implants (see p. 143–158).

Remarks

- Although there was no direct evidence regarding Sino-implant (II) among women with medical conditions, studies were identified that looked at safety of the implant among healthy women compared to those who do not use the SI (II). In addition, the safety data from studies of other levonorgestrel (LNG) implants among women with medical conditions is used due to the similarity of SI (II) and other LNG implants in hormone formulation, quality profile and daily release rates. Given this, the panel decided to make the same recommendations for SI (II) as the other LNG implants. Due to heterogeneity of study designs and outcome measures, a meta-analysis was not performed.
- The Sino-implant (II) does 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.

- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

No studies were identified that provided direct evidence on the use of the Sino-implant (II) among women with medical conditions in the MEC that included a comparison group. When looking at the studies on healthy women, evidence from four studies comparing SI (II) users with users of other LNG-containing implants demonstrates that SI (II) has a similar safety profile with no significant differences in serious adverse events such as ectopic pregnancy or discontinuation due to medical problems *(1–3)*.

When investigating serious adverse events in healthy women using SI (II), three articles were identified *(1–3)*. These three articles reported on four randomized controlled trials (RCTs) and found no difference between users of SI (II) and users of SI (I) or Norplant with respect to incidence of serious adverse events. Similar effects on selected markers of disease in healthy women were seen for healthy women using SI (II) compared to women using SI (I) or Norplant. These markers of disease were liver function *(3)*, weight *(1, 4–6)*, blood pressure *(1, 6)*, bone mineral density *(7)*, ovarian cysts and benign myomas *(6)*. Two studies provided limited evidence regarding menorrhagia *(1, 8)*. The studies suggest that SI (II) is not harmful and may be beneficial for women with menorrhagia. One RCT found an increased pregnancy rate among women weighing 70 kg or over using SI (II) *(9)*, while another RCT failed to find this association and also reported no association between duration of use, weight and pregnancy *(3)*.

Quality of the evidence

Women with medical conditions or other specific characteristics:
(intervention versus comparator; outcome)

Sino-implant (II) versus non-use of Sino-implant (II); serious adverse events (direct):	no evidence

Healthy women or general population of reproductive age women:
(intervention versus comparator; outcome)

Sino-impant (II) versus non-use of Sino-implant (II); various outcomes (indirect):	
Ectopic pregnancy:	low
Weight gain:	moderate
Blood loss:	low
Bone mineral density:	very low
Blood pressure:	low
Other adverse events:	very low
Pregnancy:	very low

GRADE table 1 (Question 2): Among healthy women or among a general population of women of reproductive age, do those who use Sino-implant (II) have an increased risk for serious adverse events or other relevant outcomes compared with those who do not use Sino-implant (II)? (Indirect evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Sino-implant (II) vs Sino-implant (I) or Norplant in healthy women								
Ectopic pregnancy	4 RCTs (24 972)	Serious limitations (4 fair)	No serious inconsistency	Serious imprecision	No indirectness	None	Low	Very few ectopic pregnancies and no clear difference in risk in 4 RCTs of SI (II) vs SI (I) or Norplant
Weight gain	3 RCTs (n=4443); 1 cohort study (n=617)	Serious limitations (2 fair- and 1 poor-quality RCT, 1 very poor-quality cohort study)	No serious inconsistency	No serious imprecision	No indirectness	None	Moderate	No difference between SI (II) and SI (I) or Norplant in weight gain in 3 studies; less weight gain with SI (II) than control (no method or non-hormonal) in 1 study
Blood loss, change in haemoglobin	2 RCTs (n=389)	Serious limitations (1 fair, 1 poor)	No serious inconsistency	Serious imprecision	No indirectness	None	Low	No clear difference in blood loss or haemoglobin levels with SI (II) vs SI (I) or Norplant
Bone mineral density (BMD)	1 cross-sectional study (n=166)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	Serious indirectness (intermediate outcome)	None	Very low	No difference between SI (II), SI (I) and Norplant in BMD after ≥ 3 years
Blood pressure (BP)	1 RCT (n=2297); 1 cohort study (n=617)	Very serious limitations (1 fair-quality RCT, 1 very poor-quality cohort study)	No serious inconsistency	No serious imprecision	No indirectness	Variability in measures of blood pressure effects	Low	1 RCT found very few cases of increased BP with SI (II), SI (I), or Norplant; 1 cohort study found higher BP with control (no method or non-hormonal) than SI (II)
Other adverse events	2 RCTs (n=22 672)	Serious limitations (2 fair)	No serious inconsistency	No serious imprecision	No indirectness	Variability in outcomes measured	Very low	No difference between SI (II) and SI (I) or Norplant in various adverse events or reasons for removal

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Effects of weight on contraceptive efficacy in women using Sino-implant (II)								
Pregnancy	2 RCTs (n=10 940)	Serious limitations (2 fair)	Serious inconsistency	Serious imprecision	No indirectness	None	Very low	1 RCT found higher pregnancy rate in women ≥ 70 kg than women < 60 kg (*P* not reported); 1 RCT found no association between weight and risk of pregnancy

BMD: bone mineral density; BP: blood pressure; RCT: randomized controlled trial; SI (I): Sino-implant (I); SI (II): Sino-implant (II).

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9. Recommendations for use of emergency contraceptive pills, including adding the condition of obesity and the new method, ulipristal acetate

Question 1: Among women with certain characteristics or medical conditions, are those who use levonorgestrel (LNG), ulipristal acetate (UPA) or combined oral contraceptive (COC) regimens for emergency contraceptive pills (ECPs) at increased risk for adverse events compared with those who do not use these forms of emergency contraception? (Direct evidence)

Selection criteria for the systematic review

Study design	Primary research articles in all languages, including pharmacokinetic studies
Population	Women with characteristics or medical conditions outlined in the *Medical eligibility criteria* (MEC) update (pregnancy, breastfeeding, past ectopic pregnancy, history of severe cardiovascular complications, angina pectoris, migraine, severe liver disease, CYP3A4 inducers, repeated [ECP] use and rape).
Intervention	Use of hormonal ECPs (COCs, LNG or UPA)
Comparator	Non-use of hormonal ECPs
Outcome	Any adverse events (did not include side-effects)
Databases searched	PubMed and Cochrane Library

Question 2: Among women who use levonorgestrel (LNG), ulipristal acetate (UPA) or combined oral contraceptive (COC) regimens for emergency contraceptive pills (ECPs), are those with obesity at increased risk for adverse events or pregnancy compared with those who do not have obesity? (Direct evidence)

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women using hormonal ECPs (COCs, LNG or UPA)
Intervention	Obesity
Comparator	Non-obesity
Outcome	Any adverse events or pregnancy
Databases searched	PubMed and Cochrane Library

Recommendations

- For pregnant women, emergency contraceptive pill (ECP) use is not applicable. Although this method is not indicated for a woman with a known or suspected pregnancy, there is no known harm to the woman, the course of her pregnancy, or the fetus if ECPs are accidentally used.
- Women who are breastfeeding can use COCs or LNG regimens for ECPs without restriction (MEC Category 1). Women who are breastfeeding can generally use UPA (MEC Category 2). Breastfeeding is not recommended for one week after taking UPA since it is excreted in breast-milk. Breast-milk should be expressed and discarded during that time *(1).*
- Women who have experienced past ectopic pregnancies can use COCs, LNG or UPA for ECPs without restriction (MEC Category 1).
- Women with history of severe cardiovascular disease, including ischaemic heart disease, cerebrovascular attack, or other thromboembolic conditions, can generally use COCs, LNG or UPA for ECPs (MEC Category 2).
- Women with migraines can generally use COCs, LNG or UPA for ECPs (MEC Category 2).
- Women with severe liver disease, including jaundice, can generally use COCs, LNG or UPA for ECPs (MEC Category 2).
- Women using CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, efavirenz, fosphenytoine, nevirapine, oxcarbazepine, primidone, rifabutin, St John's wort/*Hypericum perforatum*) can use COCs, LNG or UPA for ECPs without restriction (MEC Category 1). Strong CYP3A4 inducers may reduce the effectiveness of ECPs.
- There are no restrictions on repeated ECP use for COCs, LNG or UPA (MEC Category 1). Recurrent ECP use is an indication that the woman requires further counselling on other contraceptive options. Frequently repeated ECP use may be harmful for women with conditions classified as Category 2, 3 or 4 for use of combined hormonal contraceptives (CHCs) or progestogen-only contraceptives (POCs).
- There are no restrictions for use of COCs, LNG or UPA for ECPs in cases of rape (MEC Category 1).
- Women who are obese can use COCs, LNG or UPA for ECPs without restriction (MEC Category 1). ECPs may be less effective among women with BMI $\geq$ 30 kg/m^2 than among women with BMI $<$ 25 kg/m^2. Despite this, there are no safety concerns.

Remarks

- Ulipristal acetate (UPA) was added as a new method to the MEC.
- The duration of use of ECPs is less than the duration of regular use of COCs or POPs and thus would be expected to have less clinical impact for women with history of severe cardiovascular complications, migraine or severe liver disease (including jaundice). There are no restrictions for the use of ECPs in cases of rape.
- The Guideline Development Group (GDG) decided to remove the condition "angina pectoris" from the MEC recommendations for ECPs. This condition does not appear elsewhere in the MEC and there was no evidence suggesting safety concerns for ECP use among women with angina pectoris.
- The GDG decided to change the term "history of severe cardiovascular complications" to "history of severe cardiovascular disease" to be more consistent with terminology used elsewhere in the MEC.
- According to labelling information, rifampicin markedly decreases UPA levels by 90% or more, which may decrease its efficacy *(1)*. Theoretical concerns, therefore, extend to use of other CYP3A4 inducers as well as LNG and COCs, which have similar metabolic pathways to UPA.
- Due to heterogeneity of study designs and outcome measures, a meta-analysis was not performed.
- ECPs 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

Four direct studies examined LNG-ECP use among pregnant or breastfeeding women *(2–5)*. No studies were identified that examined UPA- or COC-ECP use among women with medical conditions or characteristics. One cohort study and one randomized controlled trial analysed outcomes among breastfeeding women *(3–4),* and two cohort studies analysed outcomes among breastfeeding women *(2, 5)*. Poor pregnancy outcomes appear rare among pregnant women who used ECPs during conception cycle or early in pregnancy. Breastfeeding outcomes do not seem to differ between women exposed to LNG and those unexposed. One pharmacokinetic study demonstrates that LNG does pass to breast-milk but is found in minimal quantities *(6).*

A small pharmacokinetic study found that concomitant efavirenz use decreased LNG levels in women taking LNG-ECP (0.75 mg) by 56% compared with LNG-ECP alone *(7)*.

There is limited evidence from one study that suggests obese women with BMI $\geq$ 30 kg/m^2 experience an increased risk of pregnancy after use of LNG compared with women with BMI $<$ 25 kg/m^2 *(8)*. Evidence from two studies suggests that obese women may also experience an increased risk of pregnancy after use of UPA compared with non-obese women, though this increase was not significant in one of the studies *(8, 9)*.

Quality of the evidence

Women with certain characteristics or medical conditions:
(intervention versus comparator; outcome)

Breastfeeding women

LNG-ECP use versus non-use of LNG-ECP; breastfeeding outcomes:	very low
LNG-ECP use versus non-use of LNG-ECP; infant growth/behaviour:	very low

Currently pregnant women

LNG-ECP use versus non-use of LNG-ECP; adverse pregnancy outcomes:	very low

GRADE methodology was not used to assess quality of evidence for studies that did not report clinical outcomes, including pharmacokinetic studies.

Women using LNG-, UPA- or COC-ECPs:
(intervention versus comparator: outome)

Obesity versus non-obesity; risk of pregnancy:	moderate

GRADE tables 1 (Question 1): Among women with certain characteristics or medical conditions, are those who use levonorgestrel (LNG), ulipristal acetate (UPA) or combined oral contraceptive (COC) regimens for emergency contraceptive pills (ECPs) at increased risk for adverse events compared with those who do not use these forms of emergency contraception? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Quality	Estimate of effect
LNG-ECP during breastfeeding vs no LNG-ECP							
Breastfeeding outcomes	1 cohort study (n=143); 1 RCT (n=1158)	Serious limitations (1 poor-quality cohort, 1 fair-quality RCT); some outcomes based on subjective self-report	No inconsistency	No serious imprecision	No indirectness	Very low	No differences in breast-milk volume in 2 studies; no difference in duration of lactation, resumption of menstruation or pattern of breastfeeding in 1 study
Infant growth and behaviour	1 cohort study (n=143); 1 RCT (n=1158)	Very serious limitations (1 poor-quality cohort, 1 fair-quality RCT); outcomes poorly defined	No inconsistency	No serious imprecision	No indirectness	Very low	No differences in infant growth or behaviour
LNG-ECP during pregnancy vs no LNG-ECP							
Pregnancy outcomes	2 cohort studies (n=780)	Very serious limitations (1 poor, 1 fair)	No inconsistency	Serious imprecision	No indirectness	Very low	No differences in risk of spontaneous abortion or still birth, ectopic pregnancy, or other pregnancy complications
Neonatal or fetal outcomes	2 cohort studies (n=780)	Very serious limitations (1 poor, 1 fair)	No inconsistency	Serious imprecision	No indirectness	Very low	No differences in rates of birth defects or fetal growth

GRADE table 2 (Question 2): Among women who use levonorgestrel (LNG), ulipristal acetate (UPA) or combined oral contraceptive (COC) regimens for emergency contraceptive pills (ECPs), are those with obesity at increased risk for adverse events or pregnancy compared with those who do not have obesity? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Obese (BMI ≥ 30 kg/m^2) vs overweight (25–30 kg/m^2) vs normal or underweight (< 25 kg/m^2)								
Pregnancy	3 cohorts from clinical trials (n=4690) (analysed in 2 meta-analyses that included 2 studies each; 1 study included in both analyses)	Serious limitations (2 studies with secondary analyses from clinical trials with methodological limitations)	No serious inconsistency	No serious imprecision	No indirectness	Dose-effect observed in 1 meta-analysis (not evaluated in the other)	Moderate	Obese vs normal or underweight (n=2701, 2 studies): OR 3.6 (95% CI 2.0–6.5) for any ECP; OR 4.4 (95% CI 2.0–9.4) for LNG-ECP and OR 2.6 (95% CI 0.89–7.0) for UPA-ECPa Overweight vs normal or underweight (n=2976, 2 studies): OR 1.5 (95% CI 0.75–3.0) for any ECP; 2.1 (95% CI 0.86–4.9) for LNG-ECP and 0.97 (95% CI 0.27–2.8) for UPA-ECPa; (n=2173, 2 studies): OR 2.1 (95% CI 1.0–4.3) for UPA-ECPb

BMI: body mass index; CI: confidence interval; OR: odds ratio.

a Estimates adjusted for conception probability, further intercourse, age, time from unprotected intercourse to treatment, and pregnancy history.

b Estimate adjusted for further acts of unprotected intercourse, age, race, ever being pregnant, smoking, and hours since unprotected intercourse (up to 120 hours) not statistically significant in univariate analyses.

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10. Recommendations for intrauterine devices among women with increased risk for sexually transmitted infections

Question 1: Among women with an increased risk of sexually transmitted infections (STIs), does intrauterine device (IUD) insertion increase risk for pelvic inflammatory disease (PID) compared with women with an increased risk of STIs that do not undergo IUD insertion?

Selection criteria for the systematic review

Study design	Randomized controlled trials, cohort studies and case-control studies
Population	Women at increased risk of STIs
Intervention	Initiation of copper-bearing IUD (Cu-IUD) or levonorgestrel-releasing IUD (LNG-IUD)
Comparator	Non-initiation of Cu-IUD or LNG-IUD
Outcome	PID
Databases searched	PubMed and Cochrane Library

Recommendations

- Many women with increased risk of sexually transmitted infections (STIs) can generally undergo either Cu-IUD or LNG-IUD initiation (MEC Category 2). Some women at increased risk (very high individual likelihood) of STIs generally should not have an IUD inserted until appropriate testing and treatment occur (MEC Category 3). IUD insertion may further increase the risk of PID among women at increased risk of STIs, although limited evidence suggests that this risk is low. Current algorithms for determining increased risk of STIs have poor predictive value. Risk of STIs varies by individual behaviour and local STI prevalence. Therefore, while many women at increased risk of STIs can generally have an IUD inserted, some women at increased risk (very high individual likelihood) of STIs should generally not have an IUD inserted until appropriate testing and treatment occur.
- Women at increased risk of STIs can generally continue use of either Cu-IUD or LNG-IUD (MEC Category 2).

Remarks

- The Guideline Review Committee advised that this recommendation be revised to clarify the Category 2/3 recommendation in the MEC fourth edition. However, as no new evidence was identified to update this recommendation, there was no evidence to take through the GRADE process. This was addressed by the Guideline Development Group (GDG), who decided that the best course of action was to revise the clarification. The GDG highlighted the universal recommendation for dual protection with condoms, especially for women at increased risk of STIs.
- 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

Using an algorithm to classify STI risk status among IUD users, one study reported that 11% of women at high risk of STI experienced IUD-related complications compared with 5% of those not classified as high risk *(1)*. In another small study, the incidence of PID after IUD insertion was low (2.2%) in a cohort of women considered to be at high risk based on high background rates of STIs in the general population *(2)*.

Quality of the evidence

For STI and IUD:	No new evidence

References

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11. Recommendations for use of progesterone-releasing vaginal ring

Question 1: Among breastfeeding women and their infants, does the use of the progesterone-releasing contraceptive vaginal ring (PVR), compared with non-use of progestogen-only contraceptive (POC) methods, affect maternal health, breastfeeding performance, infant growth or infant health? (Direct evidence)

Selection criteria for the systematic review

Study Design	Randomized controlled trials, cohort studies and case-control studies
Population	Breastfeeding women
Intervention	PVR
Comparator	Non-use of a POC method (i.e. either use of no contraceptive method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcome	Maternal adverse events, breastfeeding performance (e.g. duration of lactation, continuation, supplementation), infant health (growth, development, or adverse health events), pregnancy
Databases searched	PubMed and Cochrane Library

Recommendations

- Women who breastfeed and are ≥ 4 weeks postpartum, can use without restrictions the progesterone-releasing vaginal ring (PVR) (MEC Category 1). A woman who uses the PVR must be actively breastfeeding (e.g. at least four breastfeeding episodes per day) to maintain the efficacy of the method.

Remarks

- If the progesterone-releasing vaginal ring (PVR) is accidentally used during pregnancy, there is no known harm to the woman, the course of her pregnancy, or the fetus.
- Due to heterogeneity of study designs and outcome measures, a meta-analysis was not performed.
- The PVR does 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.
- Voluntary use of contraception by women is critical for upholding their reproductive rights. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence

Seven prospective cohort studies examined the effect of using the progesterone-releasing vaginal ring (PVR) on maternal health, breastfeeding performance, infant health and infant growth, compared with other hormonal and non-hormonal contraceptive methods, during the first year postpartum or longer *(1–7)*.

Of the six studies that evaluated various measures of breastfeeding performance, neither duration of lactation *(1, 4, 7)*, the proportion of women fully breastfeeding *(2)*, the number of breastfeeding episodes *(2, 5)*, nor the timing of supplementary food introduction *(6)* significantly differed among PVR users compared with users of non-hormonal or progestogen-only contraceptives (POCs) during 12 months of observation.

No statistically significant differences in infant weight gain were observed among PVR users compared with women using non-hormonal or POCs *(3, 4, 6)* and similar patterns of infant weight gain were observed in another study that compared PVR and IUD users *(5)*. One study reported no significant difference in infant health *(5)*.

Quality of the evidence

Among breastfeeding women, use of PVR versus non-PVR contraceptive; various outcomes:

Pregnancy:	low
Breastfeeding outcomes:	low
Infant weight:	low

GRADE table 1 (Question 1): Among breastfeeding women and their infants, does the use of the progesterone-releasing contraceptive vaginal ring (PVR), compared with non-use of progestogen-only contraceptive (POC) methods, affect maternal health, breastfeeding performance, infant growth and infant health? (Direct evidence)

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Progesterone-releasing vaginal ring (PVR) vs intrauterine device (IUD), Norplant or progesterone-only pill (POP)								
Pregnancy	7 cohort studies (n=3397)	Serious limitations (5 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	Few pregnancies and similar pregnancy rates in breastfeeding women using PVR vs IUD (6 studies), Norplant (2 studies), or POP (1 study)
Use of supplementation	4 cohort studies (n=1129)	Serious limitations (3 fair, 1 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	No difference between PVR and IUD (3 studies), Norplant (2 studies), or POP (1 study) in proportion fully breastfeeding; 1 study found ring associated with fewer supplementation episodes and days than IUD at all follow-up periods ($P < 0.001$)
Breastfeeding duration	4 cohort studies (n=1117)	Serious limitations (2 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	No difference between PVR and IUD (4 studies), Norplant (2 studies), or POP (1 study)
Breastfeeding episodes	2 cohort studies (n=2083)	Serious limitations (2 fair)	No serious inconsistency	No serious imprecision	No directness	None	Low	No differences between PVR and IUD (2 studies)
Continuation of use	5 cohort studies (n=2722)	Serious limitations (3 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	4 studies found PVR associated with lower continuation/higher discontinuation vs IUD; 1 study found PVR associated with higher continuation/lower discontinuation
Bleeding episodes	3 cohort studies (n=2279)	Very serious limitations (1 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	No clear differences between PVR vs IUD (3 studies), Norplant (1 study), or POP (1 study)
Infant weight gain	7 cohort studies (n=3397)	Serious limitations (5 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	None	Low	No difference between ring vs IUD (7 studies), Norplant (2 studies), or POP (1 study)

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12. Recommendations for use of hormonal contraception among women at high risk of HIV, women living with HIV, and women living with HIV using antiretroviral therapy

Background

Owing to the public health importance of recommendations on hormonal contraceptive use for women at risk of HIV and women living with HIV, the following recommendations were issued ahead of this fifth edition of the MEC in the document entitled *Hormonal contraceptive methods for women at high risk of HIV and living with HIV: 2014 guidance statement,* which was approved by the WHO Guidelines Review Committee (GRC) on 7 July 2014 *(1).*

Question 1: Does the use of a particular method of hormonal contraception directly increase the risk of HIV acquisition in women?

Selection criteria for the systematic review

Study design	Randomized controlled trials and observational cohort studies
Population	Women of reproductive age at risk of HIV infection
Intervention	Use of a hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	Non-use of a hormonal contraceptive method (i.e. either use of no contraceptive method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcome	Incident, laboratory-confirmed HIV infection in women

Question 2: Does the use of various hormonal contraceptive methods accelerate HIV disease progression in women living with HIV?

Selection criteria for the systematic review

Study design	Randomized trials and cohort studies
Population	Women of reproductive age living with HIV
Intervention	Use of a hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	Non-use of hormonal contraceptive methods (i.e. either use of no method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcomes	Risk of HIV disease progression (as indicated by HIV viral load, CD4 count, progression to AIDS, ART initiation, death, or a composite outcome of progression to AIDS, ART initiation or death).

Question 3: Does the use of various hormonal contraceptive methods increase the risk of female-to-male HIV sexual transmission?

Selection criteria for the systematic review

Study designs	(a) Randomized trials and cohort studies (reporting direct evidence, with incident HIV infection rates in male sexual partners as an outcome variable); (b) randomized controlled trials, cohort studies, cross-sectional studies (reporting indirect evidence, assessing proxy measures for infectivity in women)
Population	Women of reproductive age living with HIV
Intervention	Use of a hormonal contraceptive method (injectables, oral contraceptives, implants, patches, rings or LNG-IUDs)
Comparator	Non-use of hormonal contraceptive methods (i.e. either use of no method or use of a non-hormonal method such as condoms or other barrier methods, withdrawal, copper-bearing IUDs, tubal ligation/vasectomy, etc.)
Outcomes	Risk of HIV transmission to male partners (measured either directly by HIV seroconversion among previously HIV-negative male partners, or indirectly by measurement of genital HIV shedding or plasma viral load in women as a proxy for infectivity).

Question 4: Are there any possible interactions between hormonal contraceptive methods and antiretroviral (ARV) medications?

Selection criteria for the systematic review

Study design	Clinical trials, observational studies, case series and pharmacokinetic studies
Population	Women of reproductive age
Intervention	Hormonal contraception and antiretroviral therapy (ART)
Comparator	Hormonal contraception and no ART; non-comparative studies examining changes in outcomes over time
Outcome	Contraceptive hormone pharmacokinetics, contraceptive effectiveness (pregnancy, ovulation, ovarian activity, breakthrough bleeding), ARV pharmacokinetics, ARV effectiveness (HIV disease progression, viral load, CD4 count), and adverse effects of either the hormonal contraceptive or the ARV medication.

12a. Recommendations among women at high risk of HIV infection:

- Women at high risk of acquiring HIV can use the following hormonal contraceptive methods without restriction: combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), contraceptive patches and rings, progestogen-only pills (POPs), progestogen-only injectables (DMPA and NET-EN), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC Category 1).
- Women at high risk of HIV who are using progestogen-only injectables (POIs) should be informed that available studies on the association between POI contraception and HIV acquisition have important methodological limitations hindering interpretation. Some studies suggest that women using POI contraception may be at increased risk of HIV acquisition; other studies have not found this association. The public health impact of any such association would depend upon the local context, including rates of injectable contraceptive use, maternal mortality and HIV prevalence. This must be considered when adapting guidelines to local contexts. WHO expert groups continue to actively monitor any emerging evidence. At the meeting in 2014, as at the 2012 technical consultation, it was agreed that the epidemiological data did not warrant a change to the MEC. Given the importance of this issue, women at high risk of HIV infection should be informed that POIs may or may not increase their risk of HIV acquisition. Women and couples at high risk of HIV acquisition considering POIs should also be informed about and have access to HIV preventive measures, including male and female condoms.
- Women at high risk of acquiring HIV can generally use LNG-releasing IUDs (LNG-IUDs) (MEC Category 2).

Remarks

- It is critically important that women and couples at risk of HIV infection be informed about and have access to male and female condoms, and other measures to prevent and reduce their risk of HIV infection and sexually transmitted infections (STIs), regardless of which form of contraception they choose.
- Hormonal contraceptives, including COCs, CICs, POPs, POIs, progestogen-only implants, and LNG-IUDs do not protect against STIs/HIV.

Summary of the evidence (Question 1: HIV acquisition)

Twenty-two prospective observational studies have assessed the risk of HIV acquisition among women using a method of hormonal contraception versus the risk of HIV acquisition in women using a non-hormonal contraceptive method (i.e. condoms, Cu-IUD, withdrawal) or no contraceptive method *(2–27)*.

Combined hormonal contraceptives

Eight studies assessed the use of COCs and were considered to be "informative but with important limitations" *(28)*. Seven of these studies found no statistically significant association between use of COCs and HIV acquisition *(3, 5-11)*, although one study among sex workers in Kenya did *(12)*.

Progestogen-only contraceptives

Five studies assessed the use of NET-EN injectables and were considered to be "informative but with important limitations" *(28)*. Four of them reported no statistically significant association with HIV acquisition *(3, 8, 9, 13)*, while one did *(11)*.

Nine studies assessed DMPA, or, if a DMPA-specific result was unavailable, assessed non-specified injectables; these studies were considered to be "informative but with important limitations" *(28)*. The results were mixed: three of the studies showed a significant increase in risk *(5, 11, 12)*, one showed a significant increase in risk using one statistical model but this association was not statistically significant using another statistical model *(6, 7)*, and five showed no significant increase in risk *(3, 8–10, 13)*.

Two studies assessed implants, one of which was classified as "unlikely to inform the primary question" *(4, 28)*. Neither of these studies reported a statistically significant increased risk of HIV acquisition, but confidence intervals were wide *(4, 21)*.

Quality of the evidence (Question 1: HIV acquisition)

For progestogen-only injectables (DMPA and NET-EN) and COCs:	low
For implants:	very low

12b. Recommendations among women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2):

- Women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) can use the following hormonal contraceptive methods without restriction: combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), contraceptive patches and rings, progestogen-only pills (POPs), progestogen-only injectables (DMPA and NET-EN), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC Category 1).
- Women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2) can generally use the LNG-IUD (MEC Category 2).
- Because there may be interactions between certain methods of hormonal contraception and certain antiretroviral medications (ARVs), refer to the recommendations on ART medication interactions (see p. 72).

Remarks

- Hormonal contraceptives do not protect against sexually transmitted infections (STIs), including HIV. Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission to non-infected sexual partners, and for protection against other STIs. Female condoms are effective and safe, but are not used as widely by national programmes as male condoms.
- Voluntary use of contraception by women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence (Question 2: disease progression; Question 3: female-to-male transmission)

Two systematic reviews investigating Questions 2 and 3 informed the contraceptive eligibility recommendations for women living with asymptomatic or mild HIV clinical disease (WHO stage 1 or 2).

Combined hormonal contraceptives (CHCs)

Out of eight available studies, seven suggested no association between use of COCs and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(29–35)*. One randomized controlled trial found an increased risk of a composite outcome of declining CD4 count or death among COC users when compared with users of copper-bearing IUDs (Cu-IUDs) *(36, 37)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women known to be using hormonal contraceptives. One of these studies reported an elevated, but not statistically significant, point estimate for COCs *(5)*. The other study also did not find a statistically significant association for COCs *(4)*.

Studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have had mixed results. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(38–53)*.

Progestogen-only contraceptives (POCs)

Out of six available studies, five suggested no association between use of progestogen-only injectable (POI) contraceptives and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(31–35)*. One randomized trial found an increased risk of a composite outcome of declining CD4 count or death among oral contraceptive (OC) users (COCs and POPs) when compared with users of Cu-IUDs; this study, however, had significant loss to follow-up and method-switching among groups, limiting its interpretation *(36, 37)*. One study found no difference in ART

initiation or CD4 count between users and non-users of the LNG-IUD *(54)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women known to be using hormonal contraceptives. One study reported a statistically significant association between POI contraception and female-to-male transmission of HIV *(5)*, while another study did not find a statistically significant association between use of DMPA and female-to-male HIV transmission *(4)*. The findings of studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have been mixed. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(38–53)*.

Quality of the evidence

Disease progression – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs):	low
Disease progression – LNG-IUD:	very low
Disease transmission (direct evidence) – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs):	very low

Note: As there remains considerable uncertainty regarding the best way to measure genital HIV shedding (with respect to collection method, RNA versus DNA, and cell-associated versus cell/free measures of DNA and RNA), studies providing indirect evidence assessing proxy measures of transmission did not undergo a GRADE assessment.

12c. Recommendations among women living with severe or advanced HIV clinical disease (WHO stage 3 or 4)

- Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) can use the following hormonal contraceptive methods without restriction: combined oral contraceptive pills (COCs), combined injectable contraceptives (CICs), contraceptive patches and rings, preogestogen-only pills (POPs), progestogen-only injectables (DMPA and NET-EN), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC Category 1).
- Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) should generally not initiate use of the LNG-IUD (MEC Category 3 for initiation) until their illness has improved to asymptomatic or mild HIV clinical disease (WHO stage 1 or 2). 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.
- Because there may be interactions between certain methods of hormonal contraception and certain antiretroviral medications (ARVs), refer to the recommendations on ART medication interactions (see p. 72).

Remarks

- Hormonal contraceptives do not protect against sexually transmitted infections (STIs), including HIV. Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission to non-infected sexual partners, and for protection against other STIs. Female condoms are effective and safe, but are not used as widely by national programmes as male condoms.
- Voluntary use of contraception by women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.

Summary of the evidence (Question 2: disease progression; Question 3: female-to-male transmission)

Two systematic reviews investigating Questions 2 and 3 informed the contraceptive eligibility recommendations for women living with severe or advanced HIV clinical disease (WHO stage 3 or 4).

All of the identified studies excluded women with severe or advanced HIV clinical disease (WHO stage 3 or 4) from enrolment, although some participants experienced progression to severe or advanced disease during the trials.

Combined hormonal contraceptives (CHCs)

Out of eight available studies, seven suggest no association between use of COCs and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(29–35)*. One randomized trial found an increased risk of a composite outcome of declining CD4 count or death among COC users when compared with users of copper-bearing IUDs (Cu-IUDs) *(36, 37)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women known to be using hormonal contraceptives. One of these studies reported an elevated, but not statistically significant, point estimate for oral contraceptives (OCs) *(5)*. The other study also did not find a statistically significant association for OCs *(4)*.

Studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have had mixed results. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(38–53)*.

Progestogen-only contraceptives (POCs), including LNG-IUD

Out of six available studies, five suggested no association between use of progestogen-only injectable contraceptives and progression of HIV, as measured by CD4 count < 200 cells/mm^3, initiation of ART, or mortality *(31–35).* One randomized trial found an increased risk of a composite outcome of declining CD4 count or death among OC (COC and POP) users when compared with Cu-IUD users; this study, however, had significant loss to follow-up and method-switching among groups, limiting its interpretation *(36, 37)*. One study found no difference in ART initiation or CD4 count between users and non-users of the LNG-IUD *(54)*.

Two prospective observational studies directly assessed the effects of different hormonal contraceptive methods on female-to-male HIV transmission by measuring seroconversions in male partners of women with known hormonal contraceptive use status. One of these studies reported a statistically significant association between injectable contraception and female-to-male transmission of HIV *(5)*, while the other study did not find a statistically significant association between use of DMPA and female-to-male HIV transmission *(4)*.

The findings of studies indirectly assessing the effect of various hormonal contraceptive methods on female-to-male HIV transmission by measuring genital viral shedding as a proxy for infectivity have been mixed. The majority of indirect studies measuring whether various hormonal contraceptive methods affect plasma HIV viral load have found no effect *(38–53)*.

Quality of the evidence

Disease progression – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs):	low
Disease progression – LNG-IUD:	very low
Disease transmission (direct evidence) – progestogen-only injectables (DMPA and NET-EN) and OCs (COCs and POPs):	very low

Note: As there remains considerable uncertainty regarding the best way to measure genital HIV shedding (with respect to collection method, RNA versus DNA, and cell-associated versus cell/free measures of DNA and RNA), studies providing indirect evidence assessing proxy measures of transmission did not undergo a GRADE assessment.

12d. Recommendations among women living with HIV using antiretroviral therapy (ART)

- Women taking any nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) can use all hormonal contraceptive methods without restriction: combined oral contraceptive pills (COCs), contraceptive patches and rings, combined injectable contraceptives (CICs), progestogen-only pills (POPs), progestogen-only injectables (DMPA and NET-EN), and levonorgestrel (LNG) and etonogestrel (ETG) implants (MEC Category 1).
- Women using ART containing either efavirenz or nevirapine can generally use COCs, patches, rings, CICs, POPs, NET-EN and implants (MEC Category 2). However, women using efavirenz or nevirapine can use DMPA without restriction (MEC Category 1).
- Women using the newer non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs), etravirine and rilpivirine, can use all hormonal contraceptive methods without restriction (MEC Category 1).
- Women using protease inhibitors (e.g. ritonavir and ARVs boosted with ritonavir) can generally use COCs, contraceptive patches and rings, CICs, POPs, NET-EN, and LNG and ETG implants (MEC Category 2), and can use DMPA without restriction (MEC Category 1).

- Women using the integrase inhibitor raltegravir can use all hormonal contraceptive methods without restriction (MEC Category 1).
- Women using ARV medication can generally use LNG-IUDs (MEC Category 2), provided that their HIV clinical disease is asymptomatic or mild (WHO stage 1 or 2). Women living with severe or advanced HIV clinical disease (WHO stage 3 or 4) generally should not initiate use of the LNG-IUD (MEC Category 3 for initiation) until their illness has improved to asymptomatic or mild HIV clinical disease. 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.

Remarks

- Hormonal contraceptives do not protect against sexually transmitted infections (STIs), including HIV. Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission to non-infected sexual partners, and for protection against other STIs. Female condoms are effective and safe, but are not used as widely by national programmes as male condoms.
- Voluntary use of contraception by women living with HIV who wish to prevent pregnancy is critical for upholding their reproductive rights and continues to be an important strategy for reducing vertical HIV transmission. All women have the right to evidence-based, comprehensive contraceptive information, education and counselling to ensure informed choice. Women's contraceptive choices are made in a particular time, societal and cultural context; choices are complex, multifactorial and subject to change. Decision-making for contraceptive methods usually requires the need to make trade-offs among the different methods, with advantages and disadvantages of specific contraceptive methods varying according to individual circumstances, perceptions and interpretations.
- Women living with HIV and using ARVs should discuss the potential impact of certain ARVs on contraceptive efficacy with their health-care provider.

Summary of the evidence (Question 4: hormonal contraception–ART interactions)

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)

NRTIs do not appear to have significant risk of interactions with hormonal contraceptive methods *(55, 56)*.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Three clinical studies, including one large study, found use of nevirapine-containing ART did not increase ovulation or pregnancy rates in women using COCs *(57–60)*. For efavirenz-containing ART, a pharmacokinetic study showed consistent significant decreases in contraceptive hormone levels in women using COCs, and a small clinical study showed higher ovulation rates in women taking efavirenz-containing ART and COCs *(57, 61, 62)*. Etravirine and rilpivirine do not interact with COCs *(63, 64)*. One retrospective chart review of women using efavirenz-containing ART showed increased contraceptive failure rates for women using LNG implants *(65)*. Based primarily on pharmacokinetic data, the effectiveness of DMPA is likely not affected by NNRTIs, and vice versa *(66, 67)*.

Protease inhibitors (PIs)

Pharmacokinetic data suggest decreases in COC progestin levels with ritonavir and ritonavir-boosted PIs. In women using the patch, co-administration resulted in higher progestin levels *(68)*. One study found higher progestin levels with concurrent PI use in users of POPs *(69)*. Based primarily on pharmacokinetic data, the effectiveness of DMPA is likely not affected by PIs, and vice versa *(66, 67)*.

Integrase inhibitors

The integrase inhibitor raltegravir does not appear to interact with COCs *(55, 56, 70, 71)*.

Quality of the evidence

Hormonal contraception + ART versus hormonal contraception alone:	very low
Efavirenz-containing ART versus other ART in women using hormonal contraception:	very low
ART + hormonal contraception versus ART alone:	low

GRADE table 1 (Question 1): Does the use of a particular method of hormonal contraception directly increase the risk of HIV acquisition in women?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Overall quality	Estimate of effect
Injectable contraceptive use vs non-use							
HIV acquisition	9 cohort studies[a] (n=28 219)	Serious limitations[a]	Serious inconsistency	No serious imprecision	No indirectness	Low	Injectables overall: hazard ratio (HR) or incidence rate ratio (IRR) range 0.94–2.0 in 9 studies: 6 studies increased risk (HR range 1.1–2.0), with statistically significant effects in 4 studies; 1 study no effect (HR 0.94, 95% CI 0.46–1.92); 2 studies no clear effect (NET-EN and DMPA reported separately with no clear association and opposite effects for each type of hormonal contraceptive) DMPA: HR range 0.46–2.0 in 6 studies: 4 studies increased risk (HR range 1.3–2.0), with statistically significant effects in 1 study; 2 studies trend towards decreased effect (HRs 0.46 and 0.75) NET-EN: HR range 0.87–2.5 in 5 studies: 4 studies increased risk (HR range 1.3–2.5), with statistically significant effects in 1 study; 1 study no effect (HR 0.87, 95% CI 0.60–1.2)
Oral contraceptive use vs non-use							
HIV acquisition	8 cohort studies[a] (n=27 585)	Serious limitations[a]	Serious inconsistency	No serious imprecision	No indirectness	Low to moderate	HR or IRR range 0.66–1.8 in 8 studies: 1 study increased risk (HR 1.5, 95% CI 1.0–2.1); 1 study trend towards increased risk (HR 1.8, 95% CI 0.55–5.8); 1 study trend towards decreased risk (IRR 0.66, 95% CI 0.09–4.78); 5 studies no effect (HR range 0.86–0.99)[b]
Implant use vs non-use							
HIV acquisition	1 cohort study (n=1272)	Serious limitations	Cannot determine (1 study)	Serious imprecision		Very low	HR 1.6 (95% CI 0.5–5.7)

CI: confidence interval; DMPA: depot medroxyprogesterone acetate; HR: hazard ratio; IRR: incidence rate ratio; NET-EN: norethisterone enanthate.

Note: For all the studies summarized for this question, effects are based on adjusted risk estimates; Cox model analysis results were used when different statistical methods were presented.

[a] Restricted to studies classified as "considered informative with important limitations"; while all of these studies had important limitations or risk of bias, no study had all three major flaws – i.e.: (i) no adjustment for any measure of condom use; (ii) unclear measurement of exposure to hormonal contraception; (iii) inter-survey interval (time between study visits) < 6 months – and therefore were given an overall quality rating of "low" rather than "very low". An explanation of the quality assessment for each study included in this table is described in the systematic review by Polis et al., 2014 *(28)*.

[b] One study (McCoy et al., 2013) stratified estimates for COC (HR 0.78, 95% CI 0.53–1.12) and POP (HR 0.91, 95% CI 0.49–1.50) *(3)*.

GRADE table 2 (Question 2): Does the use of various hormonal contraceptive methods accelerate HIV disease progression in women living with HIV?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Quality	Estimate of effect
Hormonal contraception (oral or injectable) vs copper-bearing intrauterine device (Cu-IUD)							
Mortality	1 RCT (n=599)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	Low	HR 1.4 (95% CI 0.7–3.0); absolute risk increase 0.88/100 woman-years; HR 1.1 (95% CI 0.38–3.0) for OC and 1.4 (95% CI 0.63–3.1) for DMPA
Progression to CD4 count < 200 cells/mm^3	1 RCT (n=599)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	Low	HR 1.6 (95% CI 1.0 to 2.3); absolute risk increase 3.7/100 woman-years; HR 1.5 (95% CI 0.98–2.4) for OC and 1.8 (95% CI 1.3–2.6) for DMPA for CD4 count progression or initiation of ART
Mortality or progression to CD4 count < 200 cells/mm^3	1 RCT (n=599)	Serious limitations (1 fair)	Cannot determine (1 study)	Serious imprecision	No indirectness	Low	HR 1.6 (95% CI 1.1–2.3); absolute risk increase 4.6/100 woman-years; HR 1.5 (95% CI 1.0–2.3) for OC and 1.8 (95% CI 1.3–2.5) for DMPA for mortality, CD4 count progression or initiation of ART
Injectable contraceptive use vs non-use							
Mortality	5 cohort studies (n=7136)	Serious limitations (1 good, 3 fair, 1 poor)	Serious inconsistency	No serious imprecision	No indirectness	Low	HR range 0.41–1.4 in 5 studies (no estimate showed statistically significant effect)
Progression to AIDS or initiation of antiretroviral therapy (ART)	4 cohort studies (n=6308)	Serious limitations (1 good, 2 fair, 1 poor)	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate	HR range 0.7–1.0 in 3 studies (no estimate showed statistically significant effect); 1 study reported HR 0.91 (95% CI 0.61–1.36) for ART initiation and HR 0.82 (95% CI 0.57–1.17) for progression to CD4 count < 200 cells/mm^3
Mortality, progression to AIDS or initiation of ART	4 cohort studies (n=6851)	Serious limitations (2 good, 2 fair)	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate	HR range 0.72–1 in 4 studies; 1 study reported HR of 0.72 (95% CI 0.53–0.98); estimate not statistically significant in other studies

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Quality	Estimate of effect
Oral contraceptive use vs non-use							
Mortality	6 cohort studies (n=6864)	Serious limitations (1 good, 3 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate	HR range 0.28–1.1 in 4 studies (no estimate showed statistically significant difference)[a]; 2< 200 cells/mm^{3}studies reported no events
Progression to AIDS or initiation of ART	5 cohort studies (n=6078)	Serious limitations (1 good, 2 fair, 2 poor)	No serious inconsistency	No serious imprecision	No indirectness	Low	HR range 0.84–1.3 in 4 studies (no estimate showed statistically significant effect)[a]; 1 study reported HR 0.61 (95% CI 0.25–1.45) for ART initiation and HR 0.96 (95% CI 0.52–1.79) for progression to CD4 count < 200 cells/mm^3
Mortality, progression to AIDS or initiation of ART	4 cohort studies (n=6059)	Serious limitations (2 good, 2 fair)	No serious inconsistency	No serious imprecision	No indirectness	Low-moderate	HR range 0.65–1.0 in 4 studies (no estimate showed statistically significant effect)[a]
Levonorgestrel IUD vs no hormonal contraception							
Initiation of ART	1 study (n=40)	Very serious limitations (1 poor)	Cannot determine (1 study)	Very serious imprecision	No indirectness	Very low	43% vs 45%, $P = 0.91$

ART: antiretroviral therapy; CI: confidence interval; DMPA: depot medroxyprogesterone acetate; HR: hazard ratio; OC: oral contraceptives; RCT: randomized controlled trial.

[a] Includes data from Heffron et al. (2013) on risk with DMPA and OC separately *(29)*.

GRADE table 3 (Question 3): Does the use of various hormonal contraceptive methods increase the risk of female-to-male HIV sexual transmission?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Quality	Estimate of effect[a]
Injectable hormonal contraceptive use vs non-use							
HIV transmission	2 cohort studies (n=2635)	Serious limitations (2 fair)[b]	Serious inconsistency	Very serious imprecision	No indirectness	Very low	HR 2.0 (95% CI 1.1–3.6) and 0.57 (95% CI 0.19–1.70)[c]
Oral hormonal contraceptive use vs non-use							
HIV transmission	2 cohort studies (n=2635)	Serious limitations (2 fair)[b]	No serious inconsistency	Very serious imprecision	No indirectness	Very low	HR 2.1 (95% CI 0.75–5.8) and 2.5 (95% CI 0.49–13)[c]

CI: confidence interval; HR: hazard ratio.

a Combined estimate from Heffron et al. (2012) for injectable or oral hormonal contraceptive use vs non-use: HR 2.0 (95% CI 1.1–3.4); absolute increase about 1 transmission/100 person-years *(5)*.

b Lutalo et al. (2013) rated fair-quality *(4)*, Heffron et al. (2012) not rated but limitations noted in assessment of condom use and potential for residual confounding *(5)*.

c HR 1.40 (95% CI 0.30–6.49) for injectable and 2.11 (95% CI 0.18–2.5) when adjusted for viral load.

GRADE table 4 (Question 4): Are there any possible interactions between hormonal contraceptive methods and ARV medications?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Hormonal contraception + antiretroviral therapy (ART) vs hormonal contraception alone								
Pregnancy	1 non-randomized trial (n=336); 1 cohort study (n=4531)	Serious limitations (1 good-quality non-randomized trial, 1 poor-quality cohort study)	No serious inconsistency	No serious imprecision	No indirectness	Variability in hormonal contraception	Very low	1 non-randomized trial found no difference in pregnancy rate with nevirapine-based ART + COC vs no ART; 1 cohort study found lower pregnancy rate prior to initiation of ART vs after initiation in women on various hormonal contraceptives, but estimates were imprecise (IRR 3.11 [95% CI 1.55–6.21] vs 5.38 [95% CI 2.89–10.00] for COC and 1.10 [95% CI 0.63–1.94] vs 1.97 [95% CI 1.28–3.01] for injectables)
Efavirenz (EFV) vs other ART in women using hormonal contraception								
Pregnancy	2 cohort studies (n=1197)	Serious limitations (2 fair)	Unclear	Serious imprecision	No indirectness	Denominators not provided in 1 study	Very low	1 study found 12.4% pregnancy rate with EFV vs 0% with nevirapine (NVP) or loopinavir (LPV)/ritonavir (RTV) in women using LNG implant; 1 study reported 1 failure with EFV vs 7 with NVP in women using various hormonal contraceptives, but denominators were unclear
ART + hormonal contraception vs ART alone								
ART effectiveness	3 cohort studies (n=679)	Serious limitations (2 fair, 1 poor)	No serious inconsistency	Serious imprecision	No indirectness	Variability in hormonal contraception, ART regimens, and measures of ART effectiveness	Low	No effect of hormonal contraception on measures of ART treatment failure in 3 studies (1 study of DMPA, 1 study of COCs, and 1 study of both)

CI: confidence interval; COC: combined oral contraceptive; DMPA: depot medroxyprogesterone acetate; IRR: incidence rate ratio.

Note: Table includes evidence from comparative studies reporting clinical outcomes.

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