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Acronyms and abbreviations

CIRE	Continuous Identification of Research Evidence
COC	combined oral contraceptive
Cu-IUD	copper-bearing intrauterine device
CVR	combined contraceptive vaginal ring
DMPA	depot medroxyprogesterone acetate
DMPA-IM	DMPA, administered intramuscularly
DMPA-SC	DMPA, administered subcutaneously
EC	emergency contraception
ECP	emergency contraceptive pill
ETG	etonogestrel
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
IM	intramuscular
IUD	intrauterine device
LNG	levonorgestrel
LNG-ECP	levonorgestrel emergency contraceptive pill
LNG-IUD	levonorgestrel-releasing intrauterine device
MEC	<i>Medical eligibility criteria for contraceptive use</i> (WHO publication)
NET-EN	norethisterone enanthate
NIH	National Institutes of Health (United States of America)
OC	oral contraceptive
PICO	population, intervention, comparator, outcome
PID	pelvic inflammatory disease
POC	progestogen-only contraceptive
POI	progestogen-only injectable
POP	progestogen-only pill
RCT	randomized controlled trial
SC	subcutaneous
SI(II)	Sino-implant (II) [®]
SPR	<i>Selected practice recommendations for contraceptive use</i> (WHO publication)
STI	sexually transmitted infection
UPA	ulipristal acetate
UPA-ECP	ulipristal acetate emergency contraceptive pill
WHO	World Health Organization

1

Background: 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 These outdated policies or practices often result in limitations to both the quality of and the access to family planning services for clients.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 and decision-makers with a set of recommendations on how to use family planning methods safely and effectively once they are deemed medically appropriate.

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 guidelines according to national health policies, needs, priorities and resources, while reflecting upon local values and preferences.

There are a total of four World Health Organization (WHO) guidance documents (cornerstones) pertaining to contraception: two focusing on evidenced-based recommendations (primarily targeted towards policy-makers and programme managers) and two focusing 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 documents are updated periodically to reflect changes in medical and scientific knowledge (see Figure 1).

Evidence-based guidelines on contraception for policy-makers and programme managers:

1. **Medical eligibility criteria for contraceptive use (MEC)**¹ – provides guidance on *who* can use contraceptive methods safely; and
2. **Selected practice recommendations for contraceptive use (SPR)**² – provides guidance on *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**³ – 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**⁴ – offers evidence-based information on service delivery, method by method.

¹ Published in 2015. Available at: http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/

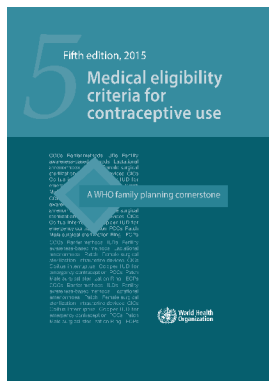
² Available at: www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

³ Published in 2005. Available at: http://www.who.int/reproductivehealth/publications/family_planning/9241593229index/en/

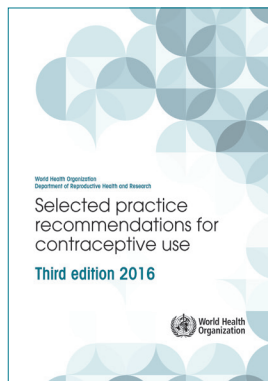
⁴ Published in 2011. Available at: http://www.who.int/reproductivehealth/publications/family_planning/9780978856304/en/

Figure 1. The four cornerstones of family planning guidance

Target audience: Policy makers and programme managers

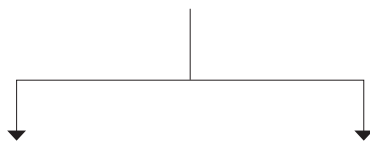


Medical eligibility criteria for contraceptive use
Guidance on *who* can use contraceptive methods safely



Selected practice recommendations for contraceptive use
Guidance on *how* to use contraceptive methods safely and effectively

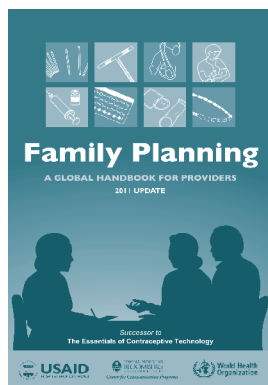
These are evidence-based guidance and consensus-driven guidelines. They provide recommendations made by expert working groups based on an appraisal of relevant evidence. They are reviewed and updated in a timely manner.



Target audience: Providers of contraceptive counselling and services

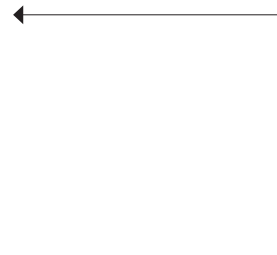


Decision-making tool for family planning clients and providers



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.

2

Methods

2.1 Development of earlier editions of the Selected practice recommendations for contraceptive use

The third edition of the SPR¹ and this Web annex build on a process initiated in 2000 that culminated in the 2002 publication of the first edition of the SPR guideline.

Since the publication of the first edition of the SPR, the guideline was revised in 2004 (1) and five recommendations were further updated in 2008 (2). For each revision, a multidisciplinary Guideline Development Group (GDG) of experts is assembled to review newly published evidence pertaining to the topics addressed in the guideline (during the previous SPR revisions, this group was called the “expert Working Group”).

The Guidelines Review Committee (GRC) was established by the WHO Director General 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 five recommendations updated in 2008 were reviewed and approved by the newly established GRC.

To assure that the guidelines remain current between guideline meetings, new evidence is identified through an ongoing comprehensive bibliographic search (the Continuous Identification of Research Evidence, or CIRE system) (3). This evidence is synthesized and reviewed. In circumstances where new evidence warrants further evaluation, the

Guideline Steering Group (GSG) is tasked with evaluating such evidence and issuing interim guidance, if necessary.

2.2 Development of the third edition of the SPR

In preparation for the third edition of the SPR guideline, approval for the proposal was obtained from the GRC, which also ultimately approved the final document. 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 (4). 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, and drafting questions relating to population, intervention, comparator and outcome (PICO) to guide the preparation of systematic reviews; and
- applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evidence review and recommendation formulation.²

The groups responsible for the development of the third edition of the SPR included: a WHO Secretariat; an Evidence Secretariat including a GRADE methodologist; a Guideline Steering Group (GSG); and a Guideline Development Group (GDG). The GSG, which has served as an external advisory group to WHO on family planning guidelines since 2003, was part of

¹ Available at: www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

² For further information on GRADE, see: www.gradeworkinggroup.org/index.htm

the larger GDG, to be compliant with WHO requirements for guideline development and to gain input from a larger advisory group. For lists of the members of the WHO Secretariat, the Evidence Secretariat and the GDG, see the Acknowledgements section at the beginning of the SPR third edition.

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 third edition of the SPR. Prior to the meeting, the CIRE system was used to identify those recommendations 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. These stakeholders 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 SPR, 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 priorities for the current revision, 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 each 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 determined by the GDG to need no further review during the revision process for the SPR third edition.

At the first GDG meeting in May 2013, the members were also asked to consider what additional guidance was needed by providers of contraceptive services, including guidance on contraceptive methods that had only recently become available. The GDG also considered practice recommendations for contraceptive methods that were added to WHO's *Medical eligibility criteria for contraceptive use, fifth edition* (MEC, 2015) (5), and thus not addressed in previous editions of the SPR guidance.

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 for which there was new evidence, such that the existing recommendation was potentially inconsistent with the updated body of evidence; and
- newly introduced contraceptive methods.

The 19 prioritized topics related to the inclusion in the third edition of the SPR of five new contraceptive methods and one additional question; these are presented in Table 1. All existing recommendations that did not fall into one of these categories were reaffirmed by the GDG and thus were not reviewed.

For each of the topics and new contraceptive methods outlined in Table 1, the GDG developed questions using the PICO format (i.e. questions with specified populations,

Table 1: Prioritized topics reviewed by the Guideline Development Group (GDG) for the SPR third edition, using the GRADE approach

New contraceptive methods added to the SPR for the third edition (5 methods)

- 2-rod levonorgestrel (LNG)-containing implant with 75 mg LNG per rod, approved for 4 years of use: Sino-implant (II)[®]
- subcutaneously administered depot medroxyprogesterone acetate (DMPA-SC)
- combined contraceptive transdermal patch (the patch)
- combined contraceptive vaginal ring (CVR)
- ulipristal acetate emergency contraceptive pills (UPA-ECPs)

Additional question on a topic identified as controversial or of particular importance to the field (1 question)

- When can a woman resume or start regular contraception after using emergency contraception?

Note: All other existing recommendations from the SPR second edition (1) and 2008 update (2) were reaffirmed by the GDG in March 2014 and thus not reviewed for the SPR third edition.³

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

³ Evidence continuously monitored using CIRE system. Topics not prioritized for update.

interventions, comparators and outcomes) to serve as the framework for the systematic reviews and GRADE evidence tables. In order to inform the SPR recommendations, the PICO questions generally guided the systematic review to focus on studies of populations using a specific contraceptive method compared with the same population not using the method, reporting on critical outcomes related to safety and effectiveness. PICO questions were also crafted to identify relevant indirect evidence that may have reported on surrogate outcomes related to safety and effectiveness. 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 edition.

2.4 Evidence identification and synthesis

For each of the priority topics listed in Table 1, systematic reviews were conducted according to PRISMA guidelines (6). The systematic reviews are listed with full reference details in Appendix 1. To inform the systematic reviews, the PubMed and Cochrane databases were searched for direct and indirect evidence published in any language in a peer-reviewed journal up to 15 January 2014. Reference lists and direct communication with experts in the field were also used to identify other studies, including those accepted by journals but not yet published; neither grey literature nor conference abstracts were included in these reviews. When no direct evidence corresponding to the PICO

questions was identified, indirect evidence such as extrapolation from studies relating to similar contraceptive methods or evidence for proxy measures of clinical outcomes was considered. For example, evidence on combined oral contraceptives (COCs) was considered for recommendations for the combined contraceptive transdermal patch and the combined contraceptive vaginal ring (CVR), evidence for one type of levonorgestrel implant was considered for another type of levonorgestrel implant, and markers of ovulation were used as a proxy measure for risk of pregnancy. Due to the heterogeneity of study design, contraceptive formulations and outcome measures, meta-analyses were generally not performed. The quality of the direct and indirect evidence presented in individual studies included within a systematic review was assessed by review authors using the United States Preventive Services Task Force system (7). GRADE evidence tables for the direct evidence were then prepared by a GRADE methodologist to assess the quality of the summarized evidence; these profiles included the range of the estimates of effect for each clinical outcome assessed. GRADE evidence tables were prepared for each PICO question for which direct evidence was found and clinical outcomes were reported. The systematic reviews that resulted from this process, which summarized the direct and indirect evidence, 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 tables for each

topic were given to GDG members during the consultations. The GDG's deliberations were based upon these written and orally presented systematic reviews and GRADE evidence tables.

2.5 Decision-making during the Guideline Development Group meetings

During 9–12 March 2014, WHO convened a series of GDG meetings to review the evidence for the prioritized topics and, where appropriate, revise specific recommendations for the third edition of the SPR. Members of the GDG and members of an External Peer Review Group (who did not participate in the GDG meeting; see Acknowledgements for members' names and institutional affiliations) submitted Declaration of Interest forms to the WHO Secretariat: 14 individuals declared an academic conflict of interest relevant to the SPR guidance. The WHO Secretariat and the GDG reviewed all declarations of interest and, with the exception of one member, Anna Glasier, found no conflicts of interest sufficient to preclude anyone from participating in the deliberations or development of recommendations. In the case of Anna Glasier, the WHO Secretariat and the GDG agreed that the disclosed academic conflict of interest was sufficient to preclude her from participating in the deliberations and development of recommendations relevant to ulipristal acetate. For details of the declared academic interests see Appendix 2.

The GDG considered the overall quality of the evidence, paying particular attention to the strength and consistency of the data, according to the GRADE approach to evidence assessment. In most cases, data came from direct evidence from observational studies, for which the quality of evidence was generally categorized as low or very low, as well as from indirect evidence, when direct evidence was not available. To arrive at the service delivery recommendations, the GDG considered the GRADE evidence tables of the direct evidence, any indirect evidence (in the absence of direct evidence), the benefits of preventing

unintended pregnancy, potential harms associated with barriers to contraceptive use, and the other GRADE constructs of values and preferences.

To document the values and preferences of contraceptive users, a systematic review was conducted of peer-reviewed studies published between 2005 and 2014 (8). Articles were included if they presented primary data (qualitative or quantitative) on contraceptive users' values, preferences, views and concerns regarding the contraceptive methods considered in the SPR guidelines. Data on health-care providers' values, preferences, views and concerns about contraception were also collected. A systematic search of 10 electronic databases and secondary references identified 1647 unique citations, of which 109 were deemed eligible for inclusion in the review. Studies were geographically diverse, representing all regions of the world. While most studies focused generally on women of reproductive age, some considered the views of specific groups, such as adolescents, nulliparous women, postpartum women, women seeking abortion services and women living with HIV. Six studies examined provider perspectives.

Across studies, values and preferences relating to contraceptive methods consistently centred on themes of choice, ease of use, side-effects and efficacy. Women wanted to have a range of contraceptive options that were simple to use, had few side-effects and worked to prevent unwanted pregnancy. Less commonly reported considerations were cost, availability and partner approval. Women desired comprehensive, accurate information about their contraceptive options. While women generally wanted control over their final choice of method, many also wanted their health-care providers to participate in the decision-making process in a way that emphasized the women's values and preferences. Providers also valued women's choices in deciding on contraceptive methods, and recommended methods based on their efficacy and safety as well as the women's preferences, although there were

some gaps between provider knowledge about contraceptive method safety and their actual practices. Specific method preferences varied by study and setting, although women generally reported satisfaction with methods they were using.

Due to the findings of this systematic review, the GDG endorsed an approach to patient preferences and values that prioritized the availability of a wide range of contraceptive options and the removal of unnecessary medical barriers. This approach facilitates access to contraceptive services by engaging a woman's unique personal preferences in contraceptive selection as well as the values she places on possible risks and benefits (9, 10). Decisions on contraceptive selection are complex, multifactorial and changeable because they are based on each woman's unique temporal, societal and cultural context. Hence, it is critical that each woman be afforded the right to choose from a wide range of contraceptive options (11, 12). Decision-making for contraceptive methods requires weighing the advantages and disadvantages of specific methods according to individual circumstances, perceptions and interpretations. The GDG incorporated information on women's values and preferences related to choice, ease of use, side-effects and efficacy by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on available evidence.

To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. While issues of potential harms associated with specific contraceptive methods (e.g. risk of venous thromboembolism associated with COC use) were considered in specific situations, these harms are thoroughly considered in WHO's *Medical eligibility criteria for contraceptive use, fifth edition* (5).

The SPR guidance does not recommend one contraceptive method over another; rather, it provides guidance on how to safely provide the method chosen by the woman through shared decision-making with her provider. Owing to the focus of this guidance on the safe provision of contraceptive methods, and since costs may vary widely throughout different regions, opportunity costs were not formally assessed during the formulation of these recommendations.

For the updated third edition of the SPR, the GRADE approach was used to classify recommendations on reviewed topics as "strong" or "conditional". Because the target audience for the SPR is primarily policy-makers, when the GDG classifies a recommendation as "strong" it is because the GDG is very certain that the desirable consequences outweigh the undesirable consequences and the recommendation can thus be adopted as policy in most situations, indicating that most individuals should adhere to the recommendations for quality family planning care. "Conditional" recommendations are issued when there is uncertainty about the balance of harms and benefits; substantial debate and involvement of various stakeholders is required before such recommendations become policy, as described in the *WHO handbook for guideline development, second edition* (4). Despite the low or very low quality of most of the evidence, the majority of updated recommendations in the revised SPR were classified as "strong".

In the SPR third edition, recommendations are presented in narrative form for readers accustomed to the format of previous SPR editions. For the recommendations on examinations and tests prior to initiating use of each contraceptive method, an A-B-C classification is employed to define whether various procedures are necessary for the safe provision of the method. Through consensus, the GDG arrived at new and revised recommendations and upheld the majority of the existing recommendations. Consensus was achieved through discussion, debate and expert consultation, with final

agreement among all the members of the GDG. For each recommendation, the Chair asked GDG members whether they agreed with the recommendation; any disagreement was documented. All GDG members agreed with all of the recommendations in the guideline.

A draft version of the entire SPR document was sent to the External Peer Review Group, comprising six 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 25 May 2016.

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3

Dissemination and evaluation

A plan for guidance dissemination and evaluation of this third edition of the *Selected practice recommendations for contraceptive use* 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 Group), 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 will be organized

following the launch of the SPR on 14th December 2016. In addition, special panel sessions will be organized during international and regional conferences convened by the International Federation of Gynecology and Obstetrics (FIGO), the International Council of Nurses (ICN) and the International Confederation of Midwives (ICM) to inform the membership of these societies about the revised recommendations. Once translations of the document become available in other official languages of the UN, 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 in national policies, and identify areas for further refinement and research gaps in contraceptive provision.

4

Reviewed recommendations

The Guideline Development Group (GDG) determined priority topics to be addressed as part of the revision process for the *Selected practice recommendations for contraceptive use, third edition*; these topics are summarized in Table 1, section 2.3.

Information on all the new, revised and confirmed practice recommendations on contraceptive use and a summary of changes between the second and third editions of the SPR are presented in the SPR third edition,¹ to which this document is an annex.

4.1 Recommendations for addition of Sino-implant (II)[®] as a new method to the SPR

Recommendations for progestogen-only implants included in the SPR second edition (2004) refer to implants containing levonorgestrel (LNG) and etonogestrel (ETG). LNG-containing implants included in that edition were Norplant[®] (a 6-rod implant, each rod containing 36 mg of LNG, approved for five years of use, but no longer in production) and Jadelle[®] (a 2-rod implant, each rod containing 75 mg of LNG, approved for five years of use). The ETG implant included in the second and third edition of the SPR is a single-rod implant containing 68 mg of ETG, approved for three years of use; brand names are Implanon[®] and Nexplanon[®].

For the third edition of the SPR, the GDG considered evidence on a newly available LNG-containing implant, Sino-implant (II). Sino-

implant (II), or SI(II), is a 2-rod LNG-containing implant, each rod containing 75 mg of LNG, approved for four years of use.

4.1.a Initiation of Sino-implant (II)

Clinical question: When can a woman start Sino-implant (II)?

PICO question for systematic review

Population	Women initiating Sino-implant (II)
Intervention	Initiation on specified days of the menstrual cycle
Comparator	Women initiating Sino-implant (II) according to different initiation schedules/different days of the menstrual cycle
Outcomes	Risk that a woman is already pregnant when initiating Sino-implant (II), contraceptive effectiveness (i.e. risk that a woman becomes pregnant after initiating Sino-implant (II)), contraceptive side-effects and contraceptive continuation

Recommendations

The GDG determined that recommendations for starting SI(II) are the same as recommendations for starting other progestogen-only implants. These recommendations include timing of initiation for women with regular menstrual cycles, women with amenorrhoea, women who are postpartum and breastfeeding or not breastfeeding, and women who are post-abortion or switching from other contraceptive methods (i.e. hormonal, nonhormonal or intrauterine devices). No changes to the earlier recommendations for the timing of initiation of progestogen-only implants were necessary with the inclusion of SI(II) as a new method in the SPR third edition.

¹ Available at: www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

NEW recommendation 1.1

A woman can start Sino-implant (II), or SI(II), within 7 days after the start of her menstrual bleeding; she can also start at any other time if it is reasonably certain that she is not pregnant. Recommendations are also available for when additional protection is needed and for women who are: amenorrhoeic, postpartum, post-abortion, switching from another method.

Quality of the evidence: No direct evidence.

Strength of the recommendation: Strong.

Evidence summary

A search for evidence on initiation of SI(II) yielded 105 articles, none of which met inclusion criteria for direct evidence (1). One small study was identified that provided evidence on LNG levels after SI(II) was inserted in 10 women on days 1–7 of the menstrual cycle. By one week post-insertion the mean LNG level was 0.65 ng/mL, and by four weeks post-insertion the mean LNG level was 0.3 ng/mL, before stabilizing at a mean of 0.28 ng/mL (2). As SI(II) is highly effective for at least four years of continuous use, during which time serum LNG levels are lower than at one week after insertion (3), this higher initial level of LNG likely indicates that the implant is effective at least as early as one week after insertion. The GDG also examined similarities between SI(II) and the LNG and ETG implants that had already been included in the second edition of the SPR and concluded that there were no major differences that would result in different recommendations for SI(II).

Rationale

No direct evidence was identified. Therefore, recommendations for initiation of SI(II) are based on indirect evidence from studies on other types of progestogen-only implants and from proxy outcomes for SI(II). Due to the similarities among progestogen-only implants with regard to safety profile, pharmacokinetic and pharmacodynamic properties, delivery system and mechanism of action (1), the GDG concluded that evidence from other progestogen-only implants can be extrapolated to SI(II). Further, the GDG reviewed additional supporting evidence from a systematic review (1) that was prepared as part of the development of WHO's *Medical*

eligibility criteria for contraceptive use, fifth edition (MEC) guideline, which noted that different progestogen-only implants exhibit similar safety profiles (4). To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC. The values and preferences of women were also integral components in the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. Delay in initiation of contraception may increase the risk of unintended pregnancy. The GDG therefore determined that the benefits of initiation far outweighed any potential harms, and thus classified these recommendations as a "strong".

4.1.b Examinations and tests needed before initiation of Sino-implant (II)

Clinical question: What examinations and tests are appropriate before initiating the SI(II)?

PICO question for systematic review

Population	Women initiating Sino-implant (II)
Intervention	Selected examinations and tests, including blood pressure measurement, lab screenings (glucose, lipids, liver enzymes), clinical examinations (clinical breast examination, pelvic examination), prior to initiating method
Comparator	Women initiating the Sino-implant (II) without these examinations and tests
Outcomes	Incidence of selected adverse health outcomes (adverse cardiovascular outcomes, adverse changes to glucose levels, incidence of diabetes, adverse changes to lipid levels, and liver disorders)

Recommendations

The GDG determined that recommendations for examinations and tests needed before initiating the SI(II) are the same as recommendations for examinations and tests needed before initiating other contraceptive

implants. Current recommendations address: breast examination by provider, pelvic/genital examination, cervical cancer screening, routine laboratory tests, haemoglobin test, sexually transmitted infection (STI) risk assessment (medical history and physical examination), STI/HIV screening (laboratory tests) and blood pressure screening.

NEW recommendation 1.2

It is desirable to have blood pressure measurements taken before initiation of SI(II). Women should not be denied use of SI(II) simply because their blood pressure cannot be measured.

NEW recommendation 1.3

Breast examination by provider, pelvic/genital examination, cervical cancer screening, routine laboratory tests, haemoglobin test, STI risk assessment (medical history and physical examination) and STI/HIV screening (laboratory tests) do not contribute substantially to the safe and effective use of SI(II).

Quality of evidence: No direct evidence.

Strength of recommendation: Strong.

Evidence summary

Three systematic reviews were conducted to review evidence on examinations and tests needed before initiating hormonal contraception. No evidence on contraceptive implants was identified in any of these reviews, which focused on other hormonal contraceptives. One systematic review examined evidence on the utility of blood pressure measurement prior to initiating combined oral contraceptive pills (COCs); evidence from this review suggests that cardiovascular outcomes are worse among women not receiving blood pressure measurement prior to initiating COCs compared with those who do have their blood pressure measured first (5). In a second systematic review, no evidence was identified comparing health outcomes among women who received laboratory screening prior to initiating COCs with those did not receive these laboratory tests (6). In a third systematic review, no evidence was identified comparing health outcomes among women who received clinical breast examinations or pelvic examinations prior to initiating COCs with those among women who did not receive these physical

examinations (7). This third review included data on the adolescent population, which showed no difference in incidence of STIs, Papanicolaou risk factors or abnormalities, or wet mount results in those who received pelvic examinations when initiating oral contraceptives or DMPA versus those who did not receive pelvic examinations (7).

Rationale

No direct evidence was identified. Therefore, recommendations for examinations and tests prior to implant initiation are based on indirect evidence from studies on COCs, and prior SPR recommendations for other progestogen-only implants. Due to the similar hormonal components and safety profiles among COCs, and similarities in safety profile, pharmacokinetic and pharmacodynamic properties, delivery system and mechanism of action among progestogen-only implants, the GDG concluded that evidence from COCs and other progestogen-only implants can be extrapolated to SI(II). Further, the GDG reviewed additional supporting evidence from a systematic review (1) that was prepared as part of the development of the MEC guideline (4), which noted that different progestogen-only implants exhibit similar safety profiles. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC. The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, into determining which examinations and tests are necessary to ensure safety of contraceptive provision while removing unnecessary medical barriers.

Examinations and tests that are not necessary to determine medical eligibility for contraception may pose barriers to

contraceptive access. The examinations or tests noted apply to persons who are presumed to be healthy. These classifications focus on the relationship of the examinations or tests to safe initiation of a contraceptive method. They are not intended to address the appropriateness of these examinations or tests in other circumstances. For example, some of the examinations or tests that are not deemed necessary for safe and effective contraceptive use may be appropriate for good preventive health care or for diagnosing or assessing suspected medical conditions. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as “strong” recommendations.

4.1.c Duration of Sino-implant (II) use

Clinical question: How long may the Sino-implant (II) be left in place?

PICO question for systematic review

Population	Women initiating Sino-implant (II)
Intervention	Duration of use
Comparator	Women initiating another contraceptive method (Norplant, Jadelle, Sino Implant [I]) beyond five years of use
Outcomes	Cumulative pregnancy rates for each year of use, starting with year 1 and ending with the completion of year 7

Recommendations

The GDG determined that recommendations for duration of use for Sino-implant (II) will follow the product labelling, which states that the implant can be left in place for up to four years.

NEW recommendation 1.4

The product labelling for SI(II) states that the implant can be left in place for up to four years.

Quality of evidence: Low (see GRADE evidence table: Duration of Sino-implant (II) use: how long may SI(II) be left in place?)

Strength of recommendation: Strong.

Evidence summary

A systematic review was conducted to assess the evidence on how long the SI(II) implants may be used continuously. Eleven studies were identified which revealed that SI(II) implants remain highly effective at preventing pregnancy through five years of continuous use, although some studies show higher pregnancy rates during the fourth and fifth years of use in comparison with users of other contraceptive implants. Evidence on the efficacy of SI(II) beyond the fifth year is limited. The method may continue to be effective during the sixth year of use, and may be less effective during the seventh year of use, but the small sample sizes and the methodologies of the studies make interpretation of these findings difficult (12).

Rationale

The direct evidence for this recommendation was categorized as low quality. To address potential harms of this recommendation, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in WHO’s Medical eligibility criteria for contraceptive use (12). The values and preferences of women were also integral components to the process of translating evidence into a recommendation. The GDG incorporated benefits and harms, women’s values and preferences of choice, ease of use, side effects and efficacy by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. The GDG agreed that the evidence aligns with the product labelling of four years for duration of continuous use and the benefits of this recommendation outweigh any potential harms, therefore, this translated to a “strong” recommendation. There are ongoing studies further investigating this question of duration of use for SI(II).

4.1.d Follow-up after Sino-implant (II) initiation

Clinical question: What is the appropriate follow-up for SI(II) users?

PICO question for systematic review

Population	Women initiating Sino-implant (II)
Intervention	Specified follow-up schedule
Comparator	Women initiating Sino-implant (II) with a different follow-up schedule or no follow-up at all
Outcomes	Measures of contraceptive use (e.g. pregnancy, correct use, consistent use, method discontinuation) or adverse health outcomes (e.g. incidence of hypertension or migraine)

Recommendations

The GDG determined that recommendations for follow-up for SI(II) are the same as recommendations for follow-up for other contraceptive implants.

NEW recommendation 1.5

No routine follow-up is required after initiating SI(II).

Quality of evidence: No direct evidence.

Strength of recommendation: Strong.

Evidence summary

Two published systematic reviews and two additional articles were identified related to follow-up after initiation of contraceptive methods. No studies were identified that focused specifically on follow-up for implant users (8–11).

One systematic review on adverse health outcomes after contraceptive initiation identified 15 articles for inclusion, five of which were studies on health outcomes (incidence of hypertension or changes to blood pressure) after COC initiation. An additional seven studies examined incidence of pelvic inflammatory disease (PID) or device removal due to PID among intrauterine device (IUD) users, and three studies examined weight gain after DMPA initiation (8). After the publication of this systematic review, one additional article was identified that evaluated the incidence of hypertension after initiation of COCs (10). These data demonstrate that limited evidence exists on health outcomes after contraceptive

initiation. However, the available evidence does not suggest an increased risk of hypertension after initiation of COCs in healthy women (8, 10). The additional study identified after the publication of the systematic review compared women initiating COCs with women initiating nonhormonal methods, all receiving follow-up at six months, and found no differences between groups (10).

The second systematic review identified four articles that provided evidence on the impact of a specific follow-up schedule on method continuation and correct use. Two of the reviewed studies looked at evidence on IUD continuation based on timing of follow-up visits and two examined the impact of follow-up phone calls on method continuation among adolescents using a variety of contraceptive methods. This limited and mostly poor-quality evidence made it difficult to determine what effect, if any, follow-up has on method continuation (9). After the publication of this review, one additional article was identified that described a randomized controlled trial (RCT) in which adolescents were randomized to receive clinic-based care or follow-up phone calls. This study found no differences in continuation between the groups at 3, 6 or 12 months follow-up (11).

Rationale

No direct evidence was identified. Therefore, the recommendation for follow-up for SI(II) is based primarily on indirect evidence from studies on other contraceptive methods, including COCs, IUDs and injectable contraceptives. Because the objective of the follow-up visit is to address any issues the woman may have after initiating her method of contraception, regardless of the type of method chosen, the GDG concluded that the evidence available on follow-up for other contraceptive methods can be extrapolated to follow-up for SI(II). To address the potential harms of this recommendation, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly

considered in the MEC (4). The values and preferences of women were also integral components to the process of translating the evidence into a recommendation. The GDG incorporated information on benefits and harms, and on women’s values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence.

These recommendations address the minimum frequency of follow-up recommended for safe and effective use of the method. The

recommendations refer to general situations and may vary for different users and different contexts. For example, women with specific medical conditions may need more frequent follow-up visits. The GDG concluded that follow-up visits or contacts should include, at a minimum, counselling to address issues such as side-effects or other problems, correct and consistent use of the method, and protection against STIs. Additional assessment may be appropriate. Unnecessary follow-up requirements may pose barriers to continued contraceptive use. The GDG determined that the benefits of this recommendation outweigh any potential harms, and therefore a “strong” recommendation was assigned.

Table 2: GRADE evidence table: Duration of Sino-implant (II) use: how long may SI(II) be left in place?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Effects of duration in women using Sino-implant (II)								
Cumulative pregnancy rate	12 cohorts (7 cohorts from RCTs) (n=27 126)	Serious limitations ^a	Serious inconsistency ^b	No serious imprecision	No indirectness	Studies did not report interaction of duration of implant use with pregnancy outcome	Low	Cumulative pregnancy rates: <ul style="list-style-type: none"> • After 2 years (6 studies): 0–1/100 women • After 4 years (4 studies): 0.01–1.1/100 women • After 5 years (6 studies): 0.3–2.1/100 women • After 6 years (2 studies): 0–0.5/100 women • After 7 years (1 study): 0.6/100 women.

RCT: randomized controlled trial

^a Studies consist of seven moderate, four low-quality and one very-low-quality studies: analytic methodology was often unclear; there was inconsistent reporting of randomization sequence generation and allocation concealment; identification of pregnancy outcome was not well defined; there was variable reporting of duration of implant use.

^b Heterogeneity of pregnancy rates after four years of implant exposure.

References for Sino-implant (II)

1. Phillips SJ, Zhang W. When can a woman start Sino-implant (II)? Systematic review (unpublished).
2. Zheng S, Wu X, Fan B. Serum concentrations of levonorgestrel, estradiol and progesterone in women using China-made Long-Acting Levonorgestrel Subdermal Implant (Sino-implant) during the first year. *Reprod Contracept*. 1993;13:172–8.
3. Steiner MJ, Lopez LM, Grimes DA, Cheng L, Shelton J, Trussell J et al. Sino-implant (II) – a levonorgestrel – releasing two rod implant: systematic review of the randomized controlled trials. *Contraception*. 2010;81:197–201.
4. Medical eligibility criteria for contraceptive use, fifth edition. Geneva: World Health Organization; 2015 (http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/, accessed 6 July 2016).
5. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Blood pressure measurement prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):631–8.
6. Tepper NK, Steenland MW, Marchbanks PA, Curtis KM. Laboratory screening prior to initiating contraception: a systematic review. *Contraception*. 2013;87(5):645–9.
7. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Physical examination prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):650–4.
8. Steenland MW, Zapata LB, Brahmi D, Brahmi D, Marchbanks P, Curtis KM. Appropriate follow up to detect potential adverse events after initiation of select contraceptive methods: a systematic review. *Contraception*. 2013;87(5):611–24.
9. Steenland MW, Zapata LB, Brahmi D, Marchbanks PA, Curtis KM. The effect of follow-up visits or contacts after contraceptive initiation on method continuation and correct use. *Contraception*. 2013;87(5):625–30.
10. Nisenbaum MG, Melo NR, Giribela CR, Morais TL, Guerra GM, de Angelis K et al. Effects of a contraceptive containing drospirenone and ethinyl estradiol on blood pressure and autonomic tone: a prospective controlled clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014;13(14).
11. Berenson AB, Rahman M. A randomized controlled study of two educational interventions on adherence with oral contraceptives and condoms. *Contraception*. 2012;86(6):716–24.
12. Phillips SJ, Steyn P, Zhang W, Curtis K. How long may the Sino-implant (II) be left in place? (unpublished).

4.2 Recommendations for addition of subcutaneously administered depot medroxyprogesterone acetate as a new method to SPR

Recommendations for progestogen-only injectable contraceptives (POIs) included in the SPR second edition refer to formulations containing depot medroxyprogesterone acetate (DMPA; 150 mg) or norethisterone enanthate (NET-EN; 200 mg), both delivered by intramuscular (IM) injection. For the third edition of the SPR, the Guideline Development Group (GDG) considered evidence on a newly available subcutaneously-administered DMPA formulation (DMPA-SC; 104 mg).

4.2.a Initiation of DMPA-SC

Clinical question: When can a woman start DMPA-SC?

PICO question for systematic review

Population	Women initiating DMPA-SC
Intervention	Initiation on specified days of the menstrual cycle
Comparator	Women initiating DMPA-SC according to different initiation schedules/different days of the menstrual cycle
Outcomes	Risk that a woman is already pregnant when initiating DMPA-SC, contraceptive effectiveness (i.e. risk that a woman becomes pregnant after initiating DMPA-SC), contraceptive side-effects and contraceptive continuation

Recommendations

The GDG determined that recommendations for starting DMPA-SC are the same as recommendations for starting other POIs. These recommendations include timing of initiation for women with regular menstrual cycles, women with amenorrhoea, women who are postpartum and breastfeeding or not breastfeeding, and women who are post-abortion or switching from other contraceptive methods (i.e. hormonal, nonhormonal or intrauterine devices). No change to the earlier recommendations for the timing of initiation of POIs (which referred to DMPA [150 mg] and NET-EN [200 mg], both administered IM) were necessary with the inclusion of DMPA-SC as a new method in the SPR.

NEW recommendation 2.1

A woman can start DMPA-SC within 7 days after the start of her menstrual bleeding; she can also start at any other time if it is reasonably certain that she is not pregnant. Recommendations are also available for when additional protection is needed and for women who are: amenorrhoeic, postpartum, post-abortion, switching from another method.

Quality of the evidence: No direct evidence.
Strength of the recommendation: Strong.

Evidence summary

There was no direct evidence available related to the timing of initiation of DMPA-SC.

A published systematic review was identified that evaluated how starting POIs on different days of the menstrual cycle affects contraceptive effectiveness, compliance and continuation (1). This review included studies identified by searching MEDLINE and Cochrane databases from inception through February 2012. An updated search was performed (through 15 January 2014) for relevant evidence using the same search strategy as published in that systematic review; among 345 retrieved citations, no additional articles met the inclusion criteria for review. All of the identified articles reported in the review presented results related to the use of intramuscular DMPA (DMPA-IM). Further, all of these data had been previously reviewed during the development of the second edition of the SPR, underpinning the earlier recommendations. Thus, GRADE evidence tables were not developed for this recommendation.

Rationale

No direct evidence was identified. Therefore, recommendations for when to start DMPA-SC are based on indirect evidence from studies on DMPA-IM. Because the safety profile, pharmacokinetic and pharmacodynamic properties, delivery system and mechanism of action are similar among POIs, the GDG concluded that the evidence available on when to start other POIs (DMPA-IM and NET-EN-IM) can be extrapolated to DMPA-SC. The GDG determined that IM and SC formulations of DMPA appear therapeutically equivalent,

noting two studies which show that these formulations demonstrate similar effects on serum estradiol levels and comparably high contraceptive efficacy (2). Further, the GDG reviewed additional supporting evidence from a systematic review prepared as part of the development of WHO's *Medical eligibility criteria for contraceptive use, fifth edition* (MEC), which noted that the IM and SC formulations exhibit similar safety profiles (3). In particular, effects on weight change, bleeding patterns and reports of other adverse effects among healthy, reproductive age women do not appear to differ (2). To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC. The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. In their review of the evidence, the GDG noted that DMPA-SC efficacy is maintained when administered in the upper arm, which may be acceptable to women in addition to subcutaneous injection in the abdomen or thigh (4). Delay in initiation of contraception may increase the risk of unintended pregnancy. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as "strong" recommendations.

4.2.b Examinations and tests needed before initiation of DMPA-SC

Clinical question: What examinations and tests are appropriate before initiating DMPA-SC?

PICO question for systematic review

Population	Women initiating DMPA-SC
Intervention	Specified examinations and tests, including blood pressure measurement, lab screenings (glucose, lipids, liver enzymes), clinical examinations (clinical breast examination, pelvic examination), prior to initiating method
Comparator	Women initiating DMPA-SC without these examinations and tests
Outcomes	Incidence of selected adverse health outcomes (adverse cardiovascular outcomes, adverse changes to glucose levels, incidence of diabetes, adverse changes to lipid levels, and liver disorders)

Recommendations

The GDG determined that recommendations for examinations and tests needed before initiating DMPA-SC are the same as recommendations for initiating other POIs (i.e. DMPA-IM and NET-EN-IM).

NEW recommendation 2.2

It is desirable to have blood pressure measurements taken before initiation of DMPA-SC. Women should not be denied use of DMPA-SC simply because their blood pressure cannot be measured.

NEW recommendation 2.3

Breast examination by provider, pelvic/genital examination, cervical cancer screening, routine laboratory tests, haemoglobin test, STI risk assessment (medical history and physical examination) and STI/HIV screening (laboratory tests) do not contribute substantially to the safe and effective use of DMPA-SC.

Quality of evidence: No direct evidence.

Strength of recommendation: Strong.

Evidence summary

Three systematic reviews were conducted to review evidence on examinations and tests needed before initiating hormonal contraception. One systematic review examined evidence on the utility of blood pressure measurement prior to initiating hormonal contraceptives (5) and a second examined evidence on laboratory screening prior to initiating hormonal contraceptives (6). No evidence on DMPA was identified in either of these reviews.

The third systematic review, which examined the impact of clinical breast or pelvic examinations prior to initiating contraceptives, included one retrospective cohort study that compared adolescents initiating oral contraceptives or DMPA at non-clinical settings without receiving pelvic examinations with adolescents initiating these methods at traditional clinics with pelvic examinations (7). This study found no differences in risk factors for cervical cancer between the groups.

Rationale

No direct evidence was identified. Therefore, recommendations for examinations and tests prior to DMPA-SC initiation are based on indirect evidence from studies on COCs, and prior SPR recommendations for other POIs. Because the safety profiles, pharmacokinetic and pharmacodynamic properties, delivery system and mechanism of action are similar among POIs, the GDG concluded that prior recommendations for other POIs can be extrapolated to DMPA-SC. Examinations and tests that are not necessary to determine medical eligibility for contraception may pose barriers to contraceptive access. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (3). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, into determining which examinations and tests were necessary to ensure safety of contraceptive provision while removing unnecessary medical barriers. The examinations or tests noted apply to persons who are presumed to be healthy. The recommendations focus on the relationship of the examinations or tests to safe initiation of a contraceptive method. They are not intended to address the appropriateness of these examinations or tests in other circumstances. For example, some of the examinations or tests that are not deemed necessary for safe and

effective contraceptive use may be appropriate for good preventive health care or for diagnosing or assessing suspected medical conditions. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as "strong" recommendations.

4.2.c Reinjection interval for DMPA-SC

Clinical question: When can a woman have repeat DMPA-SC injections?

PICO question for systematic review

Population	Women initiating DMPA-SC
Intervention	Repeat injection on specified days following initiation
Comparator	Repeat injection according to a different schedule
Outcomes	Pregnancy rates and surrogate measures of contraceptive effectiveness (e.g. ovulation, follicular development, changes in hormone levels, cervical mucus quality)

Recommendations

The GDG determined that recommendations for repeat injections of DMPA-SC are the same as recommendations for repeat injections of DMPA-IM. These recommendations include information about: a normal reinjection interval; how to manage if a woman presents early or late for a repeat injection; how to manage if she is switching between types of POIs; and how to manage a repeat injection when the previous type of POI or timing of injection is unknown.

NEW recommendation 2.4

Provide repeat DMPA-SC injections every three months. Recommendations are also available for early and late injections.

Quality of evidence: Very low (see GRADE evidence table: When can a woman have repeat DMPA-SC injections?)

Strength of recommendation: Strong.

Evidence summary

A published systematic review was identified that examined evidence on when to reinject DMPA and NET-EN for continuation (8). This review included studies identified by searching the PubMed database from its inception through November 2008. An updated search

was performed (through 15 January 2014) for relevant evidence using the same search strategy as published in that systematic review; among 327 retrieved citations, no additional articles met the inclusion criteria for review. Of the 20 studies included in the published systematic review, 10 articles examined DMPA use and two of these studies referenced DMPA-SC in particular. Both of these studies reported time to first ovulation following a single injection of DMPA, but only one of them compared the return of ovulation between users of DMPA-SC and DMPA-IM. In this randomized study, the median time to return of ovulation was 183 and 212 days (26.1 and 30.3 weeks) among DMPA-IM and DMPA-SC users, respectively (9). The earliest individual rise in serum progesterone for the DMPA-IM group was on day 70 (week 10), but additional evaluation did not support a return to ovulation; the earliest individual rise in serum progesterone indicating a return to ovulation in the DMPA-SC group was on day 106 (week 15). The second study that referenced DMPA-SC in particular was a prospective case series that followed 24 women who received a single injection of DMPA-SC and noted that ovulation was suppressed in 23 of the women for at least 112 days (16 weeks) (10). These data had previously been reviewed during the development of the second edition of the SPR, underpinning earlier recommendations.

Rationale

Recommendations for repeat injection of DMPA-SC are based on evidence for both DMPA-IM and DMPA-SC because the GDG determined that IM and SC formulations are therapeutically equivalent. The direct evidence for this recommendation was categorized as very low quality. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (3). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women’s values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. In their review of the evidence, the GDG noted that DMPA-SC efficacy is maintained when administered in the upper arm, which may be acceptable to women in addition to subcutaneous injection in the abdomen or thigh (4). DMPA injections should be administered every three months. While the repeat DMPA injection can be given up to four weeks late without requiring additional

Table 3: GRADE evidence table: When can a woman have repeat DMPA-SC injections?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Among users of DMPA-SC vs DMPA-IM, is time for return to ovulation similar?								
Return to ovulation	1 randomized study (n=58)	Serious limitations ^a	Cannot determine (1 study)	Very serious imprecision ^b	Serious indirectness ^c	None	Very low	Median time for return to ovulation for DMPA-SC 212 days (90th percentile; 125–345 days) vs DMPA-IM 183 days (85–335 days) (NS)

NS: not significant
^a One moderate-quality study. Randomization sequence and allocation concealment not described.
^b Small sample size and wide confidence intervals.
^c Return to ovulation is not a direct marker of contraceptive effectiveness, but is a proxy measure to determine interval for repeat DMPA injection.

contraceptive protection, this does not mean that the regular DMPA injection interval can be extended by four weeks. Delay in reinjection may increase the risk of unintended pregnancy. The GDG therefore felt that the benefits of these recommendations strongly outweigh the potential harms and classified them as “strong” recommendations despite the very-low-quality evidence.

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4.3 Recommendations for addition of the combined contraceptive transdermal patch and the combined contraceptive vaginal ring as new methods to the SPR

Existing recommendations for combined hormonal contraceptives (CHCs) in the SPR second edition refer only to combined oral contraceptives (COCs). For the third edition of the SPR, the Guideline Development Group (GDG) considered evidence on the combined contraceptive transdermal patch (the patch) and the combined contraceptive vaginal ring (CVR) for addition to the SPR. When evidence for the patch and CVR was not available, the GDG extrapolated from evidence on COCs.

4.3.a Initiation of the patch and CVR

Clinical question: When can a woman start the patch or CVR?

PICO question for systematic review

Population	Women initiating the patch or CVR
Intervention	Initiating on specified days of the menstrual cycle
Comparator	Women initiating the patch and CVR according to different initiation schedules/on different days of the menstrual cycle
Outcomes	Risk that a woman is already pregnant when initiating the patch or CVR, contraceptive effectiveness (i.e. risk that a woman becomes pregnant after initiating the patch or CVR), contraceptive side-effects (including bleeding patterns) and contraceptive continuation rates

Recommendations

The GDG determined that recommendations for starting the patch and CVR should be the same as recommendations for starting COCs. Current recommendations address: CHC initiation for women who are having menstrual cycles, women who are amenorrhoeic, women who are postpartum and breastfeeding or not breastfeeding, women who are post-abortion, and women who are switching from another hormonal method, switching from a nonhormonal method (other than an IUD) or switching from an IUD (including the LNG-IUD).

NEW recommendation 3.1

A woman can start the patch or CVR within 5 days after the start of her menstrual bleeding; she can also start at any other time if it is reasonably certain that she is not pregnant. Recommendations are also available for when additional protection is needed and for women who are: amenorrhoeic, postpartum, post-abortion, switching from another method.

Quality of evidence: CVR – No direct evidence; Patch – Moderate to low (see GRADE evidence table: When can a woman start the patch or CVR?)

Strength of recommendation: Strong.

Evidence summary

One published systematic review identified 18 studies related to initiation of CHCs – including COCs, the patch and the CVR – on different days of the menstrual cycle. No direct evidence for the outcomes of interest was identified for the CVR; one study was identified for the patch. The patch study reported no differences in bleeding patterns, a non-significant increased risk for nausea, and higher short-term continuation rates for women who started the patch immediately (i.e. Quick Start) compared with those who had a conventional start. The systematic review examined direct outcomes (a woman is already pregnant when initiating CHCs, measures of contraceptive effectiveness, side-effects and continuation rates) and indirect outcomes (ovulation and follicular development). Overall, the body of evidence on COCs, the patch and the CVR suggested no differences in pregnancy rates based on different starting schemes. Ovulation was more likely to occur among women initiating CHCs who had more follicular activity prior to initiation, but no ovulations were seen when COCs were initiated at a mean follicle diameter of 10 mm (mean cycle day: 7.6) or when the CVR was initiated at a follicle diameter of 13 mm (median cycle day: 11). Side-effects, including bleeding patterns, did not differ

based on initiation day. While the Quick Start method was associated with higher initial continuation rates, differences in continuation did not vary over time based on timing of initiation (1).

Rationale

Recommendations for when to start the patch and CVR are based primarily on limited direct evidence on the patch and substantial indirect evidence from studies on COCs. Due to the similarities in safety profiles and similarities among the types and doses of hormones used in COCs and other CHCs with alternate routes of administration (such as the patch and CVR), the GDG concluded that the evidence available on when to start COCs can be extrapolated to both the patch and the CVR. To address potential harms of this recommendation, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in WHO's *Medical eligibility criteria for contraceptive use, fifth edition* (MEC) (2). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. Delay in initiation of contraception may increase the risk of unintended pregnancy. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as "strong" recommendations.

Table 4: GRADE evidence table: When can a woman start the patch or CVR?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Quick Start vs conventional start								
Bleeding or spotting episodes	2 RCTs (n=174); 1 cohort study (n=193)	No serious limitations ^a	No serious inconsistency	Serious imprecision ^b	Serious indirectness ^c	None	Low	No differences in measures of bleeding or spotting were found in 2 high-quality RCTs (including 1 study of the patch) and 1 low-quality cohort study.
Nausea	1 RCT (n=60); 1 cohort study (n=193)	Serious limitations ^d	Serious inconsistency ^e	Serious imprecision ^b	Serious indirectness ^c	None	Very low	1 high-quality RCT of the patch found increased risk of nausea with Quick Start (33% vs 16%, RR 2.0 [0.78–5.2]). 1 low-quality cohort study of COC use found no difference at 3 months or 1 year.
Contraceptive continuation	3 RCTs (n=1989); 1 cohort study (n=193)	No serious limitations ^f	No serious inconsistency	No serious imprecision	Serious indirectness ^c	None	Moderate	Quick Start was associated with slightly higher early continuation rates (1 RCT with OR 2.8 [1.1–7.3]; 2 RCTs NS; 1 cohort study NS). Effects no longer seen at 3–6 months.

COC: combined oral contraceptive; CVR: combined contraceptive vaginal ring; NS: not significant; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk

^a Two high-quality RCTs and one low-quality cohort study (limited by self-selection into groups, outcome data from retrospective chart review).

^b Cohort study limited by small sample size and confidence interval crossing 1.0.

^c One RCT evaluated the patch while the other studies evaluated COCs.

^d One high-quality RCT and one low-quality cohort study (limited by self-selection into groups, outcome data from retrospective chart review).

^e Discordant results between RCT and cohort study.

^f Two high-quality RCTs, one moderate-quality RCT and one low-quality cohort study (limited by high loss to follow-up [RCT], self-selection into groups, outcome data from retrospective chart review [cohort]).

4.3.b Examinations and tests needed before initiation of the patch and CVR

Clinical question: What examinations and tests are appropriate before initiating the patch and CVR?

PICO question for systematic review

Population	Women initiating the patch or CVR
Intervention	Selected examinations and tests, including blood pressure measurement, lab screenings (glucose, lipids, liver enzymes), clinical examinations (clinical breast examination, pelvic examination), prior to initiating method
Comparator	Women initiating the patch or CVR without these examinations and tests
Outcomes	Incidence of selected adverse health outcomes (adverse cardiovascular outcomes, adverse changes to glucose levels, incidence of diabetes, adverse changes to lipid levels, and liver disorders)

Recommendations

The GDG determined that recommendations for examinations and tests needed before initiating the patch and CVR are the same as recommendations for examinations and tests needed before initiating COCs. Current recommendations address: breast examination by provider, pelvic/genital examination, cervical cancer screening, routine laboratory tests, haemoglobin test, STI risk assessment (medical history and physical examination), STI/HIV screening (laboratory tests) and blood pressure screening.

NEW recommendation 3.2

It is desirable to have blood pressure measurements taken before initiation of the patch or CVR. Women should not be denied use of the patch or CVR simply because their blood pressure cannot be measured.

NEW recommendation 3.3

Breast examination by provider, pelvic/genital examination, cervical cancer screening, routine laboratory tests, haemoglobin test, STI risk assessment (medical history and physical examination) and STI/HIV screening (laboratory tests) do not contribute substantially to the safe and effective use of the patch and CVR.

Quality of evidence: No direct evidence.

Strength of recommendation: Strong.

Evidence summary

Three systematic reviews were conducted to review evidence on examinations and tests needed before initiating hormonal contraception.

One systematic review examined evidence on cardiovascular outcomes among women who had blood pressure measurement prior to initiating CHCs compared to women who did not receive blood pressure measurement. Six articles were identified that reported on three case-control studies. All articles addressed COC use. All three studies found a lower risk for acute myocardial infarction among women who received blood pressure measurement prior to COC initiation compared with women who did not. Two of the studies found a lower risk of ischemic stroke among women who received blood pressure measurement prior to COC initiation compared with women who did not. One of the studies showed no difference in risk for haemorrhagic stroke among women who received blood pressure measurement prior to COC initiation compared with women who did not. This evidence suggests that cardiovascular outcomes are worse among women who do not receive blood pressure measurement prior to initiating COCs compared with those who do (3).

In a second systematic review, no evidence was identified comparing health outcomes among women who receive laboratory screening prior to initiating CHCs with those who do not receive these laboratory tests (4).

In the third systematic review, no evidence was identified comparing health outcomes among women who received clinical breast examinations or pelvic examinations prior to initiating CHCs with those who did not receive these physical examinations (5). One retrospective cohort study compared adolescents who received pelvic examinations at the time of initiation of oral contraceptives (OCs) with adolescents who chose to delay pelvic examination and found no differences in incidence of STIs, abnormal Papanicolaou smears, or abnormal wet mounts. A second

study found no differences in risk factors for cervical cancer among adolescents initiating OCs or DMPA at non-clinical settings without receiving pelvic examinations compared with adolescents initiating these methods at traditional clinics.

Rationale

No direct evidence was identified. Therefore, recommendations for examinations and tests prior to initiation of the patch and CVR are based on indirect evidence from COCs. Due to the similar safety profiles and similarities among the types and doses of hormones used in COCs and other CHCs with alternate routes of administration (such as the patch and CVR), the GDG concluded that the evidence available on examinations and tests prior to COC initiation can be used to generate recommendations on examinations and tests before initiation of the patch and CVR. Examinations and tests that are not necessary to determine medical eligibility for contraception may be barriers to contraceptive access. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (2). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, into determining which examinations and tests were necessary to ensure safety of contraceptive provision while removing unnecessary medical barriers. The examinations or tests noted apply to persons who are presumed to be healthy. These classifications focus on the relationship of the examinations or tests to safe initiation of a contraceptive method. They are not intended to address the appropriateness of these examinations or tests in other circumstances. For example, some of the examinations or tests that are not deemed necessary for safe and effective

contraceptive use may be appropriate for good preventive health care or for diagnosing or assessing suspected medical conditions. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as "strong" recommendations.

4.3.c Management of dosing errors during patch and CVR use

Clinical question: How should dosing errors be managed during patch and CVR use?

PICO question for systematic review

Population	Women using the patch or CVR
Intervention	Experiencing a dosing error (i.e. extension of the hormone-free interval, or unscheduled detachment of patch or removal of CVR)
Comparator	Correct use of the patch and CVR
Outcomes	Pregnancy rates and surrogate measures of contraceptive effectiveness (e.g. ovulation, follicular development, changes in hormone levels, cervical mucus quality)

Recommendations

i. Management of dosing errors during patch use

Extension of the patch-free interval (i.e. forgetting to apply a new patch after the 7-day patch-free interval)

- If the patch-free interval is extended for ≤ 48 hours (i.e. if the total patch-free interval is > 7 days and ≤ 9 days), a new patch should be applied as soon as possible. The woman should keep the same patch change day, meaning that she should start/change the patch on the scheduled patch start/change day as she would without a dosing error. No additional contraceptive protection is needed.
- If the patch-free interval is extended for > 48 hours (i.e. if the total patch-free interval is > 9 days), a new patch should be applied as soon as possible. The woman should keep the same patch change day. She should also use condoms or abstain from sex until she has worn a patch for 7 days in a row. If unprotected sexual intercourse occurred during the previous 5 days, she may wish to consider emergency contraception.

Unscheduled detachment of the patch

- If the patch becomes detached for ≤ 48 hours, a new patch should be applied as soon as possible (if detachment occurs < 24 hours after the patch was applied, the woman can try to reapply the same patch or replace with a new patch). The woman should keep the same patch change day. No additional contraceptive protection is needed.
- If the patch becomes detached for > 48 hours, a new patch should be applied as soon as possible. The woman should keep the same patch change day.
 - The woman should also use condoms or abstain from sex until she has worn a patch for 7 days in a row.
 - If the unscheduled detachment occurred during the third week of patch use, the woman should omit the patch-free week by finishing the third week of patch use and starting a new patch immediately. If she is unable to start a new patch immediately after the third week of patch use, she should also use condoms or abstain from sex until she has worn a patch for 7 days in a row.
 - If the unscheduled detachment occurred during the first week of patch use and unprotected sexual intercourse occurred during the previous 5 days, the woman may wish to consider emergency contraception.

Extended use of the patch

- If patch removal and reapplication is delayed by ≤ 48 hours (i.e. if patch use is extended from 7 to ≤ 9 days) during weeks 1–3 of patch use, a new patch should be applied as soon as possible. The woman should keep the same patch change day. No additional contraceptive protection is needed.
- If patch removal and reapplication is delayed by > 48 hours (i.e. if patch use is extended from 7 to > 9 days) during weeks 2–3 of patch use, while a woman is using the first or second patch of her cycle, the patch should be removed or replaced as soon as possible. She should keep the same patch change day. She should also use condoms or abstain

from sex until she has worn a patch for 7 days in a row.

- If delayed removal occurs during week 4 of patch use (i.e. the scheduled hormone-free week), while a woman is using the third patch of her cycle, she should remove the patch as soon as possible. She should keep the same patch start day. No additional contraceptive protection is needed.

ii. Management of dosing errors during CVR use

Extension of the CVR-free interval (i.e. forgetting to insert a new CVR after the 7-day CVR-free interval)

- If the CVR-free interval is extended for ≤ 48 hours (i.e. if the total CVR-free interval is > 7 days and ≤ 9 days), a new CVR should be inserted as soon as possible. The woman should keep the same CVR removal day, meaning that she should insert/remove the CVR on the scheduled CVR insertion/removal day as she would without a dosing error. No additional contraceptive protection is needed.
- If the CVR-free interval is extended for > 48 hours (i.e. if the total CVR-free interval is > 9 days), a new CVR should be inserted as soon as possible. The woman should keep the same CVR removal day. She should also use condoms or abstain from sex until she has worn a CVR for 7 days in a row. If unprotected sexual intercourse occurred during the previous 5 days, she may wish to consider emergency contraception.

Unscheduled removal of the CVR (i.e. CVR is removed before the end of the cycle)

- If the CVR is removed for ≤ 48 hours at an unscheduled time, it should be reinserted as soon as possible. The woman should then keep the CVR in place until the removal day as originally scheduled. No additional contraceptive protection is needed.
- If the CVR is removed for > 48 hours at an unscheduled time, it should be reinserted as soon as possible. The woman should then keep the CVR in place until the removal day as originally scheduled.
 - The woman should also use condoms or

- abstain from sex until she has worn a CVR for 7 days in a row.
- If the unscheduled removal of the CVR occurred during the third week of CVR use, the woman should omit the CVR-free week by finishing the third week of CVR use and starting a new CVR immediately. If she is unable to start a new CVR immediately after the third week of CVR use, she should use condoms or abstain from sex until she has worn a CVR for 7 days in a row.
 - If the unscheduled removal of the CVR occurred during the first week of CVR use and unprotected sexual intercourse occurred during the previous 5 days, the woman may wish to consider emergency contraception.

Extended use of the CVR

- If the same CVR is used for up to 28 days (< 4 weeks), then additional contraception is not needed. A hormone-free interval can be taken, if desired, but should not exceed 7 days.
- If the same CVR is used for 28–35 days (≥ 4 weeks but ≤ 5 weeks), insert a new CVR and skip the hormone-free interval. No additional contraceptive protection is needed.

NEW recommendation 3.4

A woman may need to take action if she has a dosing error with the patch or CVR. Recommendations are provided for management of the extension of the patch-free interval, unscheduled detachment of the patch, extended use of the patch, extension of the CVR-free interval, unscheduled removal of the CVR, and extended use of the CVR.

Quality of evidence: Patch – No direct evidence; CVR – Very low (see GRADE evidence table: Dosing errors for CVR)
Strength of recommendation: Strong.

Evidence summary

One systematic review identified 26 studies that examined outcomes related to pregnancy rates and surrogate measures of contraceptive efficacy (e.g. follicular development, hormone levels or cervical mucus quality) among women who experience dosing errors during CHC use (e.g. missed doses or extension of the hormone-free interval) (6). Of these studies,

19 examined COC use, two examined the patch and six examined CVR use. No direct evidence on the risk of pregnancy associated with dosing errors for COCs or the patch was identified. Wide variability in follicular activity and ovulation was found in studies of women deliberately extending the hormone-free interval. Risk of ovulation was generally low, and cycles were generally abnormal among women who did ovulate. Among women who missed pills or delayed patch replacement by 1–3 days on days not adjacent to the hormone-free interval, risk of ovulation was low. An additional pharmacokinetic study found that ethinyl estradiol and norelgestromin levels remained within the reference range after extending patch use by 3 days.

Three studies examining CVR use found that extension of the hormone-free interval for up to 48 hours did not increase the risk of pregnancy. One study found that insertion of the CVR after deliberate extension of the hormone-free interval resulting in the development of a 13 mm follicle caused interruption of ovarian function and further follicular growth. Another study found that when CVR use was extended by two additional weeks (from three weeks to five weeks), inhibition of ovulation was maintained. After the publication of the systematic review, an additional study was identified that examined ovulatory activity among women deliberately extending use of the CVR by three weeks (up to six weeks of continuous use), and the results were consistent with evidence included in the review (7).

Rationale

Recommendations for managing dosing errors with the patch and CVR are based primarily on limited direct evidence on the CVR and substantial indirect evidence from COCs. Due to the similarities in safety profiles and similarities among the types and doses of hormones used in COCs and other CHCs with alternate routes of administration (such as the patch and CVR), the GDG concluded that the evidence available on managing dosing errors with COCs can be extrapolated to the

Table 5: GRADE evidence table: Dosing errors for CVR

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Non-deliberate extension of CVR-free interval								
Pregnancy	4 observational studies (n=8765)	Very serious limitations ^a	No serious inconsistency	No serious imprecision	No indirectness	None	Very low	Pregnancy rates 0.0–0.3% among non-adherent women vs 0.0–0.05% among adherent women. Overall failure rate of 0.0–0.2% across all levels of adherence.

^a Four low-quality studies: exposure (duration of CVR-free interval or proportion of non-adherent cycles) not well defined; outcome (pregnancy) not consistently reported according to contraceptive adherence.

patch and CVR. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (2). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women’s values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while maintaining safety and efficacy of contraceptive provision based on the available evidence.

The GDG considered the inconsistent or incorrect use of OCs to be a major reason for unintended pregnancy. Seven days of continuous COC use was deemed necessary to reliably prevent ovulation. Women who frequently miss pills or experience usage errors with the patch or CVR should consider an alternative contraceptive method that is less dependent on the user to be effective (e.g. IUD, implant or injectable contraceptive). When doses have been missed, it is important to resume CHC use (take an active pill, reapply or apply a new patch, or reinsert or insert a new CVR) as soon as possible.

If doses are missed, the chance that pregnancy will occur depends not only on the duration of missed doses (i.e. how many days of pill, patch or CVR use were missed), but also on when those doses were missed. Based on data regarding ovulation, the GDG determined that missing 3 or more active (hormonal) pills (2 or more for pills containing $\leq 20 \mu\text{g}$ ethinyl estradiol) at any time during the cycle warrants additional precautions. The risk of pregnancy is greatest when active (hormonal) pills are missed at the beginning or at the end of the series of active pills, i.e. when the hormone-free interval is extended. Since dosing errors while using the patch or CVR may increase the risk of unintended pregnancy, the GDG determined that the benefits strongly outweigh the potential harms and thus classified these recommendations as “strong”.

4.3.d Follow-up after patch and CVR initiation

Clinical question: What is the appropriate follow-up for patch and CVR users?

PICO question for systematic review

Population	Women initiating the patch or CVR
Intervention	Specified follow-up schedule
Comparator	Women initiating the patch or CVR with a different follow-up schedule or no follow-up at all
Outcomes	Measures of contraceptive use (e.g. pregnancy, correct use, consistent use, method discontinuation) or adverse health outcomes (e.g. incidence of hypertension or migraine)

Recommendations

The GDG determined that recommendations for follow-up for the patch and CVR are the same as recommendations for follow-up for COCs.

NEW recommendation 3.5

An annual follow-up visit is recommended after initiating the patch or CVR.

Quality of evidence: No direct evidence.
Strength of recommendation: Strong.

Evidence summary

Two published systematic reviews and two additional articles were identified related to follow-up after initiation of contraceptive methods. No studies were identified that focused specifically on follow-up after patch or CVR initiation (8–11).

One systematic review on adverse health outcomes after contraceptive initiation identified 15 articles for inclusion, including five studies reporting on health outcomes (incidence of hypertension or changes to blood pressure) after COC initiation. An additional seven studies examined incidence of pelvic inflammatory disease (PID) and IUD use and three studies examined weight gain after DMPA initiation (8). After the publication of this review, an article was identified that evaluated the incidence of hypertension after OC initiation (10). These data demonstrate that limited evidence exists on health outcomes after contraceptive initiation. However, the available evidence does not suggest an increased risk of hypertension after initiation of COCs in healthy women (8, 10). The study identified after the publication of the systematic review also compared women initiating COCs with women initiating nonhormonal methods, all of whom received follow-up at six months, and found no differences between the groups (10).

The second systematic review identified four articles that provided evidence on the impact of a specific follow-up schedule on method continuation and correct use (9). Two studies looked at evidence on IUD continuation based

on timing of follow-up visits, and two examined the impact of follow-up phone calls on method continuation among adolescents using a variety of contraceptive methods. This limited, mostly poor-quality evidence made it difficult to determine what effect, if any, follow-up has on method continuation. One additional article identified after the publication of this review described a randomized controlled trial in which adolescents were randomized to receive clinic-based care or follow-up phone calls. This study found no differences in continuation between groups at 3, 6 or 12 months follow-up (11).

Rationale

No direct evidence was identified. Therefore, recommendations for follow-up for the patch and CVR are based on indirect evidence from other contraceptive methods including COCs, IUDs and injectable contraceptives. Because the objective of the follow-up visit is to address any issues the woman may have after initiating her method of contraception, regardless of the type of method chosen, the GDG concluded that the evidence available on follow-up for other contraceptive methods can be extrapolated to follow-up for users of the patch and CVR. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (2). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence.

These recommendations address the minimum frequency of follow-up recommended for safe and effective use of the method. The

recommendations refer to general situations and may vary for different users and different contexts. For example, women with specific medical conditions may need more frequent follow-up visits. The GDG concluded that follow-up visits or contacts should include, at a minimum, counselling to address issues such as side-effects or other problems, correct and consistent use of the method, and protection against STIs. Additional assessment may be appropriate. Unnecessary follow-up requirements may pose barriers to continued contraceptive use. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as “strong” recommendations.

References for the patch and CVR

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10. Nisenbaum MG, Melo NR, Giribela CR, Morais TL, Guerra GM, de Angelis K et al. Effects of a contraceptive containing drospirenone and ethinyl estradiol on blood pressure and autonomic tone: a prospective controlled clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014;13(14).
11. Berenson AB, Rahman M. A randomized controlled study of two educational interventions on adherence with oral contraceptives and condoms. *Contraception*. 2012;86(6):716–24.

4.4 Recommendations for addition of ulipristal acetate emergency contraceptive pills as a new method to the SPR

Existing recommendations for emergency contraceptive pills (ECPs) in the second edition of the SPR refer only to levonorgestrel-only ECPs (LNG-ECPs) or combined estrogen–progestogen ECPs (combined ECPs). For the third edition of the SPR, the Guideline Development Group (GDG) considered evidence on ulipristal acetate ECPs (UPA-ECPs) in order to add this method to the SPR. When evidence for UPA-ECPs was not available, the GDG extrapolated from labelling information and expert opinion.

4.4.a Initiation of UPA-ECPs

Clinical question: Can UPA-ECPs be taken later than 72 hours after unprotected intercourse?

PICO question for systematic review

Population	Women taking UPA-ECPs
Intervention	Use of UPA-ECPs more than 72 hours after unprotected intercourse
Comparator	Use of UPA-ECPs less than 72 hours after unprotected intercourse
Outcomes	Risk of pregnancy, side-effects, adverse safety outcomes

Recommendations

The GDG determined that recommendations for timing are the same for UPA-ECPs as for LNG-ECPs and combined ECPs. However, UPA-ECPs may be more effective between 72 hours and 120 hours after unprotected intercourse than other ECPs.

NEW recommendation 4.1

A woman should take a dose of UPA-ECP as early as possible after intercourse, within 120 hours.

Quality of evidence: Low (see GRADE evidence table: Can UPA-ECPs be taken later than 72 hours after unprotected intercourse?)

Strength of recommendation: Strong.

Evidence summary

One unpublished systematic review (available on request) examined the safety and effectiveness of ECPs taken 72 hours after unprotected intercourse (1). Two studies from 2010 examined the efficacy of UPA-ECPs taken after 72 hours of unprotected intercourse (2, 3).

One randomized controlled trial (RCT) randomized women to take either levonorgestrel (LNG) or UPA-ECPs within 120 hours after unprotected intercourse; pregnancy rates among those who took the ECPs after 72 hours were 0% in the UPA arm and 2.8% in the LNG group, representing a statistically significant difference ($P = 0.037$) (2). Among those who took the ECPs within 72 hours, 1.8% of women in the UPA arm and 2.6% in the LNG group became pregnant. Statistical testing comparing the rates before and after 72 hours was not performed.

The second study was a prospective cohort of 1241 women who took UPA-ECPs within 120 hours after unprotected intercourse (3). Depending on the time taken, the rate of

pregnancy among women taking UPA-ECPs after 72 hours was 2.1% (72–96 hours after) and 1.3% (97–120 hours after). No statistical testing was performed to detect a difference between these rates.

Rationale

The direct evidence identified for when to take UPA-ECPs was categorized as low quality. To address potential harms of this recommendation, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in WHO's *Medical eligibility criteria for contraceptive use, fifth edition* (MEC) (4). The benefits and harms, as well as values and preferences of women were also integral components to the process of translating the evidence into a recommendation. The GDG incorporated information on women's values and preferences related to choice, ease of use, side-effects and efficacy by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. Restricting UPA-ECP use could increase the risk of unintended pregnancy. The GDG determined that the benefits of taking UPA-ECP up to 120 hours after unprotected intercourse outweigh any potential harms, and therefore classified this as a "strong" recommendation.

Table 6: GRADE evidence table: : Can UPA-ECPs be taken later than 72 hours after unprotected intercourse?

Outcome	Type and number of studies (number of participants)	Limitations	Inconsistency	Imprecision	Indirectness	Other factors	Quality	Estimate of effect
Emergency contraception with UPA-ECPs 72–120 hours after intercourse vs ≤ 72 hours after intercourse								
Pregnancy	2 cohort studies (n=2182) ^a	Serious limitations ^b	No serious inconsistency	No serious imprecision	No indirectness	None	Low	No difference in pregnancy rates between dosing intervals (2 studies; RR=0.84 [0.42–1.66] vs RR=0.28 [0.02–4.61])

RR: relative risk

^a One cohort was an arm of women enrolled in a randomized controlled trial (RCT).

^b Limited by absence of RCTs; data are based upon two high-quality observational studies.

4.4.b Nausea and vomiting when taking UPA-ECPs

Clinical question 1: What can a woman do to prevent nausea and vomiting when taking UPA?

PICO question for systematic review

Population	Women taking ECPs
Intervention	Anti-nausea medication
Comparator	No anti-nausea medication
Outcomes	Rate of nausea and vomiting after ECP use

Recommendations

LNG-ECPs or UPA-ECPs are preferable to combined ECPs because they cause less nausea and vomiting.

Routine use of anti-emetics before taking ECPs is not recommended. Pretreatment with certain anti-emetics can be considered depending on availability and clinical judgment.

NEW recommendation 4.2

LNG-ECPs or UPA-ECPs are preferable to combined ECPs because they cause less nausea and vomiting. Routine use of anti-emetics before taking ECPs is not recommended. Pretreatment with certain anti-emetics can be considered depending on availability and clinical judgement.

Quality of evidence: No direct evidence.

Strength of recommendation: Strong.

Evidence summary

In order to consider the addition of UPA to the recommendations already in place for LNG-ECPs and combined ECPs, a search was conducted to identify studies that examined the prevention and management of nausea and vomiting with UPA. No studies provided direct evidence for this clinical question. However, one study provided indirect evidence by comparing UPA with LNG-ECPs in an effectiveness trial of 1672 women. This study reported no difference in emesis between the two groups, but the UPA group experienced a slightly higher rate of nausea (29% vs 24% of users) (5).

Given that UPA has a similar rate of nausea and emesis to LNG-ECPs, evidence from previously reviewed studies comparing LNG-ECPs to the Yuzpe method was extrapolated to address the clinical question. One published systematic review provided this indirect evidence; it identified 11 studies relevant to the prevention and management of nausea and vomiting in women taking ECPs (6). Four trials compared single-dose LNG-ECP to split-dose LNG-ECPs and found similar rates of nausea and vomiting. Three RCTs compared split-dose LNG-ECPs with the standard Yuzpe regimen of combined ECPs and each found a significantly higher rate of nausea and vomiting among women taking the Yuzpe regimen. Finally, one RCT compared the standard Yuzpe regimen to two modified regimens: changing the progestogen formulation or replacing the second dose with placebo. This study found less nausea and vomiting when the second Yuzpe dose was replaced with placebo, but no difference with an alternate progestogen formulation. Based on this indirect evidence, the GDG concluded that UPA-ECPs and LNG-ECPs both appear to cause less nausea and emesis than combined ECPs.

The same systematic review included two studies that evaluated the use of anti-nausea medications with the Yuzpe regimen, though no studies addressed anti-nausea medications with LNG-ECPs or UPA-ECPs. One double-blind RCT compared women taking meclizine one hour prior to ECPs with women taking placebo one hour prior and with women taking no treatment. Meclizine was effective in reducing nausea and vomiting compared with both control groups, but women taking meclizine were twice as likely to experience drowsiness. The other double-blind RCT compared women taking metoclopramide or placebo one hour prior to each dose of Yuzpe and found a significant decrease in nausea and a non-significant decrease in emesis (6).

In conclusion, this indirect evidence supports the determination that UPA-ECPs have similar

rates of nausea and emesis to LNG-ECPs. LNG-ECPs have previously been shown to cause less nausea and emesis than the Yuzpe method; therefore, through extrapolation of the indirect evidence from LNG-ECPs, UPA-ECPs can be judged to cause less nausea and emesis than combined ECPs. Since anti-emetics are not recommended for LNG-ECPs due to their baseline lower rates of nausea and emesis, anti-emetics are also not recommended for routine use with UPA-ECPs.

Rationale

No direct evidence was identified. Therefore, recommendations for prevention of nausea and vomiting when taking UPA-ECPs are based on indirect evidence about the prevalence of nausea and vomiting with other types of ECPs. Because prevention of nausea and vomiting would be approached similarly across ECP methods, the GDG concluded that the indirect evidence could be used to answer the clinical question. To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (4). The values and preferences of women were also integral components to the process of translating the evidence into recommendations. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. Nausea and vomiting when taking UPA-ECPs may decrease its effectiveness, thus increasing the risk of unintended pregnancy. The GDG determined that the benefits of these recommendations outweigh any potential harms, and therefore classified them as "strong" recommendations.

Clinical question 2: What can a woman do if she vomits after taking UPA-ECPs?

PICO question for systematic review

Population	Women experiencing vomiting after ECP use
Intervention	Intervention to maintain ECP effectiveness (e.g. taking another dose)
Comparator	No intervention
Outcomes	Pharmacokinetic drug levels, markers of ovulation, pregnancy

Recommendation

Vomiting within 3 hours after taking a dose of UPA-ECP

- Another UPA dose should be taken as soon as possible.

NEW recommendation 4.3

If the woman vomits within 3 hours after taking a dose of UPA-ECP, she should take another dose as soon as possible.

Quality of the evidence: No direct evidence.

Strength of the recommendation: Strong.

Rationale

An unpublished systematic review (available upon request) was conducted to identify what a woman can do if she vomits after taking ECPs, including UPA (1). No direct evidence was identified that answered this question for any of the ECPs examined. The labelling information for UPA was therefore reviewed, which recommends the consideration of a second dose if a patient vomits within 3 hours of taking UPA. Pharmacokinetic data included in the label states that maximum plasma concentrations of the drug and active metabolite following a single dose in 20 fasting women were reached at 54 minutes and 1 hour, respectively. The labelling information also noted that taking UPA with a high-fat meal delayed maximum plasma concentrations by 45 minutes to 3 hours (7). After reviewing this information, the GDG considered 3 hours sufficient for absorption of UPA.

To address potential harms of this recommendation, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (4). The values and preferences of women were also integral components to the process of translating the evidence into a recommendation. The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. Vomiting after taking UPA-ECPs may decrease its effectiveness, thus increasing the risk of unintended pregnancy. The GDG noted that LNG-ECPs and UPA-ECPs are less likely to cause nausea and vomiting than are combined ECPs. The GDG determined that the benefits of this recommendation outweigh any potential harms, and therefore classified it as a "strong" recommendation.

References for ulipristal acetate emergency contraceptive pills (UPA-ECPs)

1. Rodriguez MI, Gaffield ME. How can a woman take emergency contraceptive pills? 2015 (unpublished, available upon request).
2. Glasier A, Cameron ST, Fine P, Logan SJ, Casale W, Van Horn J et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised, non-inferiority trial and meta-analysis. *Lancet*. 2010;375(9714):555–62. doi:10.1016/S0140-6736(10)60101-8.
3. Fine P, Mathe H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48–120 hours after intercourse for emergency contraception. *Obstet Gynecol*. 2010;115(2):257–63.
4. Medical eligibility criteria for contraceptive use, fifth edition. Geneva: World Health Organization; 2015 (http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/, accessed 6 July 2016).
5. Creinin M, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M et al. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstet Gynecol*. 2006;108(5):1089–97.

6. Rodriguez MI, Godfrey EM, Warden M, Curtis KM. Prevention and management of nausea and vomiting with emergency contraception: a systematic review. *Contraception*. 2013;87(5):583–9. doi:10.1016/j.contraception.2012.09.031.
7. Ella Prescribing Information. Morristown (NJ): Watson Pharma Inc.; 2010.

4.5 Recommendations for the resumption or initiation of regular contraception after using emergency contraception as a new topic in the SPR

For the third edition of the SPR, the Guideline Development Group (GDG) considered evidence on the resumption or initiation of regular contraception after using emergency contraception in order to add this new topic to the SPR.

Clinical question: When can a woman resume or start regular contraception after taking ECPs?

PICO question for systematic review

Population	Women taking ECPs
Intervention	Resumption or initiation of regular contraception
Comparator	No intervention
Outcomes	Risk of pregnancy, pharmacokinetic drug levels, markers of ovulation

4.5.a Resumption or initiation of regular contraception after levonorgestrel-only ECPs and combined estrogen–progesterone ECPs

NEW recommendation 4.4

Following administration of LNG-ECPs or combined ECPs, a woman may resume her contraceptive method, or start any contraceptive method immediately, including a Cu-IUD.

Timing:

- Following administration of LNG-ECPs or combined ECPs, a woman may resume her contraceptive method, or start any contraceptive method immediately, including a copper-bearing intrauterine device (Cu-IUD). If she wishes to start the LNG-IUD, it can be inserted at any time if it can be determined that she is not pregnant.

- If she does not start immediately but returns for a method, she may start combined hormonal contraceptives (COCs, patch, CVR or injectable contraceptives) or progestogen-only contraceptives (POPs, DMPA or NET-EN injectable contraceptives or implants) at any time if it is reasonably certain that she is not pregnant.
- If she does not start immediately but returns for an IUD, she can have it inserted at any time if it is reasonably certain that she is not pregnant. If she is amenorrhoeic, she can have an IUD inserted at any time if it can be determined that she is not pregnant.

Need for additional contraception:

The woman should be advised to abstain from sexual intercourse or use barrier contraception for 2 days after starting progestogen-only pills (POPs) or 7 days after starting combined hormonal contraceptives (COCs, the patch, the CVR or injectable contraceptives) or other progestogen-only contraceptives (DMPA or NET-EN injectable contraceptives, implants or LNG-IUD) and to have early pregnancy testing at the appropriate time, if warranted (e.g. if no withdrawal bleed occurs within three weeks). No additional contraceptive protection is needed if she starts the Cu-IUD.

Quality of the evidence: No direct evidence.
Strength of the recommendation: Conditional.

4.5.b Starting regular contraception after UPA-ECPs

NEW recommendation 4.5
 Following administration of UPA-ECPs, the woman may resume or start any progestogen-containing method (either combined hormonal contraceptives or progestogen-only contraceptives) on the 6th day after taking UPA. She can have an LNG-IUD inserted immediately if it can be determined that she is not pregnant. She can have the Cu-IUD inserted immediately.

Timing:

- Following administration of UPA-ECPs, the woman may resume or start any progestogen-containing method (either combined hormonal contraceptives [CHCs] or progestogen-only contraceptives [POCs]) on the 6th day after taking UPA. She can

have an LNG-IUD inserted immediately if it can be determined that she is not pregnant.

- If she does not start on the 6th day but returns for a method, she may start CHCs (COCs, patch, CVR or injectable contraceptives) or POCs (POPs, DMPA or NET-EN injectable contraceptives, implants or the LNG-IUD) at any time if it is reasonably certain that she is not pregnant. If she is amenorrhoeic, she can have the LNG-IUD inserted at any time if it can be determined that she is not pregnant.

- Following administration of UPA-ECPs, she can have the Cu-IUD inserted immediately.
 - If she does not start immediately but returns for the Cu-IUD, she can have it inserted at any time if it is reasonably certain that she is not pregnant. If she is amenorrhoeic, she can have the Cu-IUD inserted at any time if it can be determined that she is not pregnant.

Need for additional contraception:

The woman should be advised to abstain from sexual intercourse or use barrier contraception from the time she takes UPA until she is protected by her new method of contraception. If regular hormonal contraception is initiated 6 days after taking UPA, she will need to continue to abstain from sexual intercourse or use barrier contraception according to the recommendations for contraceptive initiation (e.g. an additional 2 days for POPs or an additional 7 days for all other hormonal methods). She should also be advised to have pregnancy testing at the appropriate time, if warranted (e.g. if no withdrawal bleed occurs). She does not need to abstain from sexual intercourse or use additional contraceptive protection if she has a Cu-IUD inserted.

Quality of the evidence: No direct evidence.
Strength of the recommendation: Conditional.

Evidence summary

One published systematic review did not identify any published articles related to the clinical question of interest for UPA-ECPs, LNG-ECPs or combined ECPs (1).

Rationale

No direct evidence was identified for when to start regular contraception after ECP use. Therefore, recommendations for when a woman can resume or start regular contraception after taking ECPs are based on expert opinion. UPA (an anti-progestogen) and progestogen-containing contraceptive methods may interact, potentially decreasing the effectiveness of either drug. There is no concern about interactions between LNG-ECPs or combined ECPs with regular hormonal contraception, as these formulations do not have anti-progestogen properties. The GDG determined that starting a regular progestogen-containing method (including a CHC method) on the 6th day after taking UPA was sufficient time to avoid potential drug interaction while sperm is viable in the female genital tract after unprotected intercourse.

To address potential harms of these recommendations, the GDG considered common barriers to safe, correct and consistent use of contraception and the benefits of preventing unintended or unwanted pregnancy. These harms are thoroughly considered in the MEC (2). The GDG incorporated information on benefits and harms, and on women's values and preferences related to choice, ease of use, side-effects and efficacy, by making contraceptive

provision recommendations that facilitate access to methods while still maintaining safety and efficacy of contraceptive provision based on the available evidence. Initiating regular contraception as soon as possible after taking ECPs is important to decrease additional risk of unintended pregnancy; however, no evidence exists to determine the optimal interval between use of UPA-ECP and starting regular contraception to minimize drug interactions. The GDG considered that if delaying initiation of progestogen-containing methods until the 6th day after use of UPA is unacceptable, she may start any method immediately and will need early pregnancy testing at the appropriate time (e.g. if no withdrawal bleed occurs within three weeks). The GDG determined that policy-making would require substantial debate among various stakeholders, and therefore classified these recommendations as "conditional".

References for resumption or initiation of regular contraception after using emergency contraception

1. Salcedo J, Rodriguez MI, Curtis KM, Kapp N. When can a woman resume or initiate contraception after taking emergency contraceptive pills? A systematic review. *Contraception*. 2013;87:602–4.
2. Medical eligibility criteria for contraceptive use, fifth edition. Geneva: World Health Organization; 2015 (http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/, accessed 6 July 2016).

Appendix 1: Systematic reviews

The following systematic reviews of the epidemiological, clinical and pharmacological evidence were conducted as part of the development of the *Selected practice recommendations for contraceptive use, third edition*.¹ Details of methods and search strategies are included in the reviews. Reviews published in peer-reviewed journals are available through open-access. This appendix will be periodically updated as reviews are published. Access to unpublished reviews can be requested through the following address: hrx-info@who.int

1.1 Levonorgestrel (LNG) implant: Sino-implant (II)[®] Sino-implant (II) initiation

A search was performed on when a woman can initiate Sino-implant (II)[®]. No direct evidence was identified. The systematic review, which is currently in press, documents the process.

1. Phillips SJ, Zhang W. When can a woman start Sino-implant (II)? Systematic review (unpublished).

Sino-implant (II) examinations and tests

Previously published reviews exist on examinations and tests that should be done routinely before providing contraception. The search strategies from these reviews were used to search for evidence on examinations and tests that should be done routinely before providing SI(II). No new articles were identified, so we relied on the previously published reviews.

1. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Blood pressure measurement prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):631–8. doi:10.1016/j.contraception.2012.08.025.
2. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Physical examination prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):650–4. doi:10.1016/j.contraception.2012.08.010.
3. Tepper NK, Steenland MW, Marchbanks PA, Curtis KM. Laboratory screening prior to initiating contraception: a systematic review. *Contraception*. 2013;87(5):645–9. doi:10.1016/j.contraception.2012.08.009.

Sino-implant (II) follow-up

Previously published reviews exist on follow-up needed after initiation of contraception. We used the search strategies from these reviews to search for evidence on follow-up needed after insertion of SI(II). Three new articles were identified in addition to the published reviews.

Published reviews:

1. Steenland MW, Zapata LB, Brahmi D, Marchbanks P, Curtis KM. Appropriate follow up to detect potential adverse events after initiation of select contraceptive methods: a systematic review. *Contraception*. 2013;87(5):611–24. doi:10.1016/j.contraception.2012.09.017.
2. Steenland MW, Zapata LB, Brahmi D, Marchbanks PA, Curtis KM. The effect of follow-up visits or contacts after contraceptive initiation on method continuation and correct use. *Contraception*. 2013;87(5):625–30. doi:10.1016/j.contraception.2012.09.018.

¹ Available at: www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

New articles:

3. Berenson AB, Rahman M. A randomized controlled study of two educational interventions on adherence with oral contraceptives and condoms. *Contraception*. 2012;86(6):716–24. doi:10.1016/j.contraception.2012.06.007.
4. Brindis CD, Geierstanger SP, Wilcox N, McCarter V, Hubbard A. Evaluation of a peer provider reproductive health service model for adolescents. *Perspect Sex Reprod Health*. 2005;37(2):85–91. doi:10.1363/psrh.37.085.05.
5. Nisenbaum MG, Melo NR, Giribela CR, Morais TL, Guerra GM, de Angelis K et al. Effects of a contraceptive containing drospirenone and ethinyl estradiol on blood pressure and autonomic tone: a prospective controlled clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014;175:62-6. doi:10.1016/j.ejogrb.2014.01.006.

Duration of Sino-implant (II)

1. Phillips SJ, Steyn PS, Zhang W, Curtis KM. How long may the Sino-implant (II) be left in place? (unpublished).

1.2 Progestogen-only injectable contraceptive: subcutaneously administered depot medroxyprogesterone acetate (DMPA-SC) DMPA-SC initiation

Previously published reviews exist on initiation of progestogen-only injectables (POIs). We used the search strategies from these reviews to search for evidence on DMPA-SC initiation. No new articles were identified, so we relied on the previously published reviews.

1. Kapp N, Gaffield ME. Initiation of progestogen-only injectables on different days of the menstrual cycle and its effect on contraceptive effectiveness and compliance: a systematic review. *Contraception*. 2013;87(5):576–82. doi:10.1016/j.contraception.2012.08.017.

DMPA-SC examinations and tests

Previously published reviews exist on examinations and tests that should be done routinely before providing contraception. The search strategies from these reviews were used to search for evidence on examinations and tests that should be done routinely before providing DMPA-SC. No new articles were identified, so we relied on the previously published reviews.

1. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Blood pressure measurement prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):631–8. doi:10.1016/j.contraception.2012.08.025.
2. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Physical examination prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):650–4. doi:10.1016/j.contraception.2012.08.010.
3. Tepper NK, Steenland MW, Marchbanks PA, Curtis KM. Laboratory screening prior to initiating contraception: a systematic review. *Contraception*. 2013;87(5):645–9. doi:10.1016/j.contraception.2012.08.009.

DMPA-SC repeat injections

1. Paulen ME, Curtis KM. When can a woman have repeat progestogen-only injectables – depot medroxyprogesterone acetate or norethisterone enantate? *Contraception*. 2009;80(4):391–408. doi:10.1016/j.contraception.2009.03.023.

1.3 The combined contraceptive patch and the combined contraceptive vaginal ring (CVR)

Patch and CVR initiation

1. Brahma D, Curtis KM. When can a woman start combined hormonal contraceptives (CHCs)?: a systematic review. *Contraception*. 2013;87(5):524–38. doi:10.1016/j.contraception.2012.09.010.

Patch and CVR examinations and tests

Previously published reviews exist on examinations and tests that should be done routinely before providing contraception. The search strategies from these reviews were used to search for evidence on examinations and tests that should be done routinely before providing the patch or CVR.

1. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Blood pressure measurement prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):631–8. doi:10.1016/j.contraception.2012.08.025.
2. Tepper NK, Curtis KM, Steenland MW, Marchbanks PA. Physical examination prior to initiating hormonal contraception: a systematic review. *Contraception*. 2013;87(5):650–4. doi:10.1016/j.contraception.2012.08.010.
3. Tepper NK, Steenland MW, Marchbanks PA, Curtis KM. Laboratory screening prior to initiating contraception: a systematic review. *Contraception*. 2013;87(5):645–9. doi:10.1016/j.contraception.2012.08.009.

Patch and CVR dosing errors

A previously published review exists on dosing errors with combined hormonal contraceptives (including the patch and CVR). The search strategy from this review was used to search for additional evidence on dosing errors with the patch and CVR. One new study was identified in this search. This new study along with the systematic review served as the evidence base for this topic.

Published review:

1. Zapata LB, Steenland MW, Brahmi D, Marchbanks PA, Curtis KM. Effect of missed combined hormonal contraceptives on contraceptive effectiveness: a systematic review. *Contraception*. 2013;87(5):685–700. doi:10.1016/j.contraception.2012.08.035.

New article:

2. Dragoman M, Petrie K, Torgal A, Thomas T, Cremers S, Westhoff CL. Contraceptive vaginal ring effectiveness is maintained during 6 weeks of use: a prospective study of normal BMI and obese women. *Contraception*. 2013;87(4):432–6. doi:10.1016/j.contraception.2012.12.001.

Patch and CVR follow-up

Previously published reviews exist on follow-up needed after initiation of contraception. The search strategies from these reviews were used to search for evidence on follow-up needed after initiation of the patch or CVR. Three new articles were identified in addition to the published reviews.

Published reviews:

1. Steenland MW, Zapata LB, Brahmi D, Marchbanks P, Curtis KM. Appropriate follow up to detect potential adverse events after initiation of select contraceptive methods: a systematic review. *Contraception*. 2013;87(5):611–24. doi:10.1016/j.contraception.2012.09.017.
2. Steenland MW, Zapata LB, Brahmi D, Marchbanks PA, Curtis KM. The effect of follow-up visits or contacts after contraceptive initiation on method continuation and correct use. *Contraception*. 2013;87(5):625–30. doi:10.1016/j.contraception.2012.09.018.

New articles:

3. Berenson AB, Rahman M. A randomized controlled study of two educational interventions on adherence with oral contraceptives and condoms. *Contraception*. 2012;86(6):716–24. doi:10.1016/j.contraception.2012.06.007.
4. Brindis CD, Geierstanger SP, Wilcox N, McCarter V, Hubbard A. Evaluation of a peer provider reproductive health service model for adolescents. *Perspect Sex Reprod Health*. 2005;37(2):85–91. doi:10.1363/psrh.37.085.05.
5. Nisenbaum MG, Melo NR, Giribela CR, Morais TL, Guerra GM, de Angelis K et al. Effects of a contraceptive containing drospirenone and ethinyl estradiol on blood pressure and autonomic tone: a prospective controlled clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2014;175:62–6. doi:10.1016/j.ejogrb.2014.01.006.

1.4 Emergency contraception: ulipristal acetate emergency contraceptive pills (UPA-ECPs)

UPA-ECP initiation

An unpublished review exists on the initiation of emergency contraceptive pills. The search strategy from this review was expanded to include UPA-ECPs. Two new articles were identified, in addition to the articles summarized in the unpublished review.

Unpublished review:

1. Rodriguez MI, Gaffield ME. How can a woman take emergency contraceptive pills? (unpublished, available upon request).

New articles:

2. Glasier A, Cameron ST, Fine P, Logan SJ, Casale W, Van Horn J et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised, non-inferiority trial and meta-analysis. *Lancet*. 2010;375(9714):555–62. doi:10.1016/S0140-6736(10)60101-8.
3. Fine P, Mathe H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48–120 hours after intercourse for emergency contraception. *Obstet Gynecol*. 2010;115(2):257–63.

Nausea and vomiting after UPA-ECP use

1. Rodriguez MI, Godfrey EM, Warden M, Curtis KM. Prevention and management of nausea and vomiting with emergency contraception: a systematic review. *Contraception*. 2013;87(5):583–9. doi:10.1016/j.contraception.2012.09.031.

1.5 Resumption or initiation of regular contraception after using emergency contraception

1. Salcedo J, Rodriguez MI, Curtis KM, Kapp N. When can a woman resume or initiate contraception after taking emergency contraceptive pills? A systematic review. *Contraception*. 2013;87(5):602–4. doi:10.1016/j.contraception.2012.08.013.

Appendix 2: Declarations of interests

Of the 58 experts who participated in this work, 14 declared an interest related to contraception (see details below in alphabetical order). The World Health Organization (WHO) Secretariat and the Guidelines Development Group (GDG) reviewed all declarations and found that one participant, Anna Glasier, had disclosed an academic conflict of interest sufficient to preclude her from participating in the deliberations and development of recommendations relevant to ulipristal acetate (UPA).

Individuals with significant declarations:

Eliana Amaral received US\$ 100 000 from WHO to conduct research on the pericoital use of a levonorgestrel-containing emergency contraceptive pill.

Sharon Cameron works at a research unit that received funding from Pfizer Ltd (United Kingdom) to undertake a feasibility study of self-administration of an injectable method of contraception and to conduct another study that will be used to apply to the Medicines and Healthcare products Regulatory Authority (MHRA, United Kingdom) for a license for self-administration of an injectable contraceptive. HRA Pharma (France) provided funding to Cameron's research unit to conduct a trial on the effectiveness of UPA. Cameron is a paid consultant on the European Advisory Board of Exelgyn.

Alison Edelman is a co-investigator of research studies funded by the United States National Institutes of Health (NIH), the Bill & Melinda Gates Foundation and the Society of Family Planning (United States of America). The research unit that Edelman works with receives funding from Merck Sharp & Dohme Ltd (MSD) and Bayer HealthCare on an ongoing basis to undertake acceptability, efficacy and safety studies on contraceptive pills, transdermal patches and hormone-releasing intrauterine devices (IUDs).

Anna Glasier is as an expert consultant to HRA Pharma (France). Her husband also currently consults for HRA Pharma on an occasional basis (approximately once every two years), as a member of a scientific advisory board, and less frequently participates as a speaker or chairperson at international conferences on behalf of the company. Specifically, Anna Glasier works with HRA Pharma on the development of new methods of emergency contraception (EC). She was the principal investigator of a large randomized controlled trial that resulted in the marketing of UPA for EC. Glasier was not personally remunerated; the clinic where she works and conducted the research received these funds. Since the publication of the study results in 2010, Glasier has been actively involved and has been paid a regular consultancy fee to advise the company in their attempts to obtain approval for over-the-counter use of UPA, and on the work HRA Pharma has undertaken relating to EC effectiveness according to the body weight of the user. She is also paid as a member of the company's Scientific Advisory Board and participates as a speaker or chairperson at international conferences on behalf of the company (approximately twice a year). Glasier has provided expert opinion on UPA to regulatory authorities and has represented HRA Pharma at these meetings. In the light of this relationship with a

company that manufactures EC, including UPA, Glasier did not chair or take part in the discussions on EC and weight at the March 2014 GDG meeting and absented herself from the meeting room when inclusion of UPA in the *Medical eligibility criteria for contraceptive use* (MEC) and Selected practice recommendations for contraceptive use (SPR) guidelines was discussed. Glasier has an independent research grant from Pfizer Ltd (United Kingdom) to conduct a study of the feasibility of pharmacists dispensing and injecting a subcutaneously administered injectable contraceptive. In addition, Glasier has an independent research grant from HRA Pharma to pay a clinical research fellow for up to three years to undertake research on contraception.

Olav Meirik received US\$ 5000 from WHO in 2013 to conduct a survey to estimate the patterns of combined oral contraceptive use among formulations containing “third and fourth generation” progestogens. He serves as an unpaid senior research associate with the Instituto Chileno de Medicina Reproductiva (ICMER).

Carolyn Westhoff receives an honorarium from Agile Therapeutics to serve on its Scientific Advisory Board (approximately US\$ 2500 per quarter). She receives honoraria as a member of the Data Safety and Monitoring Boards of both MSD and Bayer HealthCare to monitor contraceptive safety studies conducted by these companies (about US\$ 3500 and €2700 per year, respectively). Westhoff’s research unit receives funding to conduct studies on IUDs (Bayer Healthcare and Medicine 360), a trial of the efficacy of self-administration of an injectable method of contraception (Pfizer, Inc.) and a trial on the safety and effectiveness of oral contraceptive pills (MSD).

Individuals without any conflict or with non-significant conflicts of interest:

Jean-Jacques Amy received €2500 in 2013 from MSD to present a paper at a scientific symposium, and receives an annual stipend of €5000 from the European Society of Contraception and Reproductive Health to serve as the editor-in-chief for the Society’s journal.

Andy Gray works at CAPRISA, a research unit that receives donations of antiretroviral medications from the NIH Clinical Research Products Management Center (including products manufactured by Abbott; Boehringer Ingelheim; Bristol Myers Squibb; Gilead; GlaxoSmithKline; MSD; and Roche) for use in the clinical trials conducted through the AIDS Clinical Trials Group and the International Maternal, Paediatric, Adolescent AIDS Clinical Trial network. The unit also received donated microbicide products from Gilead Sciences for a phase IIb clinical trial.

Philip Hannaford works for an academic department that received fees from several manufacturers of oral contraceptives in the past for lectures on matters related to contraception, especially oral contraception.

Francesca Martinez received honoraria of €600 from Jansen (2013), Teva (2012), Bayer (2012) and S.M.B. (2012) to give lectures on contraception during scientific meetings supported by these pharmaceutical companies.

Chelsea Polis collaborated on a trial investigating the acceptability of a subcutaneous injectable contraceptive; data collection for this study ceased in 2013. Pfizer, Inc. donated the injectable units, which were not yet commercially available, to her research unit for the conduct of the trial, but did not provide any monetary support.

Regine Sitruk-Ware received €1500 twice in a four-year period from Bayer to provide lectures on the future targets for a nonhormonal contraceptive in the female reproductive tract, and €4500 in 2014 from MSD to advise the company on the development of a progestin, nomegestrol acetate.

Lisa Soule is employed by the United States Food and Drug Administration (U.S. FDA), which is a regulatory body for hormonal contraceptives in the United States. In her role at the meeting, she represented the interests of the U.S. FDA, which serves the public health, and not any commercial interests.

Julie Williams is employed by the MHRA, United Kingdom. She was the lead rapporteur for the European Medicines Agency (EMA) Article 31 referral for combined hormonal contraceptives (CHCs), which considered the risk of venous thromboembolism across different products and how this influenced the balance of benefits and risks of these products. The review was considered by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) and the output of this review included the agreed PRAC recommendation and the Committee on Medicinal Products for Human Use (CHMP) Opinion. Both the PRAC recommendation and the CHMP Opinion have been made publically available on the EMA website and resulted in changes to the product information for CHCs included in this Article 31 referral.



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