Immediate start of hormonal contraceptives for contraception (Review)

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TABLE OF CONTENTS

ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
BACKGROUND . . . 2
OBJECTIVES . . . 3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW . . . 3
SEARCH METHODS FOR IDENTIFICATION OF STUDIES . . . 3
METHODS OF THE REVIEW . . . 4
DESCRIPTION OF STUDIES . . . 4
METHODOLOGICAL QUALITY . . . 4
RESULTS . . . 5
DISCUSSION . . . 6
AUTHORS' CONCLUSIONS . . . 6
POTENTIAL CONFLICT OF INTEREST . . . 7
ACKNOWLEDGEMENTS . . . 7
SOURCES OF SUPPORT . . . 7
REFERENCES . . . 7
TABLES . . . 9
Characteristics of included studies . . . 9
Characteristics of excluded studies . . . 11
ANALYSES . . . 11
Comparison 01. Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg) . . . 11
Comparison 02. Immediate versus conventional start of OCs . . . 12
Comparison 03. Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg) . . . 12
Comparison 04. Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg) . . . 12
Comparison 05. Immediate DMPA versus contraceptive bridge to DMPA . . . 13
COVER SHEET . . . 13
GRAPHS AND OTHER TABLES . . . 14
Analysis 01.01. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 01 Pregnancy per woman . . . 14
Analysis 01.02. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 02 Discontinued OCs during 90-day period . . . 14
Analysis 01.03. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 03 Frequent bleeding (> 4 episodes of bleeding or spotting) . . . 15
Analysis 01.04. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 04 Irregular bleeding (bleeding-free interval > 17 days) . . . 15
Analysis 01.05. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days) . . . 16
Analysis 01.06. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 06 Amenorrhea (no bleeding) . . . 16
Analysis 01.07. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 07 Overall satisfaction with OCs . . . 17
Analysis 01.08. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 08 Would make the same decision to start OCs . . . 17
Analysis 02.01. Comparison 02 Immediate versus conventional start of OCs, Outcome 01 Pregnancy per woman . . . 18
Analysis 02.02. Comparison 02 Immediate versus conventional start of OCs, Outcome 02 Serious adverse events . . . 18
Analysis 03.01. Comparison 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg), Outcome 01 Discontinuation of patch by cycle 3 . . . 19
Analysis 03.02. Comparison 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg), Outcome 02 Breakthrough bleeding . . . 19

Analysis 03.03. Comparison 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg), Outcome 03 Nausea 20
Analysis 04.01. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 01 Pregnancy per woman 20
Analysis 04.02. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 02 Discontinued method in 84-day period 21
Analysis 04.03. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 03 Frequent bleeding (> 4 episodes of bleeding or spotting) 21
Analysis 04.04. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 04 Irregular bleeding (bleeding-free interval > 17 days) 22
Analysis 04.05. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days) 22
Analysis 04.06. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 06 Amenorrhea 23
Analysis 04.07. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 07 Very satisfied with method 23
Analysis 04.08. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 08 Planned to use method 24
Analysis 04.09. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 09 Bad change in weight 24
Analysis 04.10. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 10 Bad change in bleeding 25
Analysis 04.11. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 11 Bad change in headache 25
Analysis 04.12. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 12 Bad change in breasts 26
Analysis 04.13. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 13 Bad change in mood 26
Analysis 04.14. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 14 Bad change in acne 27
Analysis 04.15. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 15 Bad change in appetite 27
Analysis 04.16. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 16 Bad change in nausea 28
Analysis 04.17. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 17 Bad change in cramps 28
Analysis 04.18. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 18 Bad change in hair 29
Analysis 04.19. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 19 Serious adverse events (total) 29
Analysis 05.01. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 01 Pregnancy per woman 30
Analysis 05.02. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 02 Discontinued method before 6 months 30
Analysis 05.03. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 03 Very satisfied with method at 6 months 31
Analysis 05.04. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 04 Adverse events 31

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ABSTRACT

Background
Health care providers often tell women to wait until the next menses to begin hormonal contraception. The main intent is to avoid contraceptive use during an undetected pregnancy. An alternative is to start hormonal contraception immediately with back-up birth control for the first seven days. Immediate initiation was first introduced with combined oral contraceptives (COCs), and has expanded to other hormonal contraceptives. How immediate start compares to conventional menses-dependent start is unclear regarding effectiveness, continuation, and acceptability. The immediate-start approach may improve women's access to, and continuation of, hormonal contraception.

Objectives
This review examined randomized controlled trials of immediate-start hormonal contraception for differences in effectiveness, continuation, and acceptability.

Search strategy
We searched MEDLINE, CENTRAL, POPLINE, EMBASE, and LILACS for trials of immediate-start hormonal contraceptives. We contacted researchers to find other studies.

Selection criteria
We included randomized controlled trials that compared immediate start to conventional start of hormonal contraception. Also included were trials that compared immediate start of different hormonal contraceptive methods with each other.

Data collection and analysis
Data were abstracted by two authors and entered into RevMan. The Peto odds ratio (OR) with 95% confidence interval (CI) was calculated.

Main results
Five studies were included. Method discontinuation was similar between groups in all trials. Bleeding patterns and side effects were similar in trials that compared immediate with conventional start.

In a study of depot medroxyprogesterone acetate (DMPA), immediate start of DMPA showed fewer pregnancies than a 'bridge' method before DMPA (OR 0.36; 95% CI 0.16 to 0.84). Further, more women in the immediate-DMPA group were very satisfied versus those with a 'bridge' method (OR 1.99; 95% CI 1.05 to 3.77).

A trial of two immediate-start methods showed the vaginal ring group had less prolonged bleeding (OR 0.42; 95% CI 0.20 to 0.89) and less frequent bleeding (OR 0.23; 95% CI 0.05 to 1.03) than COC users. The ring group also reported fewer side effects. For satisfaction, more immediate ring users were very satisfied than immediate COC users (OR 2.88; 95% CI 1.59 to 5.22).

Authors' conclusions
We found limited evidence that immediate start of hormonal contraception reduces unintended pregnancies or increases method continuation. However, the pregnancy rate was lower with immediate start of DMPA versus another method. Some differences were

associated with contraceptive type rather than initiation method, that is, immediate ring versus immediate COC. More studies are needed of immediate versus conventional start of the same hormonal contraceptive.

PLAIN LANGUAGE SUMMARY

Immediate start of hormonal birth control

Health care providers often tell women to wait until their next menstrual cycle to begin birth control pills. The main reason is to avoid using birth control during an undetected pregnancy. Another method involves starting the pills right away ('immediate start' or 'quick start'). Another birth control method should be used as back-up for the first seven days. Unclear issues are whether quick start of hormonal birth control works as well as the usual start and whether women like it. The quick start method might improve women's use of hormonal birth control.

We did computer searches for randomized controlled trials of the quick-start method for pills and other hormonal birth control. We contacted researchers to find other studies. We included trials that compared quick start to the usual start of birth control. Also included were studies that compared quick start of different types of hormonal birth control with each other. Birth control methods could have the hormones estrogen and progestin (combined hormonal birth control) or just the progestin.

Five studies were included. In a study of 'depo,' a progestin-only injection, fewer women with quick start of depo became pregnant than those who used another method for 21 days before depo. In this review, the numbers of women who stopped using their birth control method early were similar between groups in all trials. In the depo trial, more women with quick start of depo were very satisfied.

A trial of two quick-start methods showed women with the vaginal ring had less long-term bleeding and less frequent bleeding than those with pills. For six side effects, including changes in breasts, mood, and nausea, quick start of the ring showed fewer problems than quick start of pills. For satisfaction in that trial, more women in the ring group were very satisfied with their method of birth control.

We found little strong evidence that quick start leads to fewer pregnancies or fewer women stopping early. However, fewer women on quick-start of depo became pregnant than the women who started with another method. Other differences were between types of birth control rather than start times. Women using the vaginal ring had fewer problems than women using birth control pills. More studies are needed comparing quick start versus usual start of the same hormonal birth control method.

BACKGROUND

Worldwide, 75 million women use contraceptive pills and another 27 million use injectable contraceptives or implants (UNDP 2003). The optimal time to start hormonal contraception remains unknown. Traditionally, women have been instructed to start combined oral contraceptives (COCs) in relation to their menstrual cycle: either on day one or within the first five to seven days of their menses (Kubba 1993) or on the Sunday after their menses began (Williams-Deane 1992). Most health care providers and pharmaceutical companies suggest multiple options for starting oral contraceptives (OCs), all of which are timed in relation to menses (Williams-Deane 1992). These multiple options can create confusion regarding when to start the pill. Furthermore, menstruation requirements for initiation of contraception impede access to contraception for women with real or perceived irregular menses. In particular, from 41% to 92% of family planning clients in developing countries are denied contraceptive services if they are not menstruating at the time of their visit (Stanback 1997; Stanback 1999). Only 16% of providers in Kenya felt safe in giving women OCs to start taking later (Stanback 2003). In Ghana and Senegal, less than 5% of providers reported they gave pills to non-menstruating women for later use at the onset of menses (Stanback 2003).

The recommendation for women to wait until the next menses to begin hormonal contraception is intended to avoid contraceptive use during an undetected pregnancy. During this delay in contraceptive initiation, unintended pregnancies occur, women's intentions for contraceptive use may change (Stanback 1997), women may forget instructions, and fears of side effects increase (Westhoff 2002). This medically-imposed delay in starting contraception may increase the cost of family planning due to more repeat or return clinic visits. Worldwide, unintended pregnancies are associated with preventable morbidity and mortality. In contrast, reviews of epidemiological data and prospective studies have indicated that exogenous hormones during pregnancy did not increase risk of developing abnormalities in nongenital organs (Wilson 1981); oral contraceptives were not associated with congenital malformations (Bracken 1990).

An alternative is to start hormonal contraceptives immediately

with back-up birth control for the first seven days (Lara-Torre 2004). This "immediate-start" or "quick-start" method may improve initiation and continuation of hormonal contraceptives, among both adolescents and adults, compared to conventional start methods (Lara-Torre 2002; Westhoff 2002). Immediate start of birth control was introduced with combined oral contraceptives, which have both progestin and estrogen, and has been expanded to other hormonal contraceptives (Murthy 2005; Westhoff 2005; WHO 2004). How immediate start of hormonal contraception compares to conventional menses-dependent start is unclear regarding effectiveness, continuation, and acceptability.

OBJECTIVES

This review examined randomized controlled trials of immediate-start hormonal contraception for differences in effectiveness, continuation, and acceptability.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

We included randomized controlled trials in any language that compared immediate start of hormonal contraceptives to conventional start. We also included randomized trials that compared immediate start of different hormonal contraceptive methods with each other.

Types of participants

All women with data in the eligible trials were included in this review.

Types of intervention

We included any contraception initiation method: immediate start and start in relation to timing of menses. We also included any type of hormonal contraception: oral, intramuscular, transdermal, and transvaginal.

Types of outcome measures

Contraceptive effectiveness, continuation rates, bleeding patterns, acceptability, and side effects.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Fertility Regulation Group methods used in reviews.

We searched the computerized databases MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), POPLINE, LILACS, and EMBASE for studies of immediate-start hormonal contraceptives. We examined reference lists of relevant articles. We also wrote to known investigators for information about other published or unpublished trials not discovered in our search. The search strategies are shown below.

MEDLINE via PubMed
(contraceptive agents, female OR (steroid* AND contracept*) OR orthoevra OR "ortho evra" OR "norelgestromin" OR (contraceptive devices, female and ring) OR NuvaRing OR cyclofem OR lunelle OR mesigyna OR cycloprovera OR (medroxyprogesterone 17-acetate AND (contracept* OR inject* OR depo OR depot)) OR depot medroxyprogesterone OR depo medroxyprogesterone OR depotmedroxyprogesterone OR depomedroxyprogesterone OR dmpa OR "net en" OR norethisterone enantate OR norplant OR uniplant OR jadelle OR implanon OR ((levonorgestrel OR etonogestrel) AND implant) OR (levonorgestrel AND intrauterine devices) OR mirena OR ((progestational hormones OR progestin) AND contracept* AND (oral OR pill* OR tablet*))) AND (((time factors OR immediate OR timing) AND (start* OR begin* OR initiat*)) OR "quick start"OR starting day OR drug administration schedule)

CENTRAL
contracept* and (initiat* or start* or begin* or quick start or drug administration schedule) in Title, Abstract, or Keywords

POPLINE
(Contraceptive Agents Female/depo provera/dmpa/medroxyprogesterone/(steroid* & contracept*) /orthoevra/ortho evra /norelgestromin/(contraceptive devices, female and ring)/ NuvaRing /cyclofem /lunelle/ mesigyna/ cycloprovera/ (medroxyprogesterone 17-acetate & (contracept* /inject*/depo/depot))/ depot medroxyprogesterone/ depo medroxyprogesterone/ depot medroxyprogesterone/depo medroxyprogesterone/dmpa/ net en/ norethisterone-enantate/norplant/uniplant/jadelle/implanon/((levonorgestrel/ etonogestrel) & implant)/(levonorgestrel & intrauterine devices)/mirena /((progestational hormones/progestin) & contracept* & (oral/pill*/tablet*))) & (start & (quick/immediate/time/timing))/"quick start"

LILACS
contraceptive agents, female or agentes anticonceptivos femeninos or anticoncepcionais femeninos or contraceptives, oral or anticonceptivos orales or anticoncepcionais orais [Words] and start or initiator or inciador or begin or beginning or comienzo or incio or initiation or quick start or starting day or drug administation schedule [Words]

EMBASE
CONTRACEPTIVE AGENT? OR STEROID?(W)CONTRACEPT?
AND DRUG ADMINISTRATION AND (QUICK(W)START OR START? OR INITIAT?OR BEGIN?).

METHODS OF THE REVIEW

We assessed for inclusion all titles and abstracts identified during the literature searches. One author reviewed the search results and identified reports for inclusion or exclusion. Another author also examined the reports identified for appropriate categorization. Similarly, one author abstracted the data and entered the information into RevMan. Another author conducted a second data abstraction and verified correct data entry. Any discrepancies were resolved by discussion.

Studies were examined for methodological quality, according to the principles recommended in Higgins 2005. Factors considered were study design, randomization method, allocation concealment, blinding, and losses to follow up and early discontinuation. Adequate methods for allocation concealment include a centralized telephone system and the use of sequentially-numbered, opaque, sealed envelopes (Schulz 1995; Schulz 2002a). Pharmacy distribution of pill bottles is another good method. Excluding randomized persons is not consistent with an intent-to-treat analysis and can bias the results (Schulz 2002b). High losses to follow up threaten validity (Sackett 2000). Limitations in design are presented under 'Methodological quality' and were considered when interpreting the results.

For dichotomous outcomes, the Peto odds ratio (OR) with 95% Confidence Interval (CI) was calculated. Examples are the proportion of women who became pregnant or who discontinued contraception early. The Peto OR is useful when treatment effects are small and when events are not very common (Higgins 2005). This approach performs well under many circumstances, except when the study arm sizes are severely unbalanced, which rarely occurs in RCTs (Deeks 2001). In addition, the Peto OR does not require correction for zero events, which can occur when events are rare, such as for adverse events. A fixed-effect model does not require the assumption of normal distribution for the effects (Deeks 2001; Higgins 2005). Fixed-effect and random-effects models will give the same result if no heterogeneity exists, which is also the case if a comparison includes a single study. There is no consensus regarding the use of either model. We had planned to test for statistical heterogeneity. However, we did not combine data from any studies in meta-analysis due to differences in interventions.

For analysis, we used intent to treat or per protocol as data were available in the reports. Data are described in the Characteristics of included studies table (Outcomes), along with any exceptions due to reporting. Exclusions by the trial authors are described with losses in the 'Notes' of the Characteristics table.

DESCRIPTION OF STUDIES

Five randomized controlled trials met the eligibility criteria. The trials included a total of 2427 women. Sample sizes ranged from 60 to 1720 with an average of 485. All trials were conducted in the USA. Four trials were related, having been conducted by members of the same research group (Rickert 2007; Westhoff 2003; Westhoff 2005; Westhoff 2007).

Treatment duration was 3 cycles or 84 to 90 days in Murthy 2005, Westhoff 2003, and Westhoff 2005 and 6 months in Rickert 2007 and Westhoff 2007.

The comparisons differed across trials. Immediate start refers to initiating contraception during the first visit. Conventional start of contraception included instruction to start during the next menses. Only Rickert 2007 excluded women who were currently menstruating. Two studies compared immediate versus conventional start of OCs; Westhoff 2003 used a COC (norethindrone 1 mg plus ethinyl estradiol (EE) 35 µg) while in Westhoff 2007 the type of OC depended on the clinician's preference. Murthy 2005 examined immediate versus conventional start of the contraceptive patch (containing norelgestromin 6 mg plus EE 75 µg (Ortho-McNeil 2007)). Rickert 2007 examined immediate injection of depot medroxyprogesterone acetate (DMPA) versus a contraceptive bridge to DMPA. "Bridge" participants could choose pills, patch, or ring before DMPA and were given a 21-day supply; their first DMPA injection was administered 21 to 28 days later. The trial of Westhoff 2005 differed in that immediate use of the vaginal contraceptive ring (daily release: etonogestrel 120 µg plus EE 15 µg) was compared with immediate COC (norgestimate (NGM) 180/215/250 µg plus EE 30 µg).

In four trials, participants in both groups were instructed to use condoms as a back up (or abstain) for the first seven days or until they started their contraceptive method (Rickert 2007; Westhoff 2003; Westhoff 2005; Westhoff 2007). Women in Westhoff 2005 were also given emergency contraception. In Murthy 2005, reportedly just the immediate-start group was instructed to use a back-up method like condoms for seven days; however, all participants were given a prescription for emergency contraception.

The outcomes included pregnancy data for all but Murthy 2005, discontinuation of method for four trials, bleeding or cycle control data for all but Rickert 2007, and satisfaction with method in three trials (Rickert 2007; Westhoff 2003; Westhoff 2005). Data on side effects or adverse events were varied. For examples, Murthy 2005 only reported on nausea, and Westhoff 2007 reported just the serious adverse events. The Schafer 2006 report from the Westhoff 2005 trial assessed the women for 10 potential side effects; participants could report no change, good change, or bad change.

METHODOLOGICAL QUALITY

The trials were published from 2003 to 2007. All appeared to be open-label, most likely due to the differences in the interventions. However, Westhoff 2003 noted that the person who abstracted the diary information was blinded to group assignment.

The quality of reporting was uneven for some design issues. Randomization in four trials was described as generated with random numbers table or random numbers generator. One trial did not provide information on how the randomization sequence was generated and did not specify if the allocation was concealed before assignment (Murthy 2005). Two studies had adequate allocation concealment with sequentially-numbered, opaque, sealed envelopes (Westhoff 2003; Westhoff 2005). Two trials bordered on having adequate concealment, as they reported using sequential sealed envelopes (Rickert 2007) or numbered opaque envelopes (Westhoff 2007).

Sample size varied: 60 in the pilot study of Murthy 2005, 113 in Westhoff 2003, 201 in Westhoff 2005, 333 for Rickert 2007, and 1720 in Westhoff 2007. All studies reported an a priori sample size determination: three focused on discontinuation rates (Murthy 2005; Rickert 2007; Westhoff 2007) and two were based on bleeding and spotting days (Westhoff 2003; Westhoff 2005). Three studies appeared to use intent-to-treat analysis, in which all the women who were randomized and had follow-up data were included in the analysis (Murthy 2005; Rickert 2007; Westhoff 2005). Two studies excluded women from the study who had been randomized but then were found to have been ineligible due to pregnancy (Westhoff 2003; Westhoff 2007).

Losses to follow up also varied. Murthy 2005 and Westhoff 2003 had losses around 2%, while Westhoff 2005 lost 13% and Westhoff 2007 lost about 16%. The DMPA study of Rickert 2007 had high losses of 32% for each group. High losses to follow up threaten validity (Sackett 2000), and many methodologists would question whether Rickert 2007 should still be considered 'randomized' given the losses.

RESULTS

The trials examined here included several different types of comparisons. Three trials compared immediate versus conventional start of the same contraceptive method: a specific COC (Westhoff 2003), various types of OCs (Westhoff 2007), and the contraceptive patch (Murthy 2005). One study (Rickert 2007) compared immediate start of DMPA to a 'bridge' to DMPA (using pills, transdermal patch, or vaginal ring for 21 days before the first DMPA injection). Another study (Westhoff 2005), compared two immediate-start methods (vaginal ring versus COC). Most differences were found between types of contraceptives rather than between immediate and conventional initiation. No trials were combined in meta-analysis due to the differences in interventions.

Effectiveness

Four studies reported the proportions of women who became pregnant during the study. In Rickert 2007, the immediate DMPA group was less likely to become pregnant than the bridge group (OR 0.36; 95% CI 0.16 to 0.84). The groups were similar in contraceptive effectiveness in Westhoff 2003 and Westhoff 2007, which compared immediate to conventional start of OCs. When the pregnancies estimated to have occurred prior to enrollment were included in the analysis, the groups were still similar in Westhoff 2003 and Westhoff 2007.

Westhoff 2005 compared two immediate-start methods (ring and COC); no difference in pregnancy rates was evident in that study, either.

Contraceptive method discontinuation

Method discontinuation was similar across groups in the studies with such data. Murthy 2005 compared immediate to conventional start of the patch, Rickert 2007 examined immediate DMPA and a bridge to DMPA, and Westhoff 2003 studied immediate versus conventional start of the same COC. For method discontinuation, Westhoff 2007 provided percentages for the groups combined; the immediate and conventional start groups were reportedly similar. Westhoff 2007 included various OCs, according to the clinician's preference.

No difference in discontinuation was noted in the Schafer 2006 report of the Westhoff 2005 trial, which compared two immediate-start methods (ring versus COC).

Cycle control

Four trials reported bleeding data. The study groups had similar bleeding profiles in three trials that compared immediate with conventional start: Murthy 2005 (patch); Westhoff 2003 (same COC); and Westhoff 2007 (various OCs).

In Westhoff 2005, which compared two immediate start methods, prolonged bleeding (bleeding or spotting episode lasting at least 10 days) was lower for the group with the ring compared to those with COCs (OR 0.42; 95% CI 0.20 to 0.89). Frequent bleeding, defined as more than four episodes of bleeding or spotting, also differed in favor of the vaginal ring group (OR 0.23; 95% CI 0.05 to 1.03) (Westhoff 2005).

Adverse events

Information on side effects varied.

- Murthy 2005 reported on nausea, for which the immediate and conventional start of the patch groups were similar.
- Rickert 2007 reported no adverse events with either the immediate start of DMPA or the group with a bridge to DMPA.
- Westhoff 2007 only reported serious adverse events (SAEs), for which the immediate and conventional start groups were similar; various OCs were included. Examples of SAEs were cholecystectomy, pyelonephritis, and pelvic inflammatory disease (Westhoff 2007); the authors did not specify whether any SAEs were considered related to the intervention.

For the Westhoff 2005 trial, the later report of Schafer 2006 showed that 6 of 10 side effects were less common for the immediate use of the vaginal ring versus immediate start of COCs.

The vaginal ring group less frequently reported a "bad change" for weight (OR 0.42; 95% CI 0.21 to 0.87), bleeding (OR 0.28; 95% CI 0.14 to 0.55), breasts (OR 0.36; 95% CI 0.18 to 0.73), mood (OR 0.36; 95% CI 0.19 to 0.69), appetite (OR 0.44; 95% CI 0.21 to 0.95), or nausea (OR 0.30; 95% CI 0.14 to 0.62) (Westhoff 2005).

Satisfaction and future use

Three trials provided data on method satisfaction (Rickert 2007; Westhoff 2003; Westhoff 2005). In Rickert 2007, women in the immediate start of DMPA group were more likely to be very satisfied with their method at six months compared to those with use of a bridge method (OR 1.99; 95% CI 1.05 to 3.77). Westhoff 2003 showed no differences between the immediate and conventional start of the COC.

In Westhoff 2005, which studied two immediate-start methods, more women with the vaginal ring reported being very satisfied with their method compared to the group with COCs (OR 2.88; 95% CI 1.59 to 5.22). Similarly, more women with immediate start of the vaginal ring planned to use the method after the study (OR 2.51; 95% CI 1.32 to 4.77).

DISCUSSION

One of the purposes of immediate start of contraception is to improve initiation and continuation rates and decrease unintended pregnancies. In this review, pregnancy differed in one study that compared immediate start of DMPA to using a bridge to DMPA. Compared to many other contraceptive methods, DMPA is long-acting and less user-dependent. While the 'immediate-DMPA' group had proportionately fewer pregnancies, losses were high in that trial. Some of the studies were underpowered to detect differences in pregnancies. However, method discontinuation was similar between study groups in this review.

Cycle control, from bleeding diaries, only differed in a study of two immediate methods. The vaginal ring group had fewer bleeding problems than the COC group (Westhoff 2005). The same trial solicited side effect information and showed differences between the vaginal ring and COC groups (Westhoff 2005). Westhoff 2005 did not provide criteria or details for reporting side effects. Other trials showed the comparison groups to be similar for adverse events. The trials did not have consistent recording or reporting of side effects, which complicates interpretation. Furthermore, side effects may dissipate over time and these trials were relatively short-term.

For satisfaction, two trials showed some differences. In the DMPA trial, the group with immediate use of DMPA was more satisfied than those with a bridge method first. In the trial of two immediate methods, the vaginal ring group was more satisfied than the COC group. However, these studies were only three or six months in duration and satisfaction may vary over time.

All of the trials were relatively recent, yet they did not follow CONSORT guidelines for reporting (Moher 2001). Design details were sometimes lacking. In addition, CONSORT recommends the reporting of outcome data in absolute numbers, rather than percentages. For outcomes reported as means, a measure of variation is needed to interpret the results. Two trials did not follow those guidelines, which prevented the inclusion of some data in the review.

This review was limited due to having only five trials and to great variation in the comparisons. One study compared two immediate-start methods. Of the four trials comparing immediate start with conventional start, one focused on the skin patch and another on DMPA (with or without a bridge method). The remaining two trials studied OCs, but one examined the same COC with different initiation methods, while the other left the OC choice to clinicians. In addition, no study was adequately powered for contraceptive effectiveness (pregnancy), a primary outcome for this review. Trials were generally powered to detect differences in continuation or bleeding patterns.

AUTHORS' CONCLUSIONS

Implications for practice

We found little evidence that immediate start of hormonal contraceptives reduces unintended pregnancies or increases continuation. Bleeding patterns and side effects were similar in trials that compared immediate start with conventional start. Immediate start is one of several acceptable options for starting COCs although more data are needed. One trial showed a lower risk of pregnancy with immediate start of DMPA versus bridging to DMPA with another method. High losses in that trial could have biased the results.

Implications for research

More trials are needed of immediate versus conventional start of the same hormonal contraceptive method. The primary analysis should be done by intent-to-treat; that is, all enrolled participants should be included. Consistent recording and reporting of bleeding and other side effects would aid interpretation across trials. Improved follow up is critical to interpretation of trial results, as high losses threaten validity.

In general, we endorse planning for adequate power (Schulz 2005). However, if the scientific world insisted exclusively on large trials, many questions in medicine would languish unanswered. 'Underpowered' trials can be acceptable because they could be combined in a meta-analysis. Our suggestion has three caveats. First, the trial should be methodologically strong, thus eliminating bias. If designed and implemented properly, the trial would yield an unbiased estimate of effect even if it has low power (and precision). The results could then be combined with similar unbiased trials

in a meta-analysis. Second, to avoid misinterpretation, authors should report their methods and results properly. If trial results were reported using interval estimation, the wide confidence intervals around the estimated treatment effect would depict the low power. Third, low-powered trials should be published regardless of their results so they can be used in meta-analysis.

POTENTIAL CONFLICT OF INTEREST

Dr. Grimes has consulted with or served on speakers bureaus for ALZA, Berlex Laboratories, FEI Women's Health, Gynetics, GynoPharma, Mead Johnson, Organon, Ortho-McNeil, Parke-Davis, Pharmacia-Upjohn, Schering, Schmid, Searle, and Wyeth-Ayerst.

Dr. Nanda is the principal investigator of a trial on this subject; the results may be included in an update.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Murthy 2005**
Methods	Open-label, randomized controlled trial ("pilot investigation") conducted at a university hospital in Pittsburgh (USA). Sample size calculation based on ability to detect difference in continuation rates for immediate start (87%) versus traditional start (60%).
Participants	60 women recruited via newspaper advertisements and flyers. Inclusion criteria: 18 to 45 years old, request transdermal delivery for contraception, willing to comply with protocol and visit schedule, willing to answer questionnaires. Exclusion criteria: contraindication to combined contraceptive hormones, unprotected sex since last menstrual period > 120 h before enrollment, recent abortion without a subsequent period, and weight > 90 kg.
Interventions	Immediate initiation (N=30) versus traditional start (N=30) of contraceptive patch (norelgestromin 150 µg + EE 20 µg); treatment duration 3 cycles. For traditional start, participants were to start on the first day on their next menses.
Outcomes	Continuation rates, side effects, breakthrough bleeding. Analysis was done by Intent to treat (ITT).
Notes	No mention of method for generating randomization sequence or allocation concealment before assignment. Lost to follow up: 2%; by group, quick start zero and traditional start 1/30 = 3%.
Allocation concealment	B – Unclear

Study	**Rickert 2007**
Methods	Nonblinded, randomized controlled trial at a family planning clinic in New York City (USA). Randomization sequence developed from a random number table. Allocation was concealed in sequential sealed envelopes. Sample size calculation based on ability to detect difference in continuation rates of 17%.
Participants	333 women (age 14 to 26 years) who sought care at a family planning clinic and were interested in using DMPA. Exclusion criteria: currently menstruating, pregnant, or breastfeeding; contraindication to hormonal contraception; using DMPA (within past 14 weeks); consistently used birth control pills, patch, ring, or other prescription contraception method in past 30 days; history of serious mental illness.
Interventions	Immediate DMPA (depot medroxyprogesterone acetate) (N=101) versus bridge method (choice of pills, patch, or ring with a 21-day supply prior to first DMPA injection) (N=232); treatment duration 6 months.
Outcomes	Pregnancy, continuation, satisfaction, adverse events. Analysis was by ITT, except for satisfaction, which only included those who completed the visit interview.

Characteristics of included studies (*Continued*)

Notes	Women who discontinued their method were followed for discontinuation interview by phone or face-to-face. Interview addressed sexual behaviors, current contraception, and reasons for discontinuing method. Women who completed the interview are not included in the losses to follow up. Lost to follow: 32% overall; by group, Depo Now 32/101 = 32%; bridge method 74/232 = 32%.
Allocation concealment	B – Unclear

Study	**Westhoff 2003**
Methods	Randomized controlled trial at a university medical center in New York City (USA). Randomization sequence was generated with random numbers table prior to study recruitment. Participants had 60% chance of allocation to quick start and 40% chance of allocation to conventional start. Allocation was concealed with sequentially-numbered opaque sealed envelopes. Sample size calculation was based on detecting difference of 3 or more bleeding or spotting days during 90-day reference period. Abstractor of diary data was blinded to group assignment.
Participants	113 women recruited by local advertisements. Inclusion criteria: 18 to 35 years old, English- or Spanish-speaking, regular menstrual cycles of 21 to 35 days in past 12 mos, no contraindication to OC use, no hormonal contraception for > 2 menses (or > 6 menses for injectables), > 2 menses since last pregnancy, no emergency contraception in current cycle. Exclusion criteria: positive pregnancy test or unprotected sex 10 days before screening.
Interventions	Immediate (N=67) versus conventional start (N=46) of oral contraceptives (norethindrone 1 mg + EE 35 µg). Immediate: took first pill with direct observation. Conventional: instructed to take first pill on first Sunday after menses onset. Reference period of 90 days from treatment start.
Outcomes	Bleeding patterns, discontinuation, satisfaction. Analysis was by ITT for pregnancy and discontinuation. For other outcomes, the authors reported those who had data collected (were not lost to follow up and did not discontinue method).
Notes	Lost to follow up: 1.5% overall; by group, immediate start zero; conventional start 1/46 = 2% One women was excluded (prior to receiving study product) due to not having met the inclusion criteria.
Allocation concealment	A – Adequate

Study	**Westhoff 2005**
Methods	Open-label randomized trial in metropolitan university-affiliated clinic in New York City (USA). Researcher not involved in study generated assignments with random number table and simple randomization. Assignments were concealed in sequentially-numbered, sealed, opaque envelopes. Study coordinator and interviewers were blinded to assignment before opening the envelope. Report provided information on a priori power calculation - based on detecting difference of 4 or more bleeding or spotting days during 84-day reference period.
Participants	201 women recruited through flyers and internet postings. Inclusion criteria: English-speaking, 18 to 40 years old, regular menstrual cycles, no contraindication to hormonal contraception, no hormonal contraceptive use in past 2 menses (or 6 menses for injectables), > 2 menses since pregnancy, no recent use of emergency contraception, and no unprotected sex in past 10 days.
Interventions	Immediate start: vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily (N=101) versus triphasic COC containing norgestimate 180/215/250 µg + EE 25 µg (N=100); treatment duration 84 days.
Outcomes	Pregnancy, continuation, cycle control, satisfaction, side effects. Analysis was by ITT for pregnancy. For other outcomes, the authors reported those who completed follow up and had bleeding diaries, which they referred to as ITT.
Notes	Lost to follow up: overall 27/201 = 13%; ring 12/101 = 12% and COC 15/100 = 15%.
Allocation concealment	A – Adequate

Study	Westhoff 2007
Methods	Randomized controlled trial in family planning clinics - 3 university sites in the USA. Randomization via random number generator; coordinating center generated allocation schedule and distributed them in numbered opaque envelopes. Sample size calculation based on detecting continuation increase from 50% to 60% at 6 months. Power was 63% to detect pregnancy decrease from 11% to 7%.
Participants	1720 young women requesting OCs. Inclusion criteria: < 25 years old, not pregnant, sexually active, no OC in past 7 days or DMPA in 6 mos, no desire for pregnancy in next 6 months, no lactational amenorrhea. Exclusion criteria (IRB required): postpartum or postabortion if less than 18 years old.
Interventions	Immediate start (N=856) versus conventional initiation (N=864) of OC. Immediate: first pill was taken under direct observation. Conventional: instructed to take first pill during next period. Clinician preference determined OC brand and number of pill packs or prescriptions provided. Study duration 6 months.
Outcomes	Pregnancy and serious adverse events. Insufficient data were reported for calculating method discontinuation. Analysis for pregnancy included those who "had well-dated pregnancies that began during the study." The denominator for SAEs did not include the women that the researchers excluded due to pregnancy prior to baseline and those who had other violations of inclusion criteria.
Notes	Lost to follow up: 16% overall by group, immediate start 128/846 = 15%; conventional initiation 135/837 = 16%. Excluded 4 women due to not having met the inclusion criteria and 33 women who initially had a negative pregnancy test but whose estimated conception date (based on ultrasound) preceded enrollment. Medical records were used to identify pregnancy in 96 women who missed both follow ups.
Allocation concealment	B – Unclear

OC = oral contraceptive
COC = combined oral contraceptive
DMPA = depot medroxyprogesterone acetate
EE = ethinyl estradiol
ITT = intent to treat

Characteristics of excluded studies

Study	Reason for exclusion
Paseková 2003	Non-comparative study of oral contraceptive start based on menses
Sitavarin 2003	Oral-contraceptive start at two different times (both based on menses)
Were 1997	Oral-contraceptive start based on length of time postpartum or return of menses
Yeshaya 1998	Oral-contraceptive start based on menses

ANALYSES

Comparison 01. Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy per woman	1	111	Peto Odds Ratio 95% CI	0.67 [0.04, 11.47]
02 Discontinued OCs during 90-day period	1	111	Peto Odds Ratio 95% CI	0.48 [0.10, 2.28]
03 Frequent bleeding (> 4 episodes of bleeding or spotting)	1	104	Peto Odds Ratio 95% CI	0.71 [0.28, 1.79]
04 Irregular bleeding (bleeding-free interval > 17 days)	1	104	Peto Odds Ratio 95% CI	0.82 [0.34, 1.99]

05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days)	1	104	Peto Odds Ratio 95% CI	0.89 [0.35, 2.24]
06 Amenorrhea (no bleeding)	1	104	Peto Odds Ratio 95% CI	Not estimable
07 Overall satisfaction with OCs	1	104	Peto Odds Ratio 95% CI	0.76 [0.14, 4.10]
08 Would make the same decision to start OCs	1	104	Peto Odds Ratio 95% CI	0.62 [0.13, 2.94]

Comparison 02. Immediate versus conventional start of OCs

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy per woman	1	1590	Peto Odds Ratio 95% CI	0.89 [0.63, 1.26]
02 Serious adverse events	1	1683	Peto Odds Ratio 95% CI	1.38 [0.64, 3.00]

Comparison 03. Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Discontinuation of patch by cycle 3	1	60	Peto Odds Ratio 95% CI	0.65 [0.11, 4.00]
02 Breakthrough bleeding	1	60	Peto Odds Ratio 95% CI	0.65 [0.11, 4.00]
03 Nausea	1	60	Peto Odds Ratio 95% CI	2.40 [0.75, 7.64]

Comparison 04. Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy per woman	1	201	Peto Odds Ratio 95% CI	Not estimable
02 Discontinued method in 84-day period	1	174	Peto Odds Ratio 95% CI	0.84 [0.33, 2.18]
03 Frequent bleeding (> 4 episodes of bleeding or spotting)	1	156	Peto Odds Ratio 95% CI	0.23 [0.05, 1.03]
04 Irregular bleeding (bleeding-free interval > 17 days)	1	156	Peto Odds Ratio 95% CI	0.77 [0.33, 1.75]
05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days)	1	156	Peto Odds Ratio 95% CI	0.42 [0.20, 0.89]
06 Amenorrhea	1	156	Odds Ratio (Fixed) 95% CI	Not estimable
07 Very satisfied with method	1	174	Peto Odds Ratio 95% CI	2.88 [1.59, 5.22]
08 Planned to use method	1	174	Peto Odds Ratio 95% CI	2.51 [1.32, 4.77]
09 Bad change in weight	1	174	Peto Odds Ratio 95% CI	0.42 [0.21, 0.87]
10 Bad change in bleeding	1	174	Peto Odds Ratio 95% CI	0.28 [0.14, 0.55]
11 Bad change in headache	1	174	Peto Odds Ratio 95% CI	0.53 [0.24, 1.18]
12 Bad change in breasts	1	174	Peto Odds Ratio 95% CI	0.36 [0.18, 0.73]
13 Bad change in mood	1	174	Peto Odds Ratio 95% CI	0.36 [0.19, 0.69]
14 Bad change in acne	1	174	Peto Odds Ratio 95% CI	1.39 [0.59, 3.29]
15 Bad change in appetite	1	174	Peto Odds Ratio 95% CI	0.44 [0.21, 0.95]
16 Bad change in nausea	1	174	Peto Odds Ratio 95% CI	0.30 [0.14, 0.62]
17 Bad change in cramps	1	145	Peto Odds Ratio 95% CI	0.79 [0.37, 1.67]
18 Bad change in hair	1	174	Peto Odds Ratio 95% CI	0.28 [0.05, 1.65]

19 Serious adverse events (total)	1	174	Peto Odds Ratio 95% CI	Not estimable

Comparison 05. Immediate DMPA versus contraceptive bridge to DMPA

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy per woman	1	333	Peto Odds Ratio 95% CI	0.36 [0.16, 0.84]
02 Discontinued method before 6 months	1	333	Peto Odds Ratio 95% CI	0.64 [0.37, 1.11]
03 Very satisfied with method at 6 months	1	227	Peto Odds Ratio 95% CI	1.99 [1.05, 3.77]
04 Adverse events	1	333	Peto Odds Ratio 95% CI	Not estimable

COVER SHEET

Title	Immediate start of hormonal contraceptives for contraception
Authors	Lopez LM, Newmann SJ, Grimes DA, Nanda K, Schulz KF
Contribution of author(s)	S Newmann and D Grimes developed the concept. S Newmann drafted the protocol, reviewed the initial searches, and began data abstraction. L Lopez updated the searches for the review, did the primary data abstraction, and drafted the review. D Grimes did the second data extraction and edited and advised on the review. K Nanda edited and advised on the review. K Schulz provided statistical expertise and edited the review.
Issue protocol first published	2006/4
Review first published	/
Date of most recent amendment	18 February 2008
Date of most recent SUBSTANTIVE amendment	15 January 2008
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 01 Pregnancy per woman

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 01 Pregnancy per woman

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	1/66	1/45		100.0	0.67 [0.04, 11.47]
Total (95% CI)	66	45		100.0	0.67 [0.04, 11.47]
Total events: 1 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.27 p=0.8					

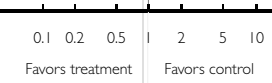
Analysis 01.02. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 02 Discontinued OCs during 90-day period

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 02 Discontinued OCs during 90-day period

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	3/66	4/45		100.0	0.48 [0.10, 2.28]
Total (95% CI)	66	45		100.0	0.48 [0.10, 2.28]
Total events: 3 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.92 p=0.4					



Analysis 01.03. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 03 Frequent bleeding (> 4 episodes of bleeding or spotting)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 03 Frequent bleeding (> 4 episodes of bleeding or spotting)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	13/63	11/41		100.0	0.71 [0.28, 1.79]
Total (95% CI)	63	41		100.0	0.71 [0.28, 1.79]
Total events: 13 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.73 p=0.5					

Analysis 01.04. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 04 Irregular bleeding (bleeding-free interval > 17 days)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 04 Irregular bleeding (bleeding-free interval > 17 days)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	16/63	12/41		100.0	0.82 [0.34, 1.99]
Total (95% CI)	63	41		100.0	0.82 [0.34, 1.99]
Total events: 16 (Treatment), 12 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.43 p=0.7					

Analysis 01.05. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	14/63	10/41		100.0	0.89 [0.35, 2.24]
Total (95% CI)	63	41		100.0	0.89 [0.35, 2.24]
Total events: 14 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.26 p=0.8					

Analysis 01.06. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 06 Amenorrhea (no bleeding)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 06 Amenorrhea (no bleeding)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Westhoff 2003	0/63	0/41		0.0	Not estimable
Total (95% CI)	63	41		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.07. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 07 Overall satisfaction with OCs

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 07 Overall satisfaction with OCs

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	59/63	39/41		100.0	0.76 [0.14, 4.10]
Total (95% CI)	63	41		100.0	0.76 [0.14, 4.10]
Total events: 59 (Treatment), 39 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.31 p=0.8					

Analysis 01.08. Comparison 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg), Outcome 08 Would make the same decision to start OCs

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 01 Immediate versus conventional start of COC (norethindrone 1 mg + EE 35 µg)

Outcome: 08 Would make the same decision to start OCs

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2003	58/63	39/41		100.0	0.62 [0.13, 2.94]
Total (95% CI)	63	41		100.0	0.62 [0.13, 2.94]
Total events: 58 (Treatment), 39 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.61 p=0.5					

Analysis 02.01. Comparison 02 Immediate versus conventional start of OCs, Outcome 01 Pregnancy per woman

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 02 Immediate versus conventional start of OCs

Outcome: 01 Pregnancy per woman

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2007	66/802	72/788		100.0	0.89 [0.63, 1.26]
Total (95% CI)	802	788		100.0	0.89 [0.63, 1.26]
Total events: 66 (Treatment), 72 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.64 p=0.5					

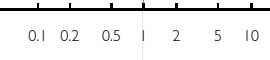
Analysis 02.02. Comparison 02 Immediate versus conventional start of OCs, Outcome 02 Serious adverse events

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 02 Immediate versus conventional start of OCs

Outcome: 02 Serious adverse events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2007	15/837	11/846		100.0	1.38 [0.64, 3.00]
Total (95% CI)	837	846		100.0	1.38 [0.64, 3.00]
Total events: 15 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.82 p=0.4					



Analysis 03.01. Comparison 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg), Outcome 01 Discontinuation of patch by cycle 3

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg)

Outcome: 01 Discontinuation of patch by cycle 3

Study	Immediate n/N	Conventional n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Murthy 2005	2/30	3/30		100.0	0.65 [0.11, 4.00]
Total (95% CI)	30	30		100.0	0.65 [0.11, 4.00]
Total events: 2 (Immediate), 3 (Conventional)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.46 p=0.6					

Analysis 03.02. Comparison 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg), Outcome 02 Breakthrough bleeding

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg)

Outcome: 02 Breakthrough bleeding

Study	Immediate n/N	Conventional n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Murthy 2005	2/30	3/30		100.0	0.65 [0.11, 4.00]
Total (95% CI)	30	30		100.0	0.65 [0.11, 4.00]
Total events: 2 (Immediate), 3 (Conventional)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.46 p=0.6					

Analysis 03.03. Comparison 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg), Outcome 03 Nausea

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 03 Immediate versus conventional start of contraceptive patch (norelgestromin 150 µg + EE 20 µg)

Outcome: 03 Nausea

Study	Immediate n/N	Conventional n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Murthy 2005	10/30	5/30		100.0	2.40 [0.75, 7.64]
Total (95% CI)	30	30		100.0	2.40 [0.75, 7.64]
Total events: 10 (Immediate), 5 (Conventional)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.48 p=0.1					

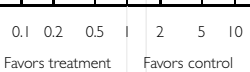
Analysis 04.01. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 01 Pregnancy per woman

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 01 Pregnancy per woman

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Westhoff 2005	0/101	0/100		0.0	Not estimable
Total (95% CI)	101	100		0.0	Not estimable
Total events: 0 (Ring), 0 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



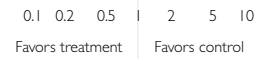
Analysis 04.02. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 02 Discontinued method in 84-day period

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 02 Discontinued method in 84-day period

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	9/89	10/85		100.0	0.84 [0.33, 2.18]
Total (95% CI)	89	85		100.0	0.84 [0.33, 2.18]
Total events: 9 (Ring), 10 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					



Analysis 04.03. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 03 Frequent bleeding (> 4 episodes of bleeding or spotting)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 03 Frequent bleeding (> 4 episodes of bleeding or spotting)

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	1/78	6/78		100.0	0.23 [0.05, 1.03]
Total (95% CI)	78	78		100.0	0.23 [0.05, 1.03]
Total events: 1 (Ring), 6 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.93 p=0.05					

Analysis 04.04. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 04 Irregular bleeding (bleeding-free interval > 17 days)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 04 Irregular bleeding (bleeding-free interval > 17 days)

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	12/78	15/78		100.0	0.77 [0.33, 1.75]
Total (95% CI)	78	78		100.0	0.77 [0.33, 1.75]
Total events: 12 (Ring), 15 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.63 p=0.5					

Analysis 04.05. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 05 Prolonged bleeding (bleeding or spotting episode lasting >= 10 days)

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	12/78	24/78		100.0	0.42 [0.20, 0.89]
Total (95% CI)	78	78		100.0	0.42 [0.20, 0.89]
Total events: 12 (Ring), 24 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.27 p=0.02					

Analysis 04.06. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 06 Amenorrhea

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 06 Amenorrhea

Study	Ring n/N	COC n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
× Westhoff 2005	0/78	0/78		0.0	Not estimable
Total (95% CI)	78	78		0.0	Not estimable
Total events: 0 (Ring), 0 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

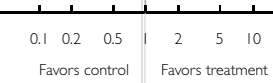
Analysis 04.07. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 07 Very satisfied with method

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 07 Very satisfied with method

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	54/89	29/85		100.0	2.88 [1.59, 5.22]
Total (95% CI)	89	85		100.0	2.88 [1.59, 5.22]
Total events: 54 (Ring), 29 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.50 p=0.0005					



Analysis 04.08. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 08 Planned to use method

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 08 Planned to use method

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	70/89	50/85		100.0	2.51 [1.32, 4.77]
Total (95% CI)	89	85		100.0	2.51 [1.32, 4.77]
Total events: 70 (Ring), 50 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.82 p=0.005					

Analysis 04.09. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 09 Bad change in weight

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 09 Bad change in weight

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	13/89	25/85		100.0	0.42 [0.21, 0.87]
Total (95% CI)	89	85		100.0	0.42 [0.21, 0.87]
Total events: 13 (Ring), 25 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.36 p=0.02					

Analysis 04.10. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 10 Bad change in bleeding

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 10 Bad change in bleeding

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	12/89	32/85		100.0	0.28 [0.14, 0.55]
Total (95% CI)	89	85		100.0	0.28 [0.14, 0.55]
Total events: 12 (Ring), 32 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.66 p=0.0003					

Analysis 04.11. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 11 Bad change in headache

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 11 Bad change in headache

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	11/89	18/85		100.0	0.53 [0.24, 1.18]
Total (95% CI)	89	85		100.0	0.53 [0.24, 1.18]
Total events: 11 (Ring), 18 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.56 p=0.1					

Analysis 04.12. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 12 Bad change in breasts

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 12 Bad change in breasts

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	13/89	28/85		100.0	0.36 [0.18, 0.73]
Total (95% CI)	89	85		100.0	0.36 [0.18, 0.73]
Total events: 13 (Ring), 28 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.84 p=0.005					

Analysis 04.13. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 13 Bad change in mood

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 13 Bad change in mood

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	16/89	33/85		100.0	0.36 [0.19, 0.69]
Total (95% CI)	89	85		100.0	0.36 [0.19, 0.69]
Total events: 16 (Ring), 33 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.05 p=0.002					

Analysis 04.14. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 14 Bad change in acne

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 14 Bad change in acne

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	14/89	10/85		100.0	1.39 [0.59, 3.29]
Total (95% CI)	89	85		100.0	1.39 [0.59, 3.29]
Total events: 14 (Ring), 10 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.76 p=0.4					

Analysis 04.15. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 15 Bad change in appetite

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 15 Bad change in appetite

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	11/89	21/85		100.0	0.44 [0.21, 0.95]
Total (95% CI)	89	85		100.0	0.44 [0.21, 0.95]
Total events: 11 (Ring), 21 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.10 p=0.04					

Analysis 04.16. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 16 Bad change in nausea

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 16 Bad change in nausea

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	9/89	25/85		100.0	0.30 [0.14, 0.62]
Total (95% CI)	89	85		100.0	0.30 [0.14, 0.62]
Total events: 9 (Ring), 25 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.20 p=0.001					

Analysis 04.17. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 17 Bad change in cramps

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 17 Bad change in cramps

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	17/75	19/70		100.0	0.79 [0.37, 1.67]
Total (95% CI)	75	70		100.0	0.79 [0.37, 1.67]
Total events: 17 (Ring), 19 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.62 p=0.5					

Analysis 04.18. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 18 Bad change in hair

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 18 Bad change in hair

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Westhoff 2005	1/89	4/85		100.0	0.28 [0.05, 1.65]
Total (95% CI)	89	85		100.0	0.28 [0.05, 1.65]
Total events: 1 (Ring), 4 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.41 p=0.2					

Analysis 04.19. Comparison 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg), Outcome 19 Serious adverse events (total)

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 04 Immediate ring (etonogestrel 120 µg + EE 15 µg) versus immediate COC (NGM 180/215/250 µg + EE 30 µg)

Outcome: 19 Serious adverse events (total)

Study	Ring n/N	COC n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Westhoff 2005	0/89	0/85		0.0	Not estimable
Total (95% CI)	89	85		0.0	Not estimable
Total events: 0 (Ring), 0 (COC)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.01. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 01 Pregnancy per woman

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 05 Immediate DMPA versus contraceptive bridge to DMPA

Outcome: 01 Pregnancy per woman

Study	Immediate DMPA n/N	Immediate bridge n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Rickert 2007	3/101	25/232		100.0	0.36 [0.16, 0.84]
Total (95% CI)	101	232		100.0	0.36 [0.16, 0.84]

Total events: 3 (Immediate DMPA), 25 (Immediate bridge)

Test for heterogeneity: not applicable

Test for overall effect z=2.36 p=0.02

Analysis 05.02. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 02 Discontinued method before 6 months

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 05 Immediate DMPA versus contraceptive bridge to DMPA

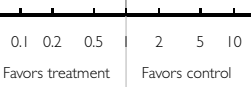
Outcome: 02 Discontinued method before 6 months

Study	Immediate DMPA n/N	Immediate bridge n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Rickert 2007	71/101	182/232		100.0	0.64 [0.37, 1.11]
Total (95% CI)	101	232		100.0	0.64 [0.37, 1.11]

Total events: 71 (Immediate DMPA), 182 (Immediate bridge)

Test for heterogeneity: not applicable

Test for overall effect z=1.60 p=0.1



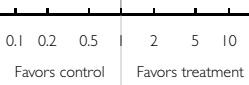
Analysis 05.03. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 03 Very satisfied with method at 6 months

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 05 Immediate DMPA versus contraceptive bridge to DMPA

Outcome: 03 Very satisfied with method at 6 months

Study	Immediate DMPA n/N	Immediate bridge n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Rickert 2007	57/69	109/158		100.0	1.99 [1.05, 3.77]
Total (95% CI)	69	158		100.0	1.99 [1.05, 3.77]
Total events: 57 (Immediate DMPA), 109 (Immediate bridge)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.12 p=0.03					



Analysis 05.04. Comparison 05 Immediate DMPA versus contraceptive bridge to DMPA, Outcome 04 Adverse events

Review: Immediate start of hormonal contraceptives for contraception

Comparison: 05 Immediate DMPA versus contraceptive bridge to DMPA

Outcome: 04 Adverse events

Study	Immediate DMPA n/N	Immediate bridge n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
× Rickert 2007	0/101	0/232		0.0	Not estimable
Total (95% CI)	101	232		0.0	Not estimable
Total events: 0 (Immediate DMPA), 0 (Immediate bridge)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable