Combined hormonal versus nonhormonal versus progestin-only contraception in lactation (Review)

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TABLE OF CONTENTS

[Intervention Review]

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ABSTRACT

Background

Each year, more than 100 million women make decisions about beginning or resuming contraception after childbirth. Choices of contraception may be limited for lactating women due to concerns about hormonal effects on quality and quantity of milk and passage of hormones to the infant. Ideally, the contraceptive method chosen should not interfere with lactation. The timing of contraception initiation is also important, since the return of menstruation and ovulation can be unpredictable in breastfeeding women.

Objectives

To determine the effect of combined oral contraceptives and progestin-only contraceptives on lactation.

Search strategy

We searched MEDLINE, POPLINE, EMBASE, LILACS, and CENTRAL along with review articles, and we contacted investigators.

Selection criteria

We sought randomized controlled trials in any language that compared hormonal contraception with another form of hormonal contraception, nonhormonal contraception, or a placebo during lactation. Hormonal contraception could include combined oral or injectable contraceptives, progestin-only oral or injectable contraceptives, implants, or intrauterine devices. Study participants included breastfeeding women of any age or parity who desired contraception.

Data collection and analysis

Principal outcomes included quantity of milk; biochemical analysis of milk composition; initiation, maintenance and duration of lactation; infant growth; efficacy of contraceptive method while breastfeeding; and timing of contraception initiation and its effects on lactation. Because the trials had different interventions, often lacked quantifiable outcomes, and had poor methods, we could not aggregate the data in a meta-analysis.

Main results

Five trials met our inclusion criteria. Most did not specify the methods for generating a random sequence or for allocation concealment, blinding of treatments, or use of an intention-to-treat analysis. Two reports comparing oral contraceptives to placebo had conflicting results. Another trial found no inhibitory effects on lactation from progestin-only contraceptives. The WHO trial found a decline in breast milk volume from combination contraceptives. High loss to follow up, however, undermined the credibility of the WHO trial. None of the trials showed a significant difference in infant growth or weight due to hormonal contraception during lactation.

Authors' conclusions

The existing trials are insufficient to establish any effect of hormonal contraception on milk quality and quantity. At least one properly conducted randomized controlled trial of adequate size is needed to address hormonal contraceptive use for lactating women.

PLAIN LANGUAGE SUMMARY

Hormonal and nonhormonal birth control during breastfeeding

Birth control for women who are breastfeeding is important worldwide. Each year, millions of women decide whether to use birth control after having a baby. The decision includes the type of birth control and when to start using it. Researchers and health care providers debate these issues. Some people worry that hormones could affect the breast milk and the baby. Ideally, the birth control would not affect the type or amount of breast milk. The best time for starting birth control is also important. It is hard to know when monthly cycles will return and when the woman could get pregnant again.

Combined birth control methods have the hormones estrogen and progestin. Other types of birth control have only progestin or no hormones. This review looked at whether combined birth control affects breastfeeding more than other kinds of birth control. We did computer searches for randomized trials of birth control used during breastfeeding. Combined hormonal methods were compared with another hormonal one or a 'dummy' method. In addition, we looked at reference lists to find trials. We also wrote to researchers to find more studies.

We found five studies that varied in quality. Some trials lost many women during the study. Two reports compared birth control pills to a 'dummy' and they had different results. Another study found that progestin-only did not affect breast milk. One trial found less breast milk produced with combined birth control. That study also lost many of the women, though. We found no major difference in infant growth or weight due to these types of birth control.

The results did not show whether hormonal birth control affects breast milk or the baby. At least one good randomized trial is needed to address these issues. Right now, information is too limited to say whether breastfeeding women should use hormonal birth control or not.

BACKGROUND

Contraception for women who are breastfeeding is a public health issue of global importance. Each year over 100 million women make decisions about beginning or resuming contraception after childbirth (Tsui 1997). These decisions include both the choice of contraceptive method and the time at which its use begins. For women who are breastfeeding, the choice and timing of hormonal contraception may influence both lactation and infant growth.

Contraception after childbirth improves the health of mothers and babies by lengthening birth intervals. Women are more likely to report births or pregnancies as unintended when they occur in an interval of 24 months or less. Preventing such unintended pregnancies helps avoid their financial, psychological, and health costs (Tsui 1997). Longer birth intervals of 27 to 32 months also decrease the risk of major maternal complications, including death, third-trimester bleeding, puerperal endometritis, and anemia (Conde-Agudelo 2000). According to a recent analysis, a three-year interval between births optimally lowers neonatal, postneonatal, and child mortality for the second child (Setty-Venugopal 2002). Hence, spacing of births yields important health benefits for mothers as well as their offspring.

Breastfeeding also has well established health benefits. Breastfeeding provides the infant with complete nutrition, a safe food source, and immunological defense against infectious diseases. It conserves funds that would be spent on milk substitutes, requires no supplies, and reduces the woman's risk of ovarian and breast cancer (Grimes 1995; PRB 1999).

Breastfeeding influences the need for and timing of postpartum contraception. An interval of anovulation occurs after delivery, and the length of time until ovulation resumes depends on breastfeeding patterns, biological variation, nutrition, geography, culture, and socioeconomic factors (Knijff 2000). Lactation itself can be an effective form of temporary contraception, referred to as the Lactational Amenorrhea Method (LAM). Women who exclusively breastfeed, have no uterine bleeding, and are within six months of delivery are unlikely to ovulate and thus are at low risk for pregnancy (Diaz 1993; Kennedy 2007). Because return of menstruation and ovulation can be unpredictable in breastfeeding women, the timing of contraception initiation is important. Ideally, the contraceptive method chosen should not interfere with lactation.

In theory, hormonal contraceptives, especially those containing estrogen, may impair lactation through their effect on prolactin, the hormone responsible for production of milk. During pregnancy, prolactin levels rise and peak at delivery. However, during pregnancy both estrogen and progesterone block the effect of prolactin on the breasts. After delivery, levels of both estrogen and progesterone drop markedly and, without their inhibitory effects, prolactin initiates milk production. Infant suckling stimulates more prolactin, which then sustains milk production. Breast engorgement and full milk secretion starts three to four days after delivery when estrogen and progesterone have sufficiently cleared from maternal circulation (Speroff 2004). Recognizing the suppressive effect of estrogen and progesterone on milk production, clinicians in past decades often administered steroid hormones immediately after delivery to women who did not want to breastfeed in order to reduce breast engorgement.

The advisability of hormonal contraception during lactation and timing of its initiation continue to be debated by experts. Choices of contraception may be limited for lactating women due to concerns regarding potential negative hormonal effects on quality and quantity of milk, passage of hormones to the infant, and infant growth and development. Some studies have found deleterious effects on lactation from combined oral contraceptives but none from progestin-only contraception (Diaz 1993; Kennedy 2007; Nelson 2007). The studies, though, had different ways of measuring effects on milk production, yielded inconsistent results, and often failed to show negative effects on the infants.

Despite potential adverse effects of combined oral contraceptives on lactation, many women strongly prefer this method (Erwin 1994). Combined oral contraceptives have many benefits, including familiarity with the method, effectiveness, safety, reversibility, excellent cycle control, a decrease in menstrual cramps and pain, decreased days of bleeding and amount of blood loss, and other non-contraceptive benefits. Other hormonal methods, including the progestin-only pill, may not offer all of these advantages (Raymond 2007). Indeed, some women quit breastfeeding early in order to start the combination pill (Erwin 1994).

Clinical recommendations need to be evidence-based if women are to make informed choices concerning contraception while breastfeeding. This review examined the a priori hypothesis that combined hormonal contraceptives have negative effects on lactation and infant growth when compared with progestin-only and nonhormonal methods.

OBJECTIVES

To determine the effect of combined hormonal contraceptives and progestin-only contraceptives on lactation. The a priori hypothesis was that combined hormonal contraception has negative influences on lactation, making it less appropriate than progestin-only or nonhormonal contraception for breastfeeding women.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled trials reported in any language that compared combination contraception during lactation versus

other hormonal contraception, nonhormonal contraception, or placebo.

Types of participants

Breastfeeding women of any age or parity who desired contraception.

Types of interventions

Any form of hormonal contraception (i.e., combined oral or injectable contraceptives, progestin-only oral or injectable contraceptives, hormonal implants, and hormonal intrauterine devices) compared with hormonal contraception, nonhormonal contraception, or placebo.

Types of outcome measures

- Quantity of milk
- Biochemical analysis of milk composition
- Initiation, maintenance and duration of lactation
- Infant growth
- Efficacy of contraceptive method while breastfeeding
- Timing of contraception initiation and its effects on lactation
- Birth interval

Search methods for identification of studies

Electronic searches

We searched the databases MEDLINE (via PubMed), POPLINE, EMBASE, LILACS, and CENTRAL. Search strategies are shown below.

1) MEDLINE (via PubMed) (1963 to present):
((breastfeeding OR lactation) AND (contraceptive devices, female OR contraceptive agents, female)) AND (randomized controlled trials [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw])

2) POPLINE (1960 to present):
(lactating / lactation / breastfed / breastfeed / breastfeeding / breastfeeding / breastfeeders / breastmilk) & contraception & clinical trials

3) Cochrane Central Register of Controlled Trials (CENTRAL):
lactat* or breastfeed* AND contracept*

4) EMBASE (1974 to present):
1. contracep?
2. contraception!
3. 1 or 2
4. breast(W)milk OR breastmilk
5. breastfeed? OR breast(W)feed?
6. lactation
7. 4 OR 5 OR 6
8. clinical trial!
9. controlled study!
10. 8 OR 9
11. 3 AND 7 AND 10
12. 11/human

5) LILACS:
lactation, breastfeeding, contraception/contraceptives, clinical trials

Searching other resources

We began the initial review with several comprehensive review articles (Chi 1993; Diaz 1993; Erwin 1994; Hull 1981; Laukaran 1981; Thomson 1975; Tsui 1997). We also examined reference lists of articles located or relevant book chapters for publications comparing different forms of contraception in breastfeeding women and their effects on lactation. We contacted other investigators in the field to find publications we might have missed, including unpublished reports.

Data collection and analysis

Our team of authors read abstracts and titles of clinical trials that literature searches had identified to determine whether they met the inclusion criteria. The full text of an article was retrieved whenever necessary. We then verified that included references were satisfactory and reviewed others that potentially could have met the inclusion criteria. Trials meeting the inclusion criteria were assessed for methodological quality using standard Cochrane criteria, including assessment of the quality of randomization, allocation concealment, blinding and analysis. A consensus among the group of authors resolved any disagreements. Additional information was sought from investigators of all five included trials. Two researchers (Miller 1970; WHO 1984) from these trials responded to clarify questions about randomization methods and blinding. Because the trials did not have uniform interventions, often lacked quantifiable outcomes, and had poor methodological quality, we could not aggregate the data in meta-analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified 50 articles as potentially eligible for inclusion. Seven reports from five trials met our inclusion criteria. Three reports from the WHO trial are included as they examined different outcomes. The WHO trial compared combination oral contraceptives with progestin-only contraceptives. Two trials (Miller 1970; Semm 1966) compared the effects of combination oral contraceptives with placebo. One trial (Velazquez 1976) compared progestin-only contraceptives to placebo. Finally, another (Were 1997) evaluated the timing of starting progestin-only contraceptives. No randomized controlled trials compared nonhormonal contraception to hormonal contraception.

We excluded 43 reports from this review. Two reports (Drury 1986; Gellen 1984) were subgroup analyses that examined similar outcomes from a larger report (WHO 1984) and were dropped from consideration. One report had outcome measures not relevant to this review (Bassol 2002). The remaining articles were excluded either because they were not randomized controlled trials or their method of participant allocation was unclear.

Risk of bias in included studies

Although the included trials span a publication period of approximately 30 years, they shared common deficiencies. Three of the five included trials did not specify the method used to generate a random sequence. Two trials (Were 1997; WHO 1984) indicated that study subjects were randomized into two groups using computer-generated sequences. The remaining three trials merely stated that study groups were "divided" on a random basis. Additionally, the Miller 1970 trial further stratified the "randomization" by gender of the infant and reported a disparity of baseline characteristics (primiparas) unlikely to be the result of a random process.

The reporting of allocation concealment was equally inadequate in the trials. Only one of the included trials published that sealed, sequentially numbered, opaque envelopes were used for allocation concealment (Were 1997). We determined through personal communication with an author that another trial also used sealed, opaque envelopes for allocation concealment (WHO 1984). The remaining trials included in this review did not report the method of allocation concealment.

Blinding in the included trials was typically in the form of identically labeled placebos. Three trials specifically mentioned double blinding but failed to describe the specifics of the method of blinding, who was blinded, the allocation schedule control (schedule location, code-breaking specifics), and whether the blinding was successful (Schulz 2002a). Written correspondence from Tankeyoon (WHO 1984) and Miller (Miller 1970) indicated that patients and clinicians were kept unaware of patient treatment assignments. One trial (Semm 1966) described identically labeled placebos but did not mention the term blinding, and the Were 1997 trial was identified as an open-label trial.

Finally, adherence to the intention-to-treat principle was poor. Only one trial (Were 1997) specifically stated that the analysis was intention-to-treat. However, the high loss to follow up (approximately 87% in both arms) precluded meaningful results. Two trials (Semm 1966; Velazquez 1976) did not mention any loss to follow up, exclusions or discontinuations. In the WHO trials (WHO 1984; WHO 1986; WHO 1988), the disposition of participants in the randomized arms was unclear. For example, Table I (WHO 1984) indicated that 50 participants in each arm completed the study, yet other tables (III and VII) reported data at 24 weeks (trial completion) for 57 and 58 participants in the randomized arms. This discrepancy was not explained. From 32% to 42% of participants in each randomized arm were not included in the analysis. The WHO trial stated that participants who discontinued or were lost to follow up were analyzed via noncompeting risk lifetable procedures, and at least one participant was excluded after randomization.

Effects of interventions

Evidence from randomized controlled trials on the effect of hormonal contraceptives during lactation was limited and of poor quality. The findings from the two reports comparing oral contraceptives to placebo were conflicting (Miller 1970; Semm 1966). Miller 1970 found inhibitory effects on milk volume and duration of lactation from the use of oral contraceptives in 25 women. However, milk volume was indirectly measured in this study by assessing the subjective need for supplemental infant feeds and infant weight as a proxy for milk adequacy. Likewise, only general estimates were given for the effects of combination oral contraceptives on lactation duration. On the other hand, Semm 1966 found no differences in milk volume, lactation initiation, or infant growth during the first ten days postpartum when comparing combination contraceptives to placebo in a larger trial. Neither study quantified the outcomes, making interpretation difficult.

Another trial (Velazquez 1976) found no significant differences in milk volume, infant growth, or milk composition when comparing progestin-only contraceptives to placebo during the first 14 days postpartum. Additionally, findings from Were 1997 indicated that the timing of progestin-only contraceptive initiation during the postpartum period (six weeks versus six months or resumption of menses) did not affect contraceptive continuation rates or pregnancy rates.

The WHO Trial (WHO 1984) found an adverse effect of combined oral contraceptives on milk volume. Breast milk volume in the trial was determined by pump expression using standardized procedures. Participants breast fed their infants in the morning, waited two hours, and pumped milk while simultaneously nursing from the other breast for a period of 20 minutes. The process was repeated two hours later using the opposite breast for pumping. The "average" amount was then reported in the WHO trial. The volume of expressed milk in the randomized arms was similar at six weeks in all centers (70 ml for combined oral contraceptive users and 74 ml for progestin-only contraceptive users). Likewise, most women had declines in milk volume over time in all centers.

Statistically significant declines in milk volume were reported for the combination oral contraceptive group compared to the progestin-only pill group. Declines began after study initiation at six weeks postpartum and continued throughout the trial period. For example, reported mean milk volumes at 12 and 24 weeks for combined oral contraceptive users were 51 ml and 41 ml, respectively, as compared to 72 ml and 65 ml for progestin-only contraceptive users. For all centers during the study period (week 6 through 24), average milk volume for combined oral contraceptive users declined by 42% versus 12% among progestin-only contraceptive users. No significant differences between groups were found for milk composition or infant growth and any differences in the biochemical composition of breast milk were small and inconsistent. Increases in milk lipid among combination contraceptive users reported in one center (WHO 1986) are of unknown clinical significance. However, because of high loss to follow up in the WHO trial (more than 30% in both groups), these data cannot be deemed credible (Schulz 2002b)

DISCUSSION

The methodological quality of all five included trials was poor, and results should be interpreted with caution. The methods of randomization for three were unclear. Selection and confounding bias are possible. The unclear blinding methods observed may have introduced information bias. Most trials do not report their method of allocation concealment, so estimates of treatment effect may be exaggerated (Schulz 1995).

Small sample sizes are problematic for at least one trial (Velazquez 1976). However, even with larger sample sizes, high loss to follow up plagued two trials (Were 1997; WHO 1984). Loss to follow up of greater than 20%, especially for short-term trials in which losses should be small, seriously threatens trial validity (Schulz 2002b).

Whether measuring milk output by extraction with a breast pump on only two occasions during the day reflects 24-hour milk production remains unclear. As noted by the authors of WHO 1984, "our method of measuring milk output may have little relationship to the amount actually ingested by the baby during that or any other 24-hour period." Moreover, marked variability occurred in the average number of breastfeedings reported per 24-hour period among participants in the WHO 1984 trial. For example, participants in Szeged, Hungary reported five to six feedings in 24 hours versus nine to ten feedings per 24 hours in Khon Kaen, Thailand, and data were not recorded for Bangkok, Thailand. Additionally, supplemental foods may have masked any putative effect of hormonal contraception on lactation. Of note, most participants were using supplemental feedings by 12 weeks. No trial to date has documented an adverse effect of hormonal contraceptives on infant growth.

AUTHORS' CONCLUSIONS

Implications for practice

The existing randomized controlled trials are insufficient to establish an effect of hormonal contraception, if any, on milk quality and quantity. The evidence is inadequate to make evidence-based recommendations regarding hormonal contraceptive use for lactating women. The World Health Organization gives lactation a category 3 rating for combination oral contraceptive use among lactating women from six weeks to six months postpartum (WHO 2004). Although this indicates that the theoretical or proven risks usually outweigh the advantages of using the method, the existing evidence is inadequate to support or refute this rating. Given the limited and poor-quality data, decisions about the appropriateness and timing of hormonal contraception must be made on other grounds. No adverse effect of hormonal contraceptives on infant growth has been documented.

Implications for research

At least one properly conducted randomized controlled trial of adequate size (Moher 2001) is urgently needed to address this question. To use a placebo arm, such a trial might enroll women who are not at risk of pregnancy because of a sterilization procedure (i.e., postpartum sterilization or partner vasectomy). One potential approach would be to randomize such women to combination oral contraceptives, progestin-only contraceptives, or placebo. Redmond 1999 demonstrated the feasibility of using placebo controls in a population not at risk of pregnancy. Special efforts will be needed to ensure follow up of participants if valid inferences are to be made, since this has been a serious limitation of randomized controlled trials performed to date.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Miller 1970

Methods	Randomized controlled trial. Method of randomization and allocation concealment not specified.
Participants	50 women delivering healthy, term infants at Iowa City Hospitals, Iowa, USA. All women expressed desire to nurse for 3 months and use oral contraceptives while nursing.
Interventions	25 women received norethindrone 1 mg and mestranol 0.08 mg daily for 21 days (postpartum days 14 to 34); 25 women received identically labeled placebos during the same time period. Study length 3 months.
Outcomes	Lactation duration, infant weight, milk volume production.
Notes	Limited details about methods of trial. Author specifies that participants and investigators were blinded but did not specify method of allocation concealment. No a priori hypothesis or sample size calculation. 1 loss to follow up per arm, 1 discontinuation in placebo arm. Numerical results are not provided, graphic variations not identified.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Semm 1966

Methods	Randomized controlled trial. Method of randomization and allocation concealment not specified.
Participants	100 women delivering in Munich, Germany, still in child-bed with a definite desire to lactate.
Interventions	50 women received lynestrenol 2.5 mg and mestranol 0.075 mg daily for 10 days (postpartum day 1 to 10); 50 women received identically labeled placebos during the same time period.
Outcomes	Lactation initiation and milk volume yield.

Semm 1966 (*Continued*)

Notes	Limited details about methods of trial. No a priori hypothesis or sample size calculation. No mention of discontinuations, loss to follow up or exclusions. Graphics not specifically labeled (mean or variance).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Velazquez 1976

Methods	Randomized controlled trial. Method of randomization and allocation concealment not specified.
Participants	20 women selected immediately after birth in Mexico. Aged 18 to 36 years, adequate health and nutrition during pregnancy.
Interventions	12 women received norethindrone 0.35 mg for 14 days (starting within 14 hours postpartum); 8 women received placebo during same time period.
Outcomes	Average milk production, biochemical composition of milk, infant weights.
Notes	Limited details about methods of trial. No a priori hypothesis or sample size calculation. Small sample size limits power. No mention of discontinuations, loss to follow up or exclusions.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Were 1997

Methods	Randomized controlled trial. Study subjects were sequentially assigned a unique patient identification number. Method of randomization listed as computer-generated, sealed envelopes.
Participants	200 women with normal deliveries in Eldoret, Kenya. Aged 18 to 35 years, planning to breastfeed for 6 months, sexually active, and relying exclusively on progestin-only pills for contraception.
Interventions	100 women received 0.075 mg norgestrel at 6 weeks postpartum; 100 women received 0.075 mg norgestrel at onset of menses or 6 months postpartum. Study length 18 months.
Outcomes	Medication continuation rates, pregnancy, and adverse experiences.

Were 1997 (*Continued*)

Notes	Loss to follow-up rates greater than 85% in both trial arms.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

WHO 1984

Methods	Multicenter randomized double-blind trial. Randomization via computer-generated sequence from WHO. Allocation concealment in sealed, opaque envelopes.	
Participants	171 women delivering in either Szeged, Hungary, Bangkok, Thailand, or Khon Kaen, Thailand. Aged 20 to 35 years, prior successful breastfeeding (3 months), hemoglobin 10g/dl or greater, singleton delivery (2700g to 3700g), no breast abnormalities, desiring to use hormonal contraception during lactation.	
Interventions	86 women received ethinyl estradiol 0.030 mg and levonorgestrel 0.150 mg; 85 women received dl-norgestrel 0.075 mg. All interventions initiated at 6 weeks postpartum (+/-3 days). Study length 24 weeks.	
Outcomes	Average breast milk volume, breast milk composition, infant growth, study withdrawal secondary to inadequate milk supply or infant growth.	
Notes	Although the trial reports that 341 women were recruited in the study, only 171 women were randomized. Actual loss to follow up is unclear. Inconsistent reporting exists among and within reports. At a minimum, loss to follow up 34% and to 32% in randomized arms.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

WHO 1986

Methods	See WHO 1984.
Participants	See WHO 1984.
Interventions	See WHO 1984.
Outcomes	Milk composition (lipids and fatty acids).

WHO 1986 (*Continued*)

Notes	Part of the WHO trial 1984.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

WHO 1988

Methods	See WHO 1984.	
Participants	See WHO 1984.	
Interventions	See WHO 1984.	
Outcomes	Milk composition (fat, nitrogen, caloric content, lactose and osmolality) and infant growth.	
Notes	Part of the WHO trial 1984.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Abdel-Aleem 1996	Not a randomized controlled trial.
Barsivala 1973	Unclear if participant allocation was random.
Bassol 2002	Outcomes not applicable for this review.
Betrabet 1987	Per correspondence with the author (Betrabet), study participants received personal choice of intervention, not random allocation.
Bhatia 1987	Not a randomized controlled trial.
Bjarnadottir 2001	Not a randomized controlled trial.

(*Continued*)

Borglin 1971	Study described as a "carefully controlled trial." No evidence of randomization.
Chen 1998	Not a randomized controlled trial.
Coutinho 1999	Not a randomized controlled trial.
Croxatto 1982	Per correspondence with the author, study participants received personal choice of intervention, not random allocation.
Croxatto 1983	Per correspondence with the author, study participants received personal choice of intervention, not random allocation.
Danli 2000	Not a randomized controlled trial.
Diaz 1983	Per correspondence with the author, study participants received personal choice of intervention, not random allocation.
Diaz 1985	Per correspondence with the author, study participants received personal choice of intervention, not random allocation.
Diaz 1997	Not a randomized controlled trial.
Drury 1986	Subgroup analysis of WHO trial 1984.
Dunson 1993	Not a randomized controlled trial.
Gellen 1984	Subgroup analysis of WHO trial 1984.
Gupta 1974	Not a randomized controlled trial.
Hannon 1997	Not a randomized controlled trial.
Hefnawi 1970	Unclear if participant allocation was random.
Kader 1969	Unclear if participant allocation was random.
Kader 1975	Unclear if participant allocation was random.
Kaern 1967	Unclear if participant allocation was random.
Kamal 1969a	Unclear if participant allocation was random.
Kamal 1969b	Unclear if participant allocation was random.
Kamal 1970	Unclear if participant allocation was random.

(*Continued*)

Karim 1971	Not a randomized controlled trial.
Koetsawang 1972a	Unclear if participant allocation was random.
Koetsawang 1972b	Unclear if participant allocation was random.
Lonnerdal 1980	Not a randomized controlled trial.
Massai 2001	Not a randomized controlled trial.
McCann 1989	Not a randomized controlled trial.
Peralta 1983	Per correspondence with the author, all trials in the series were not randomized. Participants chose their intervention.
Reinprayoon 2000	Not a randomized controlled trial.
Seth 1977	Unclear if participant allocation was random.
Sinchai 1995	Not a randomized controlled trial.
Toaff 1969	Trial does not include regularly marketed combination oral contraceptive. Intervention on postpartum days 1-5 only further limited its usefulness.
Virutamasen 1996	Not a randomized controlled trial.
WHO 1994	Not a randomized controlled trial.
Zacharias 1986	Not a randomized controlled trial.
Zanartu 1976a	Not a randomized controlled trial.
Zanartu 1976b	Not a randomized controlled trial.

DATA AND ANALYSES

This review has no analyses.

FEEDBACK

Combined hormonal versus nonhormonal versus progestin-only contraception

Summary

The exclusion of the study by Diaz et al (Contraception 1983; 27: 1-11) is not justified. In the review it is stated: "Per correspondence with the author, study participants received personal choice of intervention, not random allocation". In the methods division of this study the authors wrote: "Women requesting an oral contraceptive were assigned at random to the contraceptive pill under study or to an oral placebo on a patient-blind basis. Both pills were offered as a low-dose O.C. with no demonstrated effects upon lactation". I wrote to dr Diaz and asked her why the Cochrane review could come to a different conclusion. She answered me that the person doing the Cochrane review asked her only in general about all the studies on breastfeeding and contraception. In all the other trials women had the free choice of contraceptive method. Because the reviewer did not ask in detail about every trial she forgot to mention that in one trial the treatment was randomized.

In the discussion of the review is stated: " No trial to date has documented an adverse effect of hormonal contraceptives on infant growth". This statement is wrong because in the trial by Diaz et al (1983) the oral contraceptive group showed a significantly lower average absolute weight at days 61 and 91 postpartum and a significantly lower average daily weight increase during the first month of treatment.

In the discussion of the Cochrane review the authors criticize several trials because the putative effect of hormonal contraceptives on lactation could have been masked by the influence of supplemental foods. The reviewers apparently did not realize that it is impossible to do a months long trial on breastfeeding and forbid the mothers to give supplements to theit babies if they consider that the babies get insufficient food.

In the inplications for research the authors of the review suggest to do a trial of contraceptives versus placebo; "such a trial might enroll women who are not at risk of pregnancy because of a sterilization procedure (i.e., postpartum sterilization or partner vasectomy)".This proposal would imply that the researchers would have to ask mothers who were planning to breastfeed their infants during several months to take a pill which could potentially deteriorate her lactation, while this medication could not offer her or her baby any advantage? Is there any ethical committee that would approve such a proposal?

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

February, 2004.

Reply

Response to Treffers re:

Dr. Treffers suggests that we incorrectly excluded the report by Diaz et al. (Contraception 1983;27:1-11) and thus reached the wrong conclusion about the effect of combined oral contraceptives on infant growth. We stand by our exclusion for several reasons. First, we contacted Dr. Diaz and were advised by her in writing on April 1, 2002, that randomization had not been used in her study. Second, the report appears to describe a cohort study, with another group (not randomized) having received an intramuscular placebo. Third, the disparity in sample size between the ostensibly randomized groups (oral contraceptive, 103 participants; oral placebo, 79 participants) is unlikely to have resulted from simple randomization. By binomial theorem, the likelihood of getting a difference this large or larger due to chance is 4%. Stated alternatively, one can be 96% sure that randomization did not yield this result. Hence, we conclude that the Diaz 1983 study was not a randomized controlled trial, and our interpretation of the literature stands.

Given the absence of any demonstrable adverse effect of oral contraceptives on infant growth, the age and limited quality of existing studies, and the public health importance of the question, we believe a proper trial is both appropriate and ethical.

Contributors

Treffers, Pieter

WHAT'S NEW

Last assessed as up-to-date: 6 May 2008.

7 May 2008	New search has been performed	Searches were updated; no new trials were found.

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 2, 2003

3 October 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Sarah Truitt: Conceiving and designing the review, initial database searches and retrieval of papers, writing the protocol, writing to authors for additional information.

Anna Fraser: Screening search results and retrieved papers, editing the protocol, writing the review.

David Grimes: Supervision of review, advice for review, editing the protocol and review, screening retrieved papers, writing to authors for additional information.

Maria Gallo: Database search design, screening search results and retrieved papers, editing the protocol and review.

Kenneth Schulz: Advice for review, interpretation of data, statistical expertise.

Laureen Lopez: Writing the plain language summary, reviewing the updated search results, updating references, editing text for Cochrane style issues.

DECLARATIONS OF INTEREST

Dr. Grimes has consulted with or served on a speakers bureau for Bayer Healthcare Pharmaceuticals, Ortho-McNeil, Schering-Plough, Barr Laboratories, and Wyeth.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Child Health and Human Development, USA.
- US Agency for International Development, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Contraceptives, Oral, Combined [*pharmacology]; Contraceptives, Oral, Hormonal [*pharmacology]; Lactation [*drug effects]; Progestins [*pharmacology]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans