

Original research article

The Cochrane Fertility Regulation Group: synthesizing the best evidence about family planning

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Abstract

The Fertility Regulation Group of the Cochrane Collaboration has been assessing the best available evidence on fertility regulation, family size and birth spacing. By the end of 2005, this group had published 32 systematic reviews and 12 protocols; most reviews were on contraception. Because of suboptimal trial quality, firm conclusions could be made in only five reviews. Threats to internal validity in published trials include the absence of description of allocation concealment, intentional exclusion of participants after randomization, failure to use intention-to-treat analyses and lack of treatment blinding. The precision of results has been limited by small sample sizes. The finding that most trials of oral contraceptives were conducted by pharmaceutical companies raises concerns about potential commercial bias. Of necessity, most information about fertility regulation effectiveness and adverse effects comes from observational studies, which vary widely in quality. Systematic reviews of evidence, with an emphasis on randomized controlled trials when available, will continue to improve fertility regulation in the years ahead.

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1. Introduction

Every day, tens of millions of individuals around the world make family planning decisions based on information that may be obsolete, wrong or commercially biased. This basis for decision making indirectly translates into unplanned pregnancies, with their attendant morbidity and

mortality [1]. For example, the oral contraceptive is one of the most intensively studied medications in history (over 27,000 citations in PubMed), yet little evidence from randomized controlled trials is available to help clinicians and patients choose among scores of marketed products [2,3]. Most clinical decisions in family planning rest on observational studies, which range widely in quality. Valid reproducible evidence is as important to sexual and reproductive health as it is to other areas of medicine.

The Fertility Regulation Group of the Cochrane Collaboration (www.LUMC.nl/1060/cochrane), which is based at the Leiden University Medical Center, The Netherlands, has been assessing the best evidence on fertility regulation, family size and birth spacing. Ninety-six authors have published reviews: 40 from the European Union, 3 from the

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rest of Europe, 27 from the United States, 14 from Africa, 5 from Asia, 4 from Australia/New Zealand (Oceania) and 3 from Mid-South America. The group's systematic reviews generally include questions that can be addressed by randomized controlled trials. By evaluating and by summarizing these individual studies, the reviews provide more precise estimates of the effects of health care than those available from single studies. Cochrane reviews entail an explicit transparent search strategy, diligent search to find both published and unpublished trials, data abstraction by at least two independent researchers, assessment of methodological quality, aggregation of results in a meta-analysis when appropriate, thorough peer review, electronic publication and regular update of published reviews [4]. The methods used by the Fertility Regulation Group are provided in greater detail on its web site (<http://www.lumc.nl/1060/cochrane/module.html>). After registration of a title, a formal protocol describing the background and the search strategy is peer-reviewed and then published. Thereafter, a full review is conducted, peer-reviewed and published.

These reviews have sometimes contradicted common beliefs, such as the presumed superiority of the contraceptive sponge over other vaginal barriers [5], the greater acceptability of 20- μ g estrogen oral contraceptives over higher-estrogen pills [6], and the belief that oral contraceptives cause weight gain [7]. Cochrane systematic reviews are more likely than traditional narrative reviews and textbook chapters to produce valid conclusions [8]. We will describe our experience with systematic reviews of these trials, point out some common deficiencies and suggest ways to improve the quality of science in fertility regulation.

2. Topics

The Cochrane Fertility Regulation Group has a broad mandate. It reviews the effectiveness and safety of fertility-regulating methods (including breastfeeding, drugs, devices, barrier methods, sterilization and abortion), delivery of services (effectiveness, accessibility and acceptability), acquisition and use of information, decision making about fertility regulation, and reproductive health and policy development.

By the end of 2005, the Fertility Regulation Group had published 32 systematic reviews and 10 protocols (Table 1). To access these, one can use the web site (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clsysrev_subjects_fs.htm) and browse "fertility regulation." Abstracts of Cochrane reviews are available through PubMed, and most university libraries provide full access as well. Individual subscriptions to *The Cochrane Library* on CD-ROM are also available from John Wiley and Sons Ltd. (toll free number in the United States: +1-866-465-3817). Most topics are related to contraception (28 reviews and 10 protocols); of these, reviews on hormonal methods were most common (15 reviews and 5 protocols). Randomized trials of abortion and surgical sterilization were less frequent [9].

Most reviews have focused on fertility regulation methods rather than on how individuals utilize family planning. Important questions—such as those on the effectiveness of counseling, the impact of prescription policy (e.g., pharmacist provision of over-the-counter hormonal emergency contraception) on compliance, the effect of ancillary screening practices (e.g., cervical cytology and sexually transmitted infection screening) and the integration of those screening practices with family planning services—remain largely unaddressed. For example, a recent review of the effectiveness of strategies to improve the compliance and acceptability of hormonal contraceptives was unable to make a firm conclusion because of poor trial quality and small sample sizes [10]. Despite hundreds of millions of woman-years of oral contraceptive use worldwide, whether intensive education and counseling are better than routine information in reducing accidental pregnancies with pill use is unknown.

3. Threats to internal validity

Suboptimal trial quality has handicapped reviews to date. Indeed, a firm and clinically relevant conclusion could be made in only 5 of 32 reviews; the outcome of each of the five was contraceptive effectiveness [11–15]. Limited and poor-quality trial data are the main reasons for inconclusiveness.

Allocation concealment (keeping investigators and participants unaware of upcoming assignments) has been shown to protect against selection bias in randomized controlled trials [16]. Hence, this concealment provides a key measure of trial quality in Cochrane reviews. Lack of documentation of allocation concealment has been a common problem. More than 60% of trial reports in our reviews failed to meet this methodology standard, which has been promulgated internationally by CONSORT guidelines since 1996 [17]. As shown in Table 2, the proportion of trials included in Cochrane reviews that report adequate allocation concealment has been lower in the Fertility Regulation Group than in the Pregnancy and Childbirth Review Group, but has been higher than in the Heart Review Group. This situation is improving, however. The proportion of included trials with documentation of adequate allocation concealment has been progressively increasing, although other fields may be making more progress than fertility regulation (Fig. 1). However, even when allocation concealment is described, about half of Cochrane reviews do not incorporate the results of quality assessment in their analysis [18]. Formal incorporation of quality in the analysis is usually done by using quality criteria in subgroup analyses for summary estimates. In fertility regulation reviews, differences in regimens and outcome measures often prohibit aggregation of trials, and methodological quality of trials is incorporated into the interpretation of results.

Suboptimal reporting of trial results is a related stubborn problem. To assess the strengths and weaknesses of a trial, readers need adequate details about the methods used. Some

Table 1

Topics registered by the Fertility Regulation Group of the Cochrane Collaboration, by registration date

Registration date	Title
January 30, 2002	20 versus >20 µg of estrogen-combined oral contraceptives for contraception
May 20, 2003	Advance provision of emergency contraception for pregnancy prevention
June 27, 2000	Antibiotic prophylaxis for intrauterine contraceptive device insertion
December 17, 2003	Antibiotic prophylaxis for medical and surgical first-trimester induced abortion
June 27, 2000	Antibiotics for incomplete abortion
June 27, 2000	Biphasic versus monophasic oral contraceptives for contraception
February 19, 2002	Biphasic versus triphasic oral contraceptives for contraception
September 24, 2001	Cervical cap versus diaphragm for contraception
November 29, 2002	Chinese medicinal herbs for reducing vaginal bleeding from medical abortion
October 8, 2001	Combination contraceptives: effects on weight
May 20, 2003	Combination injectable contraceptives for contraception
October 8, 2001	Combined hormonal versus nonhormonal versus progestin-only contraception during lactation
October 8, 2002	Combined oral contraceptive pills for treatment of acne
November 29, 2002	Continuous or extended cycle versus cyclic use of combined oral contraceptives for contraception
February 17, 2005	Copper-containing intrauterine devices for contraception
October 8, 2001	Depot medroxyprogesterone versus norethisterone enanthate for long-acting progestogenic contraception
June 27, 2000	Diaphragm versus diaphragm with spermicides for contraception
June 27, 2000	Education for contraceptive use by women after childbirth
December 17, 2003	Fertility awareness-based methods for contraception
June 27, 2000	Frameless versus classical intrauterine device for contraception
October 8, 2001	Hormonal versus nonhormonal contraceptives in women with diabetes mellitus
June 27, 2000	Hormonally impregnated intrauterine systems versus other forms of reversible contraceptives as effective methods for preventing pregnancy
June 27, 2000	Immediate postabortal insertion of intrauterine devices
June 27, 2000	Immediate postpartum insertion of intrauterine devices
November 2, 2005	Immediate start of combined hormonal contraceptives for contraception
June 27, 2000	Interventions for emergency contraception
May 26, 2003	Interventions for preventing unintended pregnancies among adolescents
June 27, 2000	Lactational amenorrhea for family planning
July 4, 2000	Medical methods for first-trimester termination of pregnancy
February 3, 2004	Medical methods for second-trimester termination of pregnancy
July 4, 2000	Medical versus surgical methods for first-trimester termination of pregnancy
June 27, 2000	Minilaparotomy and endoscopic techniques for tubal sterilization
September 24, 2001	Nonlatex versus latex male condoms for contraception
February 15, 2005	Nonsteroidal anti-inflammatory drugs for heavy bleeding associated with intrauterine device use
November 2, 2005	Oral contraceptives for functional ovarian cysts
February 3, 2004	Pain control for first-trimester surgical abortion
June 27, 2000	Progestogens in combined oral contraceptives for contraception
July 10, 2000	Scalpel versus no-scalpel incision for vasectomy
September 24, 2001	Skin patch and vaginal ring versus combined oral contraceptives for contraception
August 10, 2004	Spermicide used alone for contraception
July 5, 2000	Sponge versus diaphragm for contraception
January 17, 2003	Steroid hormones for contraception in men
November 2, 2005	Steroid hormones for contraception in women with sickle cell disease
October 3, 2005	Steroidal contraceptives: effect on bone fractures in women
October 3, 2005	Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes
July 5, 2000	Strategies for increasing concurrent barrier use among women using oral contraceptives
July 16, 2002	Strategies for improving adherence and acceptability of hormonal methods for contraception
June 27, 2000	Subdermal implantable contraceptives versus other forms of reversible contraceptives as effective methods of preventing pregnancy
July 4, 2000	Surgical methods for first-trimester termination of pregnancy
March 13, 2006	Surgical versus medical methods for second-trimester induced abortion
October 8, 2001	Techniques for the interruption of tubal patency for female sterilization
October 8, 2001	Third-generation versus second-generation oral contraceptives on risk of thrombosis
July 12, 2000	Treatments for vaginal bleeding irregularities induced by progestin-only contraceptives
January 30, 2002	Triphasic versus monophasic oral contraceptives for contraception
July 10, 2000	Vasectomy occlusion techniques for male sterilization

Table 2
 Characteristics of trials included in the reviews of four Cochrane Review Groups^a

Characteristics	Fertility regulation (28 reviews)	Subfertility (36 reviews)	Pregnancy and childbirth (234 reviews)	Heart (37 reviews)
	n (%)	n (%)	n (%)	n (%)
Included trials	316	391	2066	598
Mean number/review	11	10	9	15
Range	1–48	1–59	0–81	0–58
Participants/review				
Mean	614	97	296	595
Range	20–17,542	6–781	2–18,530	8–63,732
Number of trials with adequate allocation concealment	101/316 (31.9)	123/391 (31.5)	774/2066 (37.5)	133/598 (22.2)

^a Analyzed from the data of the third issue of *The Cochrane Library* 2005.

trial reports provide more details about laboratory and ultrasound techniques than the research methods used. Inadequate reporting (e.g., failure to describe methods of randomization, allocation concealment, handling of deviations and attempts to achieve follow-up) makes the interpretation of trials difficult, if not impossible, and borders on unethical practice when biased results receive false credibility [19,20]. Despite endorsement of CONSORT guidelines by relevant journals [21], compliance has been inconsistent. Peer reviewers need to be vigilant in ensuring that CONSORT guidelines are followed. Although researchers today are using better methods and reporting trials more completely [22], more improvement is needed [23,24].

Intentional exclusion of trial participants after randomization has sabotaged many randomized controlled trials in fertility regulation. Regardless of compliance with the regimen or eventual discovery of trial ineligibility, all participants in a trial should be kept with their assigned treatment group and analyzed with them [19,25]. In practice, this often does not happen. Participants who do not adhere to the assigned regimen are often dropped from the trial and are not analyzed; this procedure introduces bias.

Another type of attrition is routine in trials sponsored by the pharmaceutical industry. According to intention-to-treat principles, all those randomized should be kept in the analysis [19,25,26]. However, the drug industry commonly uses a different incorrect definition of “intention-to-treat” — all participants who received at least one dose of the medication and who had at least one follow-up observation [27]. Some participants never begin the assigned treatment and should be retained in the analysis; however, in industry-sponsored trials, they are often excluded. Although regulatory agencies have pointed out the error, this practice continues unabatedly [28]. The impact of this problem is lessened in contraceptive effectiveness trials, since most do not measure “extended failure” (i.e., all pregnancies that occur after the beginning of contraception regardless of compliance and continuation) [29]. Instead, only pregnancies that occur while a woman considers herself to be using the method are usually considered failures.

Publication bias is another persistent problem in contraception [30], as in other areas of medicine [31]. Failure to report trials that are not beneficial for a product is unethical

[32]. Following Cochrane Collaboration guidelines, the Fertility Regulation Group tries to identify unpublished and published trials. Techniques to assess the likelihood of publication bias are available [33], and new requirements for prospective trial registration should help [34].

The safety of contemporary contraceptives, such as hormonal methods and intrauterine devices, poses unique research challenges. While established safety is great news for individuals seeking fertility regulation and for clinicians, the rarity of serious complications poses challenges to investigators. The sample sizes required to show differences between rare events in randomized controlled trials become prohibitive. Hence, information about rare events comes primarily from observational studies, particularly case-control studies. Regrettably, persistent biases in case-control studies of contraceptives have led to incorrect conclusions, which, in turn, have had adverse effects on women’s health. For example, many case-control studies have linked intrauterine device use with tubal infertility; however, when the confounding effect of chlamydial infection was controlled, the association disappeared [35]. While the quality of observational research continues to improve, it remains more susceptible to bias than randomized controlled trials [36].

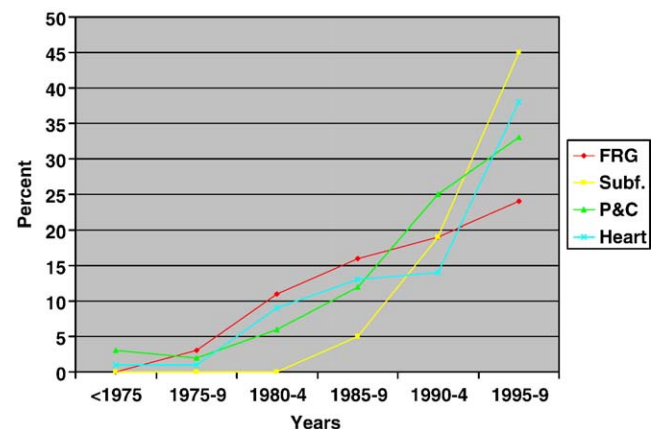


Fig. 1. Proportion of randomized controlled trials with adequate allocation concealment that are included in published Cochrane reviews in four content areas, by years. FRG, fertility regulation; Subf, subfertility; P&C, pregnancy and childbirth, and heart.

Since most randomized controlled trials are unable to study rare events, surrogate end points have been widely used. A valid surrogate marker must not only correlate with the true outcome of interest but also predict the effect of the intervention on the outcome. Most surrogate end points meet the first criterion, but few fulfill the second. Surrogate markers (serum lipids and sex-hormone-binding globulin) have been improperly used to draw inferences about the influence of hormonal contraceptives on myocardial infarction and venous thromboembolism [37]. Relying on a marker for fracture (bone mineral density) that has not met the required criteria, the US Food and Drug Administration recently restricted the use of depot medroxyprogesterone acetate [38]. In contrast, the World Health Organization (WHO) [39] advises no such limits.

Lack of treatment blinding may introduce bias, since some participants and investigators equate “new” with “improved.” Most combined oral contraceptives perform similarly, and research methods that are free from information bias are needed to make fine distinctions among different formulations. Blinding of all participants in trials of oral contraceptives is a feasible methodological requirement. Yet, of the 79 trials analyzed in five published Cochrane systematic reviews of combined oral contraceptives, only 17 had some form of blinding. The choice of an “open” trial design, in which all participants know which contraceptive they are taking, introduces several biases that favor the sponsor’s product.

Obsolete methods and inconsistent definitions create other challenges in summarizing randomized controlled trials. For example, many pharmaceutical companies measure pregnancy rates in obsolete ways, such as the Pearl formula (number of pregnancies per 100 woman-years of use). Life-table methods are preferred by demographers and epidemiologists, since the Pearl formula assumes a constant rate over time, whereas accidental pregnancies and discontinuations cluster in the early months of use [29,40–42].

The issue becomes even more difficult when assessing outcomes such as “acceptability.” Outcomes such as treatment-related discontinuations are often used to measure satisfaction with a method. But few trials address factors that may influence cycle control in their inclusion criteria for participants, thus precluding aggregation of results [43]. Standardization of criteria would be helpful. Many investigators develop new ways of assessing bleeding patterns rather than use definitions promulgated by the WHO decades ago [44]. The resultant inconsistencies in bleeding pattern definitions frustrate attempts to analyze the findings of most published trials.

4. Challenges to external validity

As in other clinical research, extrapolation of trial results to other circumstances may sometimes be hampered. Most randomized controlled trials come from developed

countries. Those who choose to participate in trials differ from the general population. Participants tend to be healthier and more health-conscious than the general population. Participants are commonly chosen because they have a high likelihood of compliance, they often have extra visits to encourage compliance and they are commonly paid for their participation. In randomized controlled trials of oral contraceptives, few accidental pregnancies occur [45]. In actual use, pregnancies are more frequent [46], largely because of less compliance with daily intake of pills. Pragmatic trials that have been influential in the perinatal field [47] are needed in fertility regulation as well. Examples include testing the impact of the ease of availability of emergency hormonal contraception on pregnancy and sexually transmitted disease rates [48,49].

5. Commercial influence

Most randomized controlled trials of oral contraceptives included in Cochrane Fertility Regulation reviews have been sponsored, conducted and often reported by the pharmaceutical industry. This raises the possibility of bias in favor of the companies’ products. As has been shown elsewhere [50,51], industry-sponsored studies are more likely than independent studies to have outcomes favoring its products. A review of observational studies found that, in studies funded by the pharmaceutical industry, the risk of venous thrombosis with third-generation versus second-generation oral contraceptives was half of that in other studies [52]. Better research methods, which are more fully described [19], could protect against these pervasive biases.

Bias in pharmaceutical research also stems from suboptimal research guidance. The Good Clinical Practice guideline governs research performed by industry and destined for regulatory bodies [53]. Regrettably, the Good Clinical Practice guideline does not even mention allocation concealment and is at least a decade behind the current research methods’ recommendations [54]. The International Conference on Harmonisation has shown no interest in correcting this deficiency. Moreover, regulatory agencies in Europe and the United States accept uncontrolled case series reports as evidence of efficacy; comparative trials are not even required [55].

6. Looking ahead

Interest in placing family planning on a more secure scientific basis is growing internationally. Organizations such as the WHO and Family Health International sponsor both randomized controlled trials and observational studies of family planning methods in developing countries worldwide. The Cochrane Fertility Regulation Group actively seeks to involve colleagues from both industrialized and developing countries in its reviews. For example, visiting researchers from New Zealand, The Netherlands, Kenya and Nigeria have come to Family Health International (North

Carolina, USA) to work on Cochrane reviews. These visiting scientists have served as first authors on several published reviews [5,56–58].

In addition to the work of the Cochrane Fertility Regulation Group, the Mottram Hall conference [59,60] and the WHO [61] have made important contributions to synthesizing the best available evidence. *Selected Practice Recommendations for Contraceptive Use* is one of the WHO's two guidelines on contraception that uses evidence-based methods. The document provides guidance on the safe and effective use of a wide range of contraceptive methods once they are deemed to be medically appropriate and serves as the companion guideline to the *Medical Eligibility Criteria for Contraceptive Use* of the WHO [62]. The latter, which is intended for use by policy makers, program managers and the scientific community, supports national programs in the preparation of service delivery guidelines.

Family planning has traditionally been well intended; regrettably, it has not always been well guided. When available, comparative evidence on effectiveness from randomized controlled trials should be given precedence. However, observational research will continue to dominate the family planning literature in terms of number of publications, as is true of obstetrics and gynecology in general [63]. Systematic reviews of the best evidence from all sources provide important clinical guidance [8,64].

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