

Hormonal contraceptives for contraception in overweight or obese women (Review)

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[Intervention Review]

Hormonal contraceptives for contraception in overweight or obese women

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ABSTRACT

Background

Obesity has reached epidemic proportions around the world. Metabolic changes in obesity and greater body mass may lead to reduced effectiveness of hormonal contraceptives, such as the skin patch, vaginal ring, implants, and injectables. We systematically reviewed the evidence on the effectiveness of hormonal contraceptives among overweight and obese women.

Objectives

To examine the effectiveness of hormonal contraceptives in preventing unplanned pregnancies among women who are overweight or obese versus women of lower weight or body mass index (BMI).

Search strategy

We searched MEDLINE, CENTRAL, POPLINE, EMBASE, ClinicalTrials.gov, and ICTRP. We also contacted investigators to identify other trials.

Selection criteria

All study designs were eligible. Any type of hormonal contraceptive could have been examined. The primary outcome was pregnancy. Overweight or obese women must have been identified by an analysis cutoff for weight or BMI (kg/m²).

Data collection and analysis

Data were abstracted by two authors; life-table rates were included where available. For dichotomous variables, we computed an odds ratio with 95% confidence interval. The main comparisons were between overweight or obese women and women of lower weight or BMI.

Main results

We found 7 reports with data from 11 trials that included 39,531 women. One of three studies using BMI found a higher pregnancy risk for overweight or obese women. In the trial of two combination oral contraceptives, women with BMI \geq 25 had greater pregnancy risk compared to those with BMI < 25 (OR 1.91; 95% CI 1.01 to 3.61). Among skin patch users, body weight was associated with pregnancy (reported P < 0.001) but BMI was not. Studies of a vaginal ring (never marketed) and a six-rod implant showed higher pregnancy rates for women weighing \geq 70 kg versus those weighing < 70 kg (reported P values: 0.0013 and < 0.05, respectively). However, two implant studies showed no trend by body weight, and trials of an injectable had no pregnancies.

Authors' conclusions

Body weight addresses overall body size, while BMI generally reflects the amount of fat. Only one of three studies using BMI found a higher pregnancy risk for overweight women. The efficacy of implants and injectable contraceptives may be unaffected by body mass. The field could use trials of contraceptive methods with groups stratified by BMI. The current evidence on effectiveness by BMI is limited. However, the contraceptive methods examined here are still among the most effective when the recommended regimen is followed.

PLAIN LANGUAGE SUMMARY

Hormones for birth control in overweight or obese women

Excess body weight has become a problem around the world. Being overweight or obese may affect how well hormonal birth control works to prevent pregnancy. Hormonal birth control includes birth control pills, the skin patch, the vaginal ring, implants, and injectables. We looked at studies of hormonal birth control for women who were overweight or obese compared to women of normal weight or body mass index (BMI). The formula for BMI is weight (kg) / height (m)².

We did computer searches for hormonal birth control among women who were overweight or obese. We also wrote to researchers to find other studies we might have missed in our search. All types of studies were considered.

We found 7 reports with data from 11 trials and 39,531 women. One of three studies using BMI found more pregnancies among overweight or obese women. That trial looked at two birth control pills. Studies of an early vaginal ring (never marketed) and of a six-rod implant showed the women weighing 70 kg or more had more pregnancies than those weighing less than 70 kg. Among skin patch users, more pregnancies were found among women weighing 80 kg or more. However, the researchers reported that BMI was not related to pregnancy. Two implant studies showed the body weight groups to be similar for pregnancy. Trials of an injectable method had no pregnancies.

Body weight shows overall body size, while BMI reflects the amount of fat. Only one of three studies using BMI found more pregnancies among overweight or obese women. Three of five reports using body weight showed a difference. Body size might not affect how well implants and injectable methods work to prevent pregnancy. Counseling women about how well birth control methods work is hard with little information on any one method. The field could use randomized trials of birth control methods with the groups divided by BMI. However, the birth control methods studied here are among the most effective when the directions are followed.

BACKGROUND

Description of the condition

Obesity has reached epidemic proportions around the world. In the United States (US), the prevalence among adults doubled from 1980 to 2004, and one-third of adults were considered obese in

2005 to 2006 (Ogden 2007). In many European countries, the prevalence of obesity has tripled in the last two decades (WHO 2009). The epidemic has also affected less developed countries, particularly among people in urban areas (Prentice 2006).

Overweight and obesity are generally determined with the body mass index (BMI), which is based on weight and height [BMI

= weight (kg) / height (m)²] (CDC 2009). The BMI does not distinguish between lean and fat body mass, but for most people (other than highly trained athletes) a higher BMI reflects more body fat (CDC 2009). Frequently used BMI categories are 25 to 29.9 (kg/m²) for overweight and 30 or higher for obesity, although these cutoffs may not be optimal for all ethnic groups (Lopez 1992; Huxley 2005). Older cutoffs still in use were derived from the National Health and Nutrition Examination Survey II (NHANES II), conducted from 1976 to 1980 in the US (Burkman 2009). Based on the NHANES II data, women with a BMI greater than 27.3 are overweight, and those with a BMI greater than 32 are considered obese. In addition, the Metropolitan Life Insurance tables for height and weight were updated in the 1990s, and are still occasionally used in the US.

Overweight and obese women may have a higher risk for failure of hormonal contraceptives (Grimes 2005a). Some studies have suggested an association between higher body weight or BMI and unintended pregnancies while using oral contraceptives (Holt 2005) or implants (Sivin 2001). However, survey research has suggested little association, especially after adjusting for demographics or socioeconomic factors (Brunner 2005; Brunner Huber 2007). The risk of oral contraceptive failure among overweight or obese women may depend on whether the assessment is based on perfect use or typical use (Trussell 2009).

Description of the intervention

Hormonal contraceptives include oral contraceptives (OCs), injectables and implants, the transdermal skin patch, the vaginal ring, and some intrauterine devices (IUDs). Oral contraceptives are the most commonly used reversible method in more developed countries (UN 2007), and include combined oral contraceptives (COCs) as well as progestin-only pills (POPs) (Grimes 2010). IUDs lead in less developed countries, most of which are non-hormonal. Hormonal IUDs are not widely used. Next in usage are injectables (combined or progestin-only) and implants (UN 2007).

How the intervention might work

Metabolic changes in obesity and greater body mass may lead to reduced effectiveness of oral contraceptives and other hormonal methods (Grimes 2005a; Trussell 2009). However, we know little about how overweight women metabolize hormonal contraceptives, since many studies exclude overweight women (Edelman 2009a; Lopez 2009). Small pharmacokinetic studies of injectables have found small but clinically unimportant differences between obese and non-obese women in levels of medroxyprogesterone acetate or estradiol (Rahimy 1999; Segall-Gutierrez 2010). A small implant study found higher body weight to be associated with lower serum levonorgestrel levels (Sivin 2001). A pharmacokinetic

study (N=20) of COCs showed levonorgestrel had a longer half-life in obese women versus women with BMI < 25, and therefore, took longer to reach steady state (Edelman 2009b). In addition, estradiol levels in the obese women suggested greater follicular activity, but the sample sizes were too small to detect significant differences. A recent clinical trial of COCs (N=266) examined ovarian suppression among normal-weight and obese women (Westhoff 2009). However, early results showed no major differences in maximum follicular diameter between the two groups.

Why it is important to do this review

We wanted to identify what was known about the relationship between excess body weight or mass and the effectiveness of hormonal contraceptives. Given the prevalence of overweight and obesity, the public health impact of any effect on contraceptive efficacy could be substantial. The results may inform researchers in the field, as well as help healthcare providers assist women in making contraceptive choices.

OBJECTIVES

The primary purpose was to examine the effectiveness of hormonal contraceptives in preventing unplanned pregnancies among women who are overweight or obese versus women in a lower weight or BMI group.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies of hormonal contraceptive effectiveness among overweight or obese women. Reports had to contain information on the specific contraceptive method(s). Treatment duration must have been at least three cycles. We did not anticipate finding randomized controlled trials stratified by body weight. Therefore, we searched for and included all study designs. All languages of publication were eligible for inclusion.

We eliminated studies focused on women with specific health problems, such as HIV or diabetes. We also excluded studies of contraceptives as treatment for specific disorders, e.g., acne, hirsutism, or polycystic ovary syndrome.

Types of participants

Participants were the women in the studies who used the hormonal contraceptive for contraception. Overweight or obese women must have been identified by an analysis cutoff for weight or body mass index. The comparison group could have been women in a lower weight or BMI group. As noted above, several criteria for defining overweight or obese are still commonly used, including a BMI (kg/m²) ≥ 25 for overweight and ≥ 30 for obesity (CDC 2009) as well as the NHANES II cutoff of > 27.3 for overweight and > 32 for obesity (Burkman 2009). Some researchers may analyze the outcome by body weight quartiles or deciles or by body weight groups, e.g., <70 kg or ≥ 70 kg. We included studies with differing criteria, as practices differ across time periods and by country and we anticipated finding few studies. The weight or BMI cutoff points must have been reported.

Types of interventions

The use of one or more hormonal contraceptives must have been studied. Any hormonal contraceptive could have been examined, such as an oral contraceptive, a transdermal skin patch, a vaginal ring, an injectable contraceptive, a subdermal implant, or a hormonal IUD. Due to the limited number of studies of overweight or obese women using contraceptives, we included non-comparative studies as well as comparative trials. The main comparisons for this review were between overweight or obese women and women of lower weight or BMI. Therefore, the comparisons of interest were possible in single-arm studies, i.e., those having only one intervention.

Types of outcome measures

Primary outcomes

The main outcome was pregnancy. Studies must have assessed pregnancies to be considered.

Secondary outcomes

Other outcomes include side effects such as bleeding and rare events such as venous thromboembolism. Adherence data would have been included, if available by weight or BMI groups, to determine if study groups differed in contraceptive use patterns. Weight gain was not an outcome of interest for this review, as weight was being examined as a potential predictor of contraceptive effectiveness. The effect of combination contraceptives on weight gain was the focus of a separate review (Gallo 2008).

We did not include ovulation, since it is not a useful surrogate endpoint for pregnancy. A valid surrogate marker captures the effect of the treatment on the true outcome (Grimes 2005b), i.e., pregnancy.

Search methods for identification of studies

Electronic searches

We searched MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and POPLINE. We also searched for current trials via ClinicalTrials.gov and ICTRP. The search strategies are given below.

MEDLINE via PubMed

1. Search for clinical trials:

(Contraceptive Agents, Female[MESH] OR Contraceptive Devices, Female[MESH] OR contraception[MeSH] OR contracept*[tiab]) AND (obesity[tiab] OR obese[tiab] OR weight[tiab] OR body mass index[MeSH] OR body weight[Mesh]) NOT (cancer*[ti] OR polycystic[ti] OR exercise[ti] OR physical activity[ti] OR postmenopaus*[ti] OR body weight changes) AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp])

2. Search for other types of studies:

(Contraceptive Agents, Female[MESH] OR Contraceptive Devices, Female[MESH] OR contraception[MeSH] OR contracept*[tiab]) AND (obesity[ti] OR obese[ti] OR overweight[ti] OR weight[ti] OR body mass index[ti] OR BMI[ti]) NOT (cancer*[ti] OR polycystic[ti] OR exercise[ti] OR physical activity[ti] OR postmenopaus*[ti] OR body weight changes) NOT (Editorial[ptyp] OR Letter[ptyp] OR Practice Guideline[ptyp] OR Review[ptyp])

POPLINE

(contraceptive agents, female/contracept*/oral contraceptives/contraceptive methods/vaginal rings/injectables/contraceptive implants/contraceptive patch*/skin patch*/vaginal contraceptive ring*/IUD, hormone releasing/(IUD & hormon*) & (efficacy/effective*/contraception failure) & (obesity/obese/overweight/body weight/weight/body mass index/ BMI) !(spermicid*/vaginal spermicides/barrier methods/weight changes/cancer/polycystic/exercise/postmenopaus*/hormone therapy/hormone replacement therapy/HRT)

CENTRAL

overweight OR obese OR obesity OR weight OR body mass index OR BMI in Abstract
AND contraceptive OR contraception in Abstract
NOT premenstrual OR dysmenor* OR endometr* OR *androgen* OR HIV OR polycystic OR PCOS OR cancer OR exercise OR anorexia OR bulimic in Record Title
NOT postmenopausal OR post-menopausal OR hormone therapy OR male hormonal in Record Title

EMBASE

- 1) s contraceptive agents or contraceptive device or contraception or female contraceptive device or contracept?
- 2) s obesity or obese or weight
- 3) s weight, mass and size
e weight, mass and size
- 4) s e3
- 5) s body(mass)index or BMI
- 6) s s2 or s4 or s5
- 7) s s1 and s6
- 8) s cancer or polycystic or exercise or physical(activity) or postmenopaus? or body(weight)change?
- 9) s s7 not s8
- 10) s efficacy or effective?
- 11) s s9 and s10
- 12) s clinical trial or clinical study or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial or randomized controlled trial or controlled clinical trial
- 13) s s11 and s12

ClinicalTrials.gov

Search terms: overweight OR obese OR obesity OR weight OR body mass index OR BMI
Condition: NOT (HIV OR polycystic OR PCOS OR cancer OR anorexia)
Intervention: contraceptive OR contraception

ICTRP

Title: overweight OR obese OR obesity OR weight OR body mass index OR BMI
Condition: contraceptive OR contraception

Searching other resources

We examined reference lists of relevant articles and contact investigators in the field to seek additional unpublished trials or published trials.

Data collection and analysis

Selection of studies

We assessed for inclusion all titles and abstracts identified during the literature searches with no language limitations. One author reviewed the search results and identified reports for inclusion or exclusion. A second author also examined the reports for appropriate categorization according to the criteria in this Protocol.

All study designs were included. Studies could have been randomized controlled trials (RCTs), prospective single-arm or multi-arm studies, case-control studies, or observational studies of contraceptive users. We considered post hoc analysis from any of these types of studies as long as the studies met the [Criteria for considering studies for this review](#).

Data extraction and management

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 or with a third author if necessary. For studies conducted within the last 10 years, we attempted to contact researchers for missing data and clarification of issues related to participants and methods.

Assessment of risk of bias in included studies

The randomized controlled trials were examined for methodological quality, according to recommended principles ([Higgins 2009](#)). The randomization was unrelated to the weight or BMI groups, but provides an indicator of study quality. Methodology considered included 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 2002](#)). In addition, high losses to follow up threaten validity ([Strauss 2005](#)).

To assess the non-randomized studies, we used the principles outlined in section 13.5 of [Higgins 2009](#) as well as the STROBE statement for reports of observational studies ([Von Elm 2007](#)). We assessed whether the analysis included adjustment for potential confounding. The study groups could differ in ways that might affect contraceptive use or effectiveness, such as socioeconomic status or health conditions.

We recorded whether pregnancies and body weight were measured or self-reported. Pregnancies may be underreported when relying on self-reports from interviews or questionnaires rather than testing. Such underreporting is unlikely to differ by study group. However, body weight is frequently underestimated by a few pounds ([Holt 2005](#)). The result would be categorizing more women in a lower weight group, which would bias the effect estimate toward no difference.

For all types of studies, limitations in design were presented in [Risk of bias in included studies](#), and were considered when interpreting the results.

Assessment of heterogeneity

As expected, we found study populations, designs, and interventions to be heterogeneous. We described the clinical and methodological diversity (or heterogeneity) of the studies. We did not

pool data from studies that had different contraceptive methods (e.g., vaginal ring or COC), different doses of the same method, or different criteria for reporting body weight. Therefore, we did not conduct formal meta-analysis due to the few studies available and the range of contraceptive methods examined. Heterogeneity is not an issue when a comparison has a single study.

Data synthesis

The main comparisons for this review were between overweight or obese women and women of lower weight or BMI. Therefore, the comparisons were possible in single-arm studies, i.e., those having only one intervention. For example, for the primary outcome of pregnancy, we compared pregnancies among 'overweight' women with those of 'normal weight' women who used Contraceptive A. Definitions of overweight and normal, or the cutoffs for weight or BMI, depended on the analytic methods used for the study reports. For two-arm studies, we planned to compare the weight or BMI groups within Contraceptive A (overweight or obese versus normal weight women) and then within Contraceptive B. However, [Burkman 2009](#) combined the COC groups for examining risk by BMI. Within COC groups, the researchers reported the results but provided insufficient data for analysis in this review. [Zieman 2002](#) only used data from those assigned to the skin patch. Two of the three trials had a COC comparison group.

Oral contraceptive studies tend to have relatively high withdrawal rates. Time-to-event measures such as life-table or incidence rates are most commonly used, as they are based on actual exposure to the contraceptive and prevent an imbalance in withdrawals from distorting the comparisons. In this review, we extracted life-table rates (actuarial or continuous) where available. We had intended to use the rate difference as the effect measure but the available data were insufficient. Pregnancy by weight or BMI group was not the primary interest for these studies. Six reports either lacked pregnancy counts by weight group ([Gu 1995](#); [Grubb 1995](#)) or woman-years for the weight or BMI groups ([Burkman 2009](#); [Sivin 1997a](#); [WHO 1990](#); [Zieman 2002](#)). [Jain 2004](#) detected no pregnancies.

Where only the crude number of events was published for dichotomous outcomes, we computed an odds ratio (OR) with 95% CI. An example is the proportion of women that reported bleeding or spotting problems.

Sensitivity analysis

From the available data, we conducted sensitivity analysis by examining only those studies that had confirmed pregnancies and measured body weight (rather than self-reported).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of ongoing studies](#).

Included studies

Seven studies representing 11 trials met our inclusion criteria, and had data from 39,531 women. The median sample size was 3319. The hormonal contraceptives studied varied:

- Combination oral contraceptives ([Burkman 2009](#)) containing norgestimate (NGM) 180-215-250 µg/ EE 25 µg or norethindrone acetate (NETA) 1.0 mg/ EE 20 µg;
- Transdermal skin patch ([Zieman 2002](#)) releasing norelgestromin 150 µg + EE 20 µg daily;
- Vaginal ring ([WHO 1990](#)) releasing levonorgestrel 20 µg daily and intended for 90-day use;
- Implants with six rods containing levonorgestrel 216 mg ([Grubb 1995](#); [Gu 1995](#)) or with two rods containing levonorgestrel 150 mg ([Sivin 1997a](#));
- Subcutaneous formulation of the injectable depot medroxyprogesterone acetate (DMPA-SC) containing 104/0.65 mL ([Jain 2004](#)).

The intervention duration also varied. Two studies lasted one year ([Jain 2004](#); [WHO 1990](#)), and two had durations of 6 and 13 cycles within the same study ([Burkman 2009](#); [Zieman 2002](#)). The three implant studies lasted five to seven years ([Grubb 1995](#); [Gu 1995](#); [Sivin 1997a](#)).

Three reports used data from RCTs ([Burkman 2009](#); [Sivin 1997a](#); [Zieman 2002](#)). The main comparisons were between contraceptive methods, and the randomization was not stratified by weight. [Burkman 2009](#) was a post-hoc analysis and [Zieman 2002](#) pooled data from three trials, two were RCTs and one was uncontrolled. The other four reports were from prospective non-comparative trials ([Grubb 1995](#); [Gu 1995](#); [Jain 2004](#); [WHO 1990](#)). [Grubb 1995](#) used data from two Protocols and [Jain 2004](#) had data from two trials.

BMI cutoffs for overweight or obesity were used by [Burkman 2009](#) and [Jain 2004](#). However, [Burkman 2009](#) also used a body weight dichotomy at 70 kg. In addition, the results for cycle control under [Burkman 2009](#) came from Hampton et al (2008); the researchers used quartiles of body weight in pounds (lb): below the 25th percentile (123 lb or less); 25th to 75th percentile (124 to 155 lb); above the 75th percentile (155 lb or more). Four studies used body weight groups of 10 kg each ([Grubb 1995](#); [Gu 1995](#); [Sivin 1997a](#); [WHO 1990](#)). [Zieman 2002](#) used body weight and BMI in the analyses, and presented results by body weight deciles as well as a dichotomy at 90 kg.

Excluded studies

Five reports were excluded after examining the full articles ([Characteristics of excluded studies](#)). A number of studies were

discarded earlier due to not assessing pregnancy; most of these were pharmacokinetic studies.

Risk of bias in included studies

Allocation

The three reports using data from RCTs provided information on how the randomization sequence was generated, and all had allocation concealment. As noted earlier, the randomization methods indicate overall study quality, but were unrelated to our comparisons of interest (overweight or obese versus not overweight).

Blinding

- [Sivin 1997a](#) was blinded.
- [Burkman 2009](#) had blinding of the NGM arm; the study originally had three NGM arms.
- Two were not blinded ([Jain 2004](#); [Zieman 2002](#)).
- Three were single-arm studies ([Grubb 1995](#); [Gu 1995](#); [WHO 1990](#)).

Incomplete outcome data

Two reports had some evidence of incomplete outcome data. [Burkman 2009](#) used an inappropriate definition of intent-to-treat (CONSORT); the researchers excluded from the analysis cycles with incorrect pill intake as well as cycles lacking data on dosing and bleeding. In [WHO 1990](#), women were dropped from study if they had three expulsions in one week or more than five within four weeks.

Losses to follow up were greater than 20% in [Jain 2004](#). Losses were not reported in [Grubb 1995](#) and [Sivin 1997a](#). Across the three trials in [Zieman 2002](#), non-completers ranged from 19% to 31%.

Other potential sources of bias

None of the studies adjusted for potential confounding related to the condition of interest here (overweight or obesity). [Zieman 2002](#) provided adjusted analysis that could account for confounding effects. For two studies, pregnancy rate by weight or BMI group was not a main outcome ([Grubb 1995](#); [Gu 1995](#)). For others, the report focused on an outcome by weight or BMI group even if the original trial did not emphasize weight ([Burkman 2009](#); [Sivin 1997a](#); [WHO 1990](#)). Confounding was not an issue for the comparison in [Jain 2004](#), as no pregnancies were detected.

Only two of the seven reports specified that pregnancy was tested and weight was measured ([Burkman 2009](#); [Jain 2004](#)). In addition, [Zieman 2002](#) tested for pregnancy and [Grubb 1995](#) mentioned objective assessment of pregnancy. [WHO 1990](#) recorded weight

at each clinic visit. Details can be found in the [Characteristics of included studies](#).

Effects of interventions

Contraceptive method

Combined oral contraceptives

With both COC groups combined in [Burkman 2009](#), overweight or obese women (BMI 25 or higher) were more likely to become pregnant compared to women of normal weight (BMI under 25) (OR 1.91; 95% CI 1.01 to 3.61; [Analysis 1.1](#)). Women with a BMI of 25 or higher were 31% of the sample. The risk was reportedly similar overall when the BMI cutoff was changed to 27.3. Within contraceptive methods, one major difference was shown between the comparison groups from the Cox proportional hazards models. In the group assigned to NETA/EE, women whose BMI was 25 or more had a higher reported risk versus those with a BMI under 25 ([Analysis 1.3](#)). The risks were reportedly similar within contraceptive groups when the BMI cutoff was 27.3 ([Analysis 1.3](#)). A separate analysis examined the 20 pregnancies within the NGM/EE group, which were distributed over body weight deciles ([Zhang 2006](#)). The highest decile, with weight greater than 175 lb (N=174), had four pregnancies. Two pregnancies occurred among women weighing 198 lb or more (N=55).

An earlier publication from [Burkman 2009](#) reported on cycle control ([Hampton et al, 2008](#)). Of eight comparisons of breakthrough bleeding or spotting, three showed a difference. Within the NGM/EE group, women above the 75th percentile for weight (more than 155 lb) were less likely to report breakthrough bleeding or spotting at cycle 13 than those below the 25th percentile (123 lb or less) ([Analysis 1.6](#)) or those in the 25th to 75th percentiles (124 to 155 lb) ([Analysis 1.7](#)). Within the NETA/EE group, women above the 75th percentile (more than 155 lb) were less likely to report breakthrough bleeding or spotting at cycle 6 than the women below the 25th percentile (123 lb or less) ([Analysis 1.8](#)).

Skin patch

[Zieman 2002](#) reported 15 pregnancies in 3319 women over one year in the pooled data from three trials ([Analysis 2.1](#)). The top three deciles of women weighed 69 kg or more (about 30% of the sample). Of the 15 pregnancies detected among the patch users, 7 were in the top decile of women weighing 80 kg or more. Five of those seven pregnancies were among a subgroup of women weighing 90 kg or more (198 lb), who comprised 3% of the study population. The researchers reported baseline body weight was significantly associated with pregnancy risk in a proportional hazards model (reported $P < 0.001$) in which potential prognostic variables

were also assessed (i.e., age, race, BMI, and body surface area). However, pregnancies were reportedly not clustered in any BMI subgroup (no data provided).

Progestin-only vaginal ring

The experimental ring in WHO 1990 was never marketed. The group weighing 70 kg or more had a cumulative discontinuation rate for pregnancy of 8.2 (Analysis 3.1), and represented about 10% of the sample. The rates for the other three weight groups were 1.8 (49 kg or less), 2.6 (50 to 59 kg), and 5.3 (60 to 69 kg). From the chi-square test across groups, the reported P value was 0.0013. The researchers also fitted a Cox proportional hazards model to examine the relationship between body weight and pregnancy. Based on that model, they estimated pregnancy risk increased by 61% with a 10 kg increase in body weight. The risk of pregnancy more than doubled with a 20 kg increase (e.g., from 60 kg to 80 kg). The estimated hazards ratio is 2.60 for this increase in body weight; however, statistical significance was not reported. The researchers also estimated the cumulative life-table pregnancy rates. The pregnancy rate for a woman weighing 80 kg was 9.8 or more than twice the 4.4 rate for a woman weighing 60 kg (Analysis 3.2).

Implants

Several implants were examined in three studies. Grubb 1995 and Gu 1995 studied a six-rod implant that contained levonorgestrel 216 mg. Sivin 1997a examined a two-rod implant containing levonorgestrel 150 mg; this included an implant in current use ('original') and a similar implant with a new elastomer. More detail can be found in Characteristics of included studies.

Outcome data by weight group for Grubb 1995 were shown in a figure without specific rates or counts. Reportedly, contiguous weight groups differed in their fifth-year pregnancy rates (life-table method). The 40 to 49 kg group apparently had a lower rate than the 50 to 59 kg group, which had a lower rate than the 60 to 69 kg group. The P value was reported as < 0.01. Women who weighed 70 kg or more had seven pregnancies, and the rate was reportedly similar to that of the 60 to 69 kg group. The numbers of women in each weight group were not reported.

In Gu 1995, weight was associated with pregnancy rate; the P value was reported as < 0.05. The cumulative pregnancy rate for the group that weighed 70 kg or more was 4.58 at Years 5 and 6 and 6.62 at Year 7. The women in this highest weight group represented about 3% of the study sample. These life-table rates were nearly twice those of the group weighing 60 to 69 kg (Analysis 4.1). Annual pregnancy rates were also provided (Analysis 4.2).

In Sivin 1997a, no pregnancies were noted in the first three years (Analysis 5.1). In a follow-up study of the newer two-rod implant, five pregnancies were reported. Only one occurred in the group that weighed 70 kg or more (Analysis 5.1), which represented 16% of the study population.

Depot medroxyprogesterone acetate, subcutaneous (DMPA-SC)

In two trials, Jain 2004 examined a subcutaneous form of depot medroxyprogesterone acetate (DMPA-SC) containing 104 mg/0.65 mL. No pregnancies were detected in the one-year trials (Analysis 6.1). Overweight or obese women were 27% of the sample in the European and Asian trial, but only 6% had a BMI greater than 30. In contrast, 44% of the women in the 'Americas' trial were overweight or obese with 17.5% having a BMI higher than 30.

Sensitivity analysis

Our criteria for the sensitivity analysis included having tested for pregnancy and measured weight. Only two studies met those criteria: one of COCs (Burkman 2009) and one of DMPA-SC (Jain 2004). Both were approximately one-year studies. Jain 2004 had no pregnancies. Burkman 2009 showed a higher risk for pregnancy among overweight or obese women overall, using a BMI cutoff of 25 or higher. Within contraceptive method, the groups were generally similar for pregnancy, which may be attributed to lack of power. Women with higher body weights had fewer bleeding problems.

When we include studies that appeared to have either 1) tested for pregnancy (Zieman 2002; Grubb 1995) or 2) measured weight (WHO 1990), the results are still split. The reports are not clear on whether both were objectively assessed. The heaviest women did not have an increased risk in Grubb 1995, but they did in WHO 1990. In Zieman 2002, the difference in pregnancies for the heavier women was not apparent when the analysis was conducted with BMI rather than weight.

DISCUSSION

Summary of main results

Results were mixed in terms of whether body weight or mass was associated with unintended pregnancy. Of seven studies, four showed a higher risk for pregnancy among the heaviest women. One was a trial of COCs that used BMI to compare groups (Burkman 2009); about 31% of the women were overweight or obese. Zieman 2002 examined three studies of the transdermal skin patch and reported an association for body weight but not for BMI. About 30% of the women in Zieman 2002 weighed 69 kg or more. Two studies that showed a difference used body weight alone: WHO 1990 examined a progestin-only vaginal ring and Gu 1995 was an implant study. In contrast, two implant studies did not report a significant difference by weight. In Grubb 1995, with more than 16,000 implant users, the heaviest group did not

have a significantly higher risk, although the lower weight groups differed from each other. In the implant studies of [Sivin 1997a](#), few pregnancies were reported with no trend by body weight group. For the injectable trials, [Jain 2004](#) used BMI but found no pregnancies; 27% to 44% of the women were overweight or obese in those studies.

The included studies used varying methods of assessing relative body size. Three studies compared groups according to BMI as well as body weight. [Burkman 2009](#) used two different cutoffs for BMI (25 and 27.3), but the risks were reportedly the same. Four older studies used some categorization of body weight alone. As noted earlier, a higher BMI generally reflects more body fat, except in highly trained athletes. Body weight indicates total body mass but does not inform as to whether the person is overweight for a particular height. For example, a woman weighing 70 kg and 1.65 meters in height would have a BMI of 25.7 and be considered slightly overweight ([CDC 2009](#)). If she were 1.5 meters tall, her BMI would be 31.1, obese by current standards. At 1.75 meters, the 70 kg woman would have a BMI of 22.9, well within the normal range.

The studies using body weight groups implicitly addressed a different issue than those using BMI. A study of body weight may examine whether a different dose was needed for larger women. On the other hand, studying BMI might inform whether body composition (amount of fat in particular) plays a role in effectiveness. The pharmacokinetics of obesity are poorly understood ([Edelman 2009b](#)). Only one of the three studies that used BMI found a higher pregnancy risk for overweight (or obese) women and that trial examined two COCs ([Burkman 2009](#)). The two that did not find a significant difference by BMI studied an injectable ([Jain 2004](#)) and the transdermal skin patch ([Zieman 2002](#)).

Overall completeness and applicability of evidence

The variety of contraceptive methods examined in these studies limits the conclusions. The higher risk for heavier women was found in four reports (that included six trials), all of which examined different contraceptive methods: an implant, an early experimental ring, the skin patch, and two COCs. Therefore, we had limited information on any one method and none on the currently available vaginal ring or the hormonal IUD. No significant differences were noted in the reports of two implant studies (three trials) or the injectable study (two trials).

Risk of unintended pregnancy depends on regimen adherence, often presented as method failure versus user failure ([Trussell 2009](#)). Adherence is less of a concern for long-acting methods like implants than, e.g., for COCs or the skin patch. [Burkman 2009](#) had adherence data from daily diaries, but only reported method failures per COC group not for the BMI groups. A sub-analysis of the NGM/EE group reported the BMI and weight groups were

similar in method or total failures ([Zhang 2006](#)). [Zieman 2002](#) examined adherence for the overall report but not for the post-hoc analysis by weight and BMI.

Inclusion/exclusion criteria can limit the ability to generalize the results. The trials included in [Zieman 2002](#) limited weight to 135% of ideal body weight. Many obese women were likely to have been excluded with that cutoff. [Burkman 2009](#) reported that women with a BMI greater than 32.4 were excluded from participation. However, the reported cutoff for BMI may have been an error, as the authors noted elsewhere that the highest BMI of enrollees was 47.6. Other reports did not specify a cutoff, but contraceptive studies often restrict weight to 115% or 120% of ideal ([Lopez 2009](#)). Recent studies have specifically included overweight or obese women, but do not address pregnancy: [Westhoff 2009](#) is focused on ovarian suppression with COCs; [Segall-Gutierrez 2010](#) is a pharmacokinetic study of an injectable. However, [NCT00724438](#) is a pharmacokinetic study of an implant that should yield information on reasons for discontinuation, including pregnancy.

Quality of the evidence

RCTs are generally considered the gold standard for experimental research. Study design is usually stronger for RCTs than for other types of studies. Three of the eight reports in this review used data from RCTs. However, the main comparisons in this review were not the contraceptive methods but the weight or BMI groups, which were not used for stratification. Allocation concealment and blinding seem less relevant when the comparisons are not the contraceptive methods, and were not applicable to the single-arm studies. Further, while one study provided adjusted analysis, confounding factors for overweight may differ from those for a contraceptive method.

The non-comparative trials were all multi-site trials. Four of the five had specific eligibility criteria and follow-up schedules, indicating a planned approach.

Two studies had incomplete outcome data and two had high losses to follow up. Exclusions after assignment and high losses can bias the results.

Agreements and disagreements with other studies or reviews

Several relevant studies did not meet the inclusion criteria but are summarized in [Table 1](#). Most included any oral contraceptive rather than one specific method. One abstract did not report the duration of use; the data were from multiple trials of the vaginal ring. However, many of these reports have been cited in reviews of body weight and COC effectiveness ([Edelman 2009a](#); [Trussell 2009](#)) are worthy of examination. Most used BMI rather than body weight for constructing the comparison groups.

Table 1. Additional studies of interest

Study	Type of study; N	Data collected	N	Hormonal contraceptive	Analytic method	Comparison groups	Pregnancy results as reported
Brunner 2005	Retrospective cohort analysis	1993 to 1995	1916	Any OC	Hazard ratio (HR) adjusted for age, demographics, parity, dual method use	BMI <20, 20 to 24.9 (referent), 25 to 29.9, >= 30	BMI <20: HR 0.59 (95% CI 0.32 to 1.07)
							BMI 25 to 29.9: HR 0.73 (95% CI 0.42 to 1.28)
							BMI >=30: HR 1.51 (95% CI 0.81 to 2.82)
						Weight by 20 lb increments (80 to >190; referent 111 to 130)	Weight groups were similar (adjusted HR from 0.89 to 1.10)
Brunner Huber 2006	Case-cohort	1999 and 2000	358	Any OC	OR (logistic model adjusted for education, ethnicity, income)	BMI <20, 20 to 24.9 (referent), 25 to 29.9, >= 30	BMI <20: OR 1.07 (95% CI 0.31 to 3.73)
							BMI 25 to 29.9: OR 1.87 (95% CI 0.73 to 4.78)
							BMI >=30: OR 1.58 (95% CI 0.49 to 5.10)
							BMI >25 vs <25: OR 1.90 (95% CI 0.82 to 4.41)
Brunner Huber 2007	Retrospective cohort analysis	2002 to 2003	1301	Any OC	Hazard ratio (adjusted for age, ethnicity, parity)	BMI <20, 20 to 24.9 (referent), 25 to 29.9, >= 30	BMI <20: HR 1.28 (95% CI 0.55 to 2.98)

Table 1. Additional studies of interest (Continued)

							BMI 25 to 29.9: HR 0.93 (95% CI 0.56 to 1.53)
							BMI >=30: HR 1.35 (95% CI 0.79 to 2.30)
						BMI <18.5, 18.5 to 24.9 (referent), 25 to 29.9, >= 30	Results were similar to those above
Dinger 2009	Prospective; active surveil- lance	2000 to 2005	58,674	Any OC	Life-table rates	BMI <20, 20 to 24.9, 25 to 29.9, >= 30 Ex- amined by type of progestin	BMI data shown in figures; fail- ure rates similar across groups. CMA- containing OC had higher fail- ure rate for BMI >=30.
						Weight (kg): <55, 55 to 59.9, 60 to 64.9, 65 to 69.9, 70 to 74.9, >=75;	Weight results reportedly simi- lar to those for BMI.
Holt 2002	Ret- rospective co- hort analysis	1990 to 1994	618	Any OC	Relative risk ad- justed for parity:	Weight quar- tiles (kg): <56.5, 56.5 to <62.5, 62.5 to <70.5, >=70.5	Weight >=70.5 vs <70.5: RR 1.6 (95% CI 1.1 to 2.4)
Holt 2005	Case control	1998 to 2001	816	Any OC	OR (logistic model adjusted for age, refer- ence year, and parity)	BMI quartiles: <=21.3, >21.3 to 23.6, >23.6 to 27.3, >27.3 (split at 32.2)	BMI >27.3 vs <=21.3: 1.62 (95% CI 1.02 to 2.57);
							BMI >27.3 vs <=27.3: OR 1.58 (95% CI 1.11 to 2.24);

Table 1. Additional studies of interest (Continued)

							BMI >32.2 vs <=27.3: OR 1.72 (95% CI 1.04 to 2.82);
						Weight quartiles (kg) : <=56.7, >56.7 to 63.5, >63.5 to 74.8, >74.8 (split at 86.2)	Weight >74.8 vs <=56.7: OR 1.33 (95% CI 0.84 to 2.11) ;
							Weight >74.8 vs <=74.8: OR 1.36 (95% CI 0.95 to 1.95) ;
							Weight >86.2 vs <=74.8: OR 1.62 (95% CI 0.99 to 2.64)
Vessey 2001	Prospective	Recruited 1968 to 1974; follow up to 1994	17,032	Any OC	Life-table rates adjusted for age and parity	Weight groups (kg): <51, 51 to 57, 58 to 64, 64 to 70, 70 to 76, >= 77	Similar rates across groups: 0.26, 0.27, 0.25, 0.17, 0.21, 0.25
						Weight (kg) <82 vs >=82	Weight <82 kg: 0.24 (95% CI 0.20 to 0.28); Weight >=82 kg: 0.38 (95% CI 0.08 to 1.12)
Westhoff 2005 ¹	Phase III trial database	Not specified	3259	Vaginal ring; duration not specified	Rate	Body weight deciles (weight per decile not reported)	Pregnancies = 27, all in women 106 to 188 lb; none in women >= 189 lb (N=74)
Westhoff 2008 ²	5 multicenter trials	1999 to 2007	6465	LNG 100/ EE 20 or LNG 150/ EE 30 or DSG 150/ EE 20	Crude rate	<90 kg vs >=90 kg; (>=90 kg = 15.5% of sam-	Weight >90 kg: 0.70% (7/61 of "on drug" pregnancies);

Table 1. Additional studies of interest (Continued)

						ple)	Weight <90 kg: 0.99%
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¹Abstract

²Abstract; includes data in [Kroll 2010](#).

Once the models in these additional studies were adjusted for potential confounding, overweight or obese women had similar pregnancy risk to women of normal BMI ([Brunner 2005](#); [Brunner Huber 2006](#); [Brunner Huber 2007](#); [Dinger 2009](#)) or weight ([Vessey 2001](#)). Two studies with unadjusted rates showed no relationship of weight to pregnancy risk ([Westhoff 2005](#); [Westhoff 2008](#)). Two often-cited studies using adjusted models were the exceptions: in [Holt 2002](#), heavier women by body weight had a higher risk; in [Holt 2005](#), women with a higher BMI had greater risk but the body weight groups had similar risks.

We excluded the implant data of [Sivin 1988](#) in this review, since half appeared to overlap those in [Gu 1995](#). The report also included data from several other countries. The researchers examined pregnancies by four weight groups (< 50, 50 to 59, 60 to 69, and ≥ 70 kg). The gross cumulative rates at 60 months were 0.2, 3.5, 3.5, and 7.6, respectively, suggesting an association of weight with pregnancy risk. [Graesslin 2008](#) provided post-marketing surveillance data on implant use. By body weight (10 kg groups), the frequency of method failures was reportedly similar to the distribution of users. However, nearly half of the reported pregnancies had insufficient documentation for classification and inclusion.

AUTHORS' CONCLUSIONS

Implications for practice

Studies using BMI (rather than body weight) are more informative about the role of body composition (especially fat) in contra-

ceptive effectiveness. Only one of three studies using BMI found a higher pregnancy risk for overweight (or obese) women and that trial examined two COCs. Trials of the skin patch indicated some difference for the highest weight group but not by BMI group. Two studies showing a difference by body weight alone examined an experimental vaginal ring and an implant. In contrast, two other implant studies and an injectable study suggested those methods may be unaffected by body mass. We did not see a consistently higher risk for overweight or obese women. The contraceptive methods examined here are among the most effective when the regimen is followed.

Implications for research

The current evidence on effectiveness by BMI is limited for any particular contraceptive method. Recent research is examining potential mechanisms for contraceptive failure among overweight or obese women. However, pregnancy is not always an outcome in pharmacokinetic studies. Randomized controlled trials of contraceptive methods could further inform the field, if the groups were stratified by body mass index (overweight or obese versus not overweight).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Burkman 2009

Methods	Post hoc analysis from RCT conducted at 100 sites in USA and 10 in Canada. Sample size was reportedly based on US regulatory requirements of at least 10,000 cycles for the evaluation of safety and efficacy of OCs with at least 200 participants evaluated for 13 cycles.
Participants	6022 women; one-third participated in the study for 13 cycles, two-thirds of the women participated for 6 cycles. Inclusion criteria: sexually active, healthy women aged 18 to 45 years at risk for pregnancy with regular menses. The 2009 report states that the upper limit for BMI was 32.4 but notes elsewhere that 47.6 was the highest BMI of enrollees. Exclusion criteria: pregnancy or lactation in past 42 days, contraindications to oral contraceptives, certain diseases, smokers aged 35 or more years, receipt of certain drugs or devices, DMPA use in past 6 months, and alcohol or substance abuse in past 12 months.
Interventions	1) Norgestimate (NGM) 180-215-250 µg/ EE 25 µg (N=1236 for 6 cycles; N=487 for 13 cycles) 2) Norethindrone acetate (NETA) 1.0 mg/ EE 20 µg with 75 mg ferrous fumarate on days 22-28 (N=853 for 6 cycles; N=318 for 13 cycles) Study duration: First 1/3 of participants were to have 13 treatment cycles and the remaining 2/3 were to have 6 treatment cycles. Comparison groups for pregnancy (primary article): body weight \geq 70 kg versus $<$ 70 kg (75th percentile); BMI \geq 25 versus $<$ 25 and BMI $>$ 27.3 versus \leq 27.3. Comparison groups for cycle control (secondary article): weight \leq 25th percentile (\leq 123 lb); 25th to 75th percentile (124 to 155 lb); $>$ 75th percentile ($>$ 155 lb)
Outcomes	Primary outcomes: pregnancy (serum β -hCG); cycle control, side effects; body weight. Use of daily diary cards to collect data on pill intake, cycle control and side effects. Data on side effects were recorded if reported in response to a general question or observed during physical examination. Secondary article (Hampton 2008) examined breakthrough bleeding and spotting by age and weight subgroups.
Notes	Body weight and height were measured at baseline and cycles 1, 3, 6, 9 and within 7 to 14 days of last active tablet of last cycle.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Communication with the authors indicated a computer-generated random allocation sequence. Randomization in a 3:3:3:2 ratio; blocks of size 11:9. Randomization was balanced using permuted blocks and stratified by study center.

Burkman 2009 (Continued)

Allocation concealment?	Yes	Communication with the authors indicated allocation concealment by a centralized voice-activated randomization system
Blinding? All outcomes	Yes	NGM/EE regimens were blinded and NETA/EE was open. Study originally had 4 arms (see Incomplete outcome data below).
Incomplete outcome data addressed? All outcomes	Unclear	Report inaccurately states evaluation of contraceptive efficacy was based on intent-to-treat (ITT). Cycles in which data on dosing and bleeding was lacking and cycles with incorrect pill intake were excluded from the analysis. The analysis population differs across reports and 75th percentile of weight also differs. Lost to follow up: 6.5% of triphasic group and 5.8% of monophasic group were lost to follow up; no numerator provided. Data from two additional arms of NGM were not provided in the main report (Hampton 2001). The group assigned NGM 180-60 µg/20 µg EE had the poorest cycle control and was discontinued early. The other was assigned to NGM 180-60 µg /25 µg EE, which would not be developed for clinical use.
Free of other bias?	Unclear	No adjustment for potential confounding. While this was an RCT, the analysis by BMI or weight was post hoc.

Grubb 1995

Methods	Non-comparative trials conducted in 17 countries by Family Health International and the Population Council from 1984 to 1991 (2 study protocols)
Participants	16,282 women. Inclusion criteria: 18 to 40 years old, sexually active, previously pregnant, no injectable use in past 6 months, within first 7 days of menstrual cycle, and able to return for follow up. Exclusion: history of liver disease, jaundice, sickle-cell anemia, or herpes; evidence on exam of thromboembolic disease, hypertension, pelvic inflammatory disease, undiagnosed vaginal bleeding, cancer or pregnancy. In 1988, original exclusion criterion was dropped regarding postpartum women (6 months postpartum or breastfeeding), and all postpartum women were included.

Grubb 1995 (Continued)

Interventions	Six-capsule levonorgestrel implant (Norplant®); follow-up visits at 1, 3, and 6 months after insertion then every 6 or 12 months until removal or 5 years. Comparison groups for analysis: 5 body weight categories (< 40, 40 to 49, 50 to 59, 60 to 69, and ≥ 70 kg)	
Outcomes	Life table rates for pregnancy overall (“objective-determined”); rates by weight group were presented in a Figure without sufficient data for analysis here. Rates per country presented in Table but not by weight.	
Notes	Sample sizes not reported for weight groups. No method specified for assessment of weight at admission.	
Risk of bias		
Item	Authors’ judgement	Description
Adequate sequence generation?	Unclear	Not applicable (NA)
Allocation concealment?	Unclear	NA
Blinding? All outcomes	Unclear	NA
Incomplete outcome data addressed? All outcomes	Unclear	Losses to follow up: unknown. Report provides discontinuation rates only.
Free of other bias?	Unclear	No adjustment for potential confounding. Pregnancy by weight group was not a primary outcome of this study.

Gu 1995

Methods	Non-comparative trial conducted in China; outpatient clinics in teaching hospitals, medical colleges, and research institutes in large urban areas; enrollment from 1984 to 1987	
Participants	10,718 women at admission; 7554 at end of year 5. Inclusion criteria: 18 to 40 years old, had at least one living child, good health, no contraindications to hormonal contraceptives. Exclusion criteria: pregnant or breastfeeding.	
Interventions	Six-capsule levonorgestrel implant (Norplant®); follow up at 1, 3, and 6 months then semiannually through 24 months, then annually through 5 years. Women were then given the option of continuing into the sixth year then asked again for the seventh year. Comparison groups for analysis: 4 weight categories (< 50, 50 to 59, 60 to 69, and ≥ 70 kg)	

Gu 1995 (Continued)

Outcomes	Pregnancy status determined at each visit (method not specified). Life table estimates and Pearl rates were calculated.	
Notes	Weight assessed at admission (method not specified).	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	NA
Allocation concealment?	Unclear	NA
Blinding? All outcomes	Unclear	NA
Incomplete outcome data addressed? All outcomes	Unclear	Losses to follow up: reportedly 1%
Free of other bias?	Unclear	No adjustment for potential confounding. Pregnancy by weight group was not a primary outcome of this study.

Jain 2004

Methods	Two Phase 3 trials, non-comparative; one conducted in North and South America (36 sites) and one in Europe and Asia (64 sites).	
Participants	1787 women, 18 to 49 years old, sexually active and wanting long-term contraception. Inclusion criteria: no OC use for past 2 months, regular menstruation in past 3 months, willing to rely on DMPA-SC for a year. Exclusion criteria: used OCs, implants, or hormonal IUD in past 2 months or DMPA in past 10 months, pregnant or infertile, abnormal Pap, undiagnosed genital bleeding, other contraindications to hormonal contraceptives.	
Interventions	Subcutaneous form of depot medroxyprogesterone acetate (DMPA-SC) 104/ 0.65 mL injected every 3 months for 1 year Comparison groups for analysis (pregnancy): BMI ≤ 25, 25 to 30, > 30 kg/m ²	
Outcomes	Treatment failure cumulative pregnancy rate at 1 year, i.e., positive pregnancy test prior to next scheduled injection. Secondary outcomes: amenorrhea, irregular bleeding, adverse events	
Notes	Weight assessed as safety endpoint. In the 'Americas trial', nearly 44% were reportedly overweight or obese. About 27% were reportedly overweight or obese in the European and Asian trial.	

Jain 2004 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	NA
Allocation concealment?	Unclear	NA
Blinding? All outcomes	No	Open-label
Incomplete outcome data addressed? All outcomes	Unclear	Lost to follow up: 7% in Americas trial and 3% in European/Asian trial
Free of other bias?	Unclear	No adjustment for potential confounding. No pregnancies detected, though.

Sivin 1997a

Methods	Randomized controlled trial conducted in 8 centers (4 USA and 4 unspecified countries) ; enrollment 1990 to 1992
Participants	398 healthy women, 18 to 40 years old, who sought implant contraception. Inclusion criteria: no contraindications to implant use, willing to undergo study procedures, lived in area accessible to the clinic. Exclusion criteria: history of cancer, severe cardiovascular problem, hyperlipidemia, or diabetes mellitus; no OC use in past month or injectable steroids in past year.
Interventions	Levonorgestrel implants: 1) LNG ROD - new 2-rod implant containing levonorgestrel 150 mg (different elastomer in core than earlier implant); 2) earlier 2-rod implant (Norplant®-2) Follow up: 1, 3, 6, 9, and 12 months, and then semi-annually. At 3 years, LNG ROD group was invited to continue for 2 more years; at the end of 5 years, they were invited to continue for 2 more years (Sivin 2001). Comparison groups for analysis: 4 weight groups (< 50, 50 to 59, 60 to 69, >= 70 kg)
Outcomes	Pregnancy (assessment method not specified); serum levonorgestrel concentrations
Notes	Weight assessed at admission (method not specified). Highest weight group (>=70 kg) included about 16% of sample.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Linear congruential method"; block of 50 per clinic with 25 assigned to each group

Sivin 1997a (Continued)

Allocation concealment?	Yes	Implants were in sealed opaque envelopes numbered according to randomization lists (sequential).
Blinding? All outcomes	Yes	Implants were similar in appearance; neither investigators nor subjects could distinguish between them.
Incomplete outcome data addressed? All outcomes	Yes	1 set of each implant was contaminated and not used; 398 women were enrolled. Not all subjects had 3 years of use by Dec 1994 data collection. Lost to follow up: not specified.
Free of other bias?	Unclear	No adjustment for potential confounding. This was an RCT but not stratified by weight. Pregnancy by weight group was not a primary outcome, but serum LNG by weight group was of interest.

WHO 1990

Methods	Non-comparative trial in 19 centers in Africa, China, Europe, Asian, and Latin America; conducted from 1980 to 1986.
Participants	1005 women attending family planning services. Inclusion criteria: age 18 to <35 years, regular menses for at least 2 months, sexually active (2 times/week), at least one living child or abortion by this marriage, no injectable or implant contraceptive for past 3 months and no OC for past month, able to use menstrual diary card. Exclusion criteria: malignancy, genital prolapse, severe incontinence of urine, severe or chronic constipation, recurrent urinary tract infections; pelvic inflammatory disease, purulent cervical discharge, or vaginal infection; congenital disorder of renal or hepatic excretion; dyspareunia or coital difficulty; recurrent jaundice; pruritus of late pregnancy; liver disease in past 6 months.
Interventions	Vaginal ring releasing levonorgestrel 20 µg daily. Ring was designed for 90-day protection (continuous use), after which a new ring was provided to each woman. Duration: one year Follow-up schedule: monthly until June 1982, when schedule was changed to every 3 months. Comparison groups for analysis: 4 weight groups (< 40, 50 to 59, 60 to 69, >= 70 kg)
Outcomes	Pregnancy
Notes	Gynecological exam conducted at each follow-up visit; weight recorded at each visit (assessment method not specified).

WHO 1990 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	NA
Allocation concealment?	Unclear	NA
Blinding? All outcomes	Unclear	NA
Incomplete outcome data addressed? All outcomes	Yes	Lost to follow up: reportedly 12.7% at 1 year (99 women; denominator not specified) includes late for follow up as per protocol Women were also dropped from study if they had 3 expulsions in 1 week or > 5 within 4 weeks. Discontinuation data provided.
Free of other bias?	Unclear	No adjustment for potential confounding. Report was published at the same time as two others from the main study. Authors did examine demographics regarding expulsion.

Zieman 2002

Methods	Post hoc analysis with data from 3 studies: 1) Audet 2001 - RCT in 39 centers in USA and 6 centers in Canada; 2) Urdl 2005 - RCT in 54 centers in Europe and 11 in South Africa; 3) Smallwood 2001 - non-comparative trial in 73 centers: 31 in USA, 36 in Europe, 4 in Israel, and 2 in Australia.
Participants	3319 women from 3 studies. Inclusion criteria: sexually active, healthy, aged 18 to 45 years, within 35% of ideal body weight, blood pressure <140/90 mm Hg, not pregnant in 42 days prior to study admission, not lactating, normal menses including one normal period since last pregnancy. Exclusion criteria: contraindications to hormonal contraceptives, dermal hypersensitivity, smoking if > 35 years old, alcohol or substance abuse in past 12 months, injectable progestin in past 6 months, experimental drug or device use in past 30 days.
Interventions	Patch (norgestromin 150 µg + EE 20 µg daily); two studies had comparison COC groups that were not included in this analysis. Treatment duration: 13 cycles for first 1/3 enrolled and 6 cycles for the other 2/3 Follow-up schedule: cycles 1, 3, 6; also at cycle 9 and 13 for those with 13 treatment cycles. Comparison groups for analysis: deciles of baseline weight; < 90 versus ≥ 90 kg. BMI

Zieman 2002 (Continued)

	also used in analysis but no details were provided.	
Outcomes	Pregnancy (serum β -hCG) when pregnancy suspected; urine pregnancy test 10 days after final cycle; if pregnant, ultrasound to establish date) Method and user failure estimated overall but not by body weight groups	
Notes	Baseline body weight (assessment method not mentioned)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Studies 1 & 2: interactive voice-activated randomization system with permuted blocks stratified by study center; #2 used 4:3 ratio; Study 3: not applicable
Allocation concealment?	Yes	Studies 1 & 2: interactive voice-activated randomization system
Blinding? All outcomes	No	Open-label
Incomplete outcome data addressed? All outcomes	Yes	Efficacy analysis included all women who returned at least one diary card (96% of those assigned to patch). Non-completers ranged from 19% to 31%. Losses to follow up: study 1, 4%; study 2, 2%; study 3, not reported.
Free of other bias?	Unclear	No adjustment for potential confounding. Data pooled from 3 trials (2 were RCTs but not stratified by weight). Pregnancy by weight group was not a primary outcome of this study.

Characteristics of excluded studies [ordered by study ID]

Banerjee 1984	Association of body weight and method failures focused on 'thin' women (≤ 40 kg versus > 40 kg).
Cirkel 1990	Side effects reported by weight group; pregnancy reported overall.

(Continued)

Graesslin 2008	Insufficient data on weight. For efficacy analysis, 14.5% were > 70kg. Six pregnancies were confirmed that occurred within 14 days of removal; US FDA requires those to be counted as in-treatment. The 6 pregnancies were not categorized by weight. Report also provides post-marketing surveillance data. Method failures are shown in a Figure by body weight (10 kg groups) without actual counts or percentages.
Sivin 1988	Data appeared to overlap those in Gu 1995 .
Sivin 1997b	Insufficient data on weight; only mean weight was reported.
Sivin 2000	Data appeared to overlap those in Sivin 1997a .
Weisberg 1999	Insufficient data on weight; no cutoffs or percent of sample provided.

Characteristics of ongoing studies [ordered by study ID]

NCT00724438

Trial name or title	Pharmacokinetics of Implanon in Obese Women
Methods	Observational, cohort, prospective
Participants	18 women: obese, body mass index (BMI) >30; or normal weight, BMI <25
Interventions	Implanon; 6-month duration
Outcomes	Primary: pharmacokinetic profile. Secondary includes discontinuation rates and reason for discontinuation (which should include pregnancy).
Starting date	July 2008
Contact information	AB Neustadt, University of Chicago, aneustadt@babies.bsd.uchicago.edu
Notes	Estimated completion for primary outcome: Aug 2009

DATA AND ANALYSES

Comparison 1. COC: Norgestimate 180/215/250 µg/ EE 25 or norethindrone acetate 1mg/EE 20 µg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy by BMI (kg/m ²)	1	2810	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [1.01, 3.61]
2 Pregnancy by weight (kg)	1	2810	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.66, 2.61]
3 Relative risk of pregnancy by body weight or BMI			Other data	No numeric data
4 Breakthrough bleeding or spotting with NGM/EE (cycle 6): weight (lb) >155 versus <=123	1	745	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.56, 1.43]
5 Breakthrough bleeding or spotting with NGM/EE (cycle 6): weight (lb) >155 versus 124 to 155	1	1135	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.67, 1.52]
6 Breakthrough bleeding or spotting with NGM/EE (cycle 13): weight (lb) >155 versus <=123	1	745	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.26, 0.83]
7 Breakthrough bleeding or spotting with NGM/EE (cycle 13): weight (lb) >155 versus 124 to 155	1	1135	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.32, 0.94]
8 Breakthrough bleeding or spotting with NETA/EE (cycle 6): weight (lb) >155 versus <=123	1	520	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.43, 1.01]
9 Breakthrough bleeding or spotting with NETA/EE (cycle 6): weight (lb) >155 versus 124 to 155	1	783	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.53, 1.13]
10 Breakthrough bleeding or spotting with NETA/EE (cycle 13): weight (lb) >155 versus <=123	1	520	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.43]
11 Breakthrough bleeding or spotting with NETA/EE (cycle 13): weight (lb) >155 versus 124 to 155	1	783	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.78, 1.91]

Comparison 2. Skin patch: norelgestromin 150 µg + EE 20 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancies by body weight decile			Other data	No numeric data

Comparison 3. Vaginal ring: levonorgestrel 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation rate due to pregnancy at 12 months by body weight			Other data	No numeric data
2 Pregnancy life-table rates by body weight			Other data	No numeric data

Comparison 4. Implant: 6-rod levonorgestrel 216 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cumulative pregnancy rates per 100 women by body weight			Other data	No numeric data
2 Annual pregnancy rates per 100 women by body weight			Other data	No numeric data

Comparison 5. Implant: 2-rod levonorgestrel 150 mg (original or with new elastomer)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancies by body weight			Other data	No numeric data
