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Combined hormonal contraceptive (CHC) use among obese women and contraceptive effectiveness: a systematic review

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Abstract

Objective: To evaluate from the literature whether combined hormonal contraception (CHC), including combined oral contraception pills (COCs), transdermal patch, vaginal ring or combined injectables, have different effectiveness or failure rates by body weight or body mass index (BMI).

Study design: We searched PubMed and the Cochrane Library databases for all articles in all languages published between inception and February 2016, for evidence relevant to body weight or BMI, CHC use and contraceptive effectiveness. The quality of each individual study was assessed using the system for evaluating evidence developed by the United States Preventive Services Task Force.

Results: From 2874 articles, we identified 15 reports for inclusion, all of fair to poor quality. Fourteen studies measured the association of obesity status and contraceptive failure among COC users. Three fair quality and one poor quality study reported increased COC failure among a heterogeneous population of overweight and obese women compared with normal weight women, while eight fair quality and two poor quality studies did not find an association. Two fair quality studies reported on contraceptive transdermal patches. One pooled analysis described a higher proportion of pregnancies among women using the patch who weighed ≥90 kg; another secondary analysis suggested BMI>30 was associated with increased failure. No studies directly compared contraceptive effectiveness using the combined vaginal ring or combined injectable.

Conclusion: Current available evidence addressing the risk of CHC failure in obese compared to normal weight women is limited to fair and poor quality studies. Studies of COCs show mixed results, though absolute differences in COC failure by body weight and BMI are small. Based on limited evidence, it appears that increasing body weight and BMI may contribute to decreasing contraceptive patch effectiveness.

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Keywords

Combined hormonal contraception; Obesity; Contraceptive effectiveness; Oral contraception

1. Introduction

The latest global estimates from the World Health Organization (WHO) note that more than 1.9 billion adults were overweight [body mass index (BMI) ≥ 25 kg/m^2] in 2014; 13% of these individuals were obese (BMI≥30 kg/m^2) [1]. Worldwide, 40% of all pregnancies are unintended (mistimed or unwanted) [2]. While unintended pregnancy carries significant public health consequences for all women, women with obesity are at higher risk for a number of pregnancy-related complications, including preeclampsia, gestational diabetes, spontaneous abortion, venous thromboembolic disease, pregnancy-induced hypertension and cesarean delivery [3–5]. Access to safe and effective contraception is therefore particularly important for women with obesity when they do not desire pregnancy.

Both the WHO and the United States (US) Medical Eligibility Criteria for Contraceptive Use consider combined hormonal contraceptives (CHCs) Category 2 for obesity (advantages generally outweigh theoretical or proven risks) [6,7]. Despite their safety, there is some concern that the effectiveness of CHCs may vary by body weight or BMI through alterations in steroid hormone pharmacokinetics, potentially exposing obese women to a higher risk of contraceptive failure and unintended pregnancy than normal weight women using the same methods [8]. The objective of this systematic review is to determine whether reproductive age women who are overweight or obese and using combined hormonal contraception (HC) (pill, patch, ring or combined injectables) have an increased risk of decreased contraceptive effectiveness compared to normal weight users.

2. Materials and methods

2.1. Evidence retrieval

We conducted this systematic review according to PRISMA guidelines [9]. We searched the PubMed and Cochrane Library databases for articles (in all languages) published in peer-reviewed journals from inception through February 2016, for evidence relating to CHCs, body weight or BMI and pregnancy rates (Appendix A). We hand-searched reference lists from articles identified by the search, as well as key reviews, to identify additional articles. We did not attempt to identify unpublished studies or abstracts from scientific conferences or contact any experts in the field. Both individual studies and pooled analyses were included, though any studies included in pooled analyses were not included individually. Previously published systematic reviews that did not pool data were examined for relevant articles but were excluded from this review.

2.2. Study selection

We were interested in including direct evidence to answer the following PICO-formatted question: Among reproductive age women who are overweight or obese, do those who use combined HC have an increased risk of decreased contraceptive effectiveness compared

to normal weight users? We reviewed titles and abstracts, as well as the full article when necessary, to identify studies that included rates of pregnancy among CHC users according to body weight or BMI categories. While WHO defines obesity as having a BMI≥30 kg/m^2, we gathered evidence that used other BMI or weight cutoff values as well. CHCs were defined as contraceptive methods containing estrogen and a progestogen, including pills, patches, rings and combined injectables; studies of formulations under investigation were included only if they have since been approved by the Food and Drug Administration (FDA). We included a number of studies describing women using "oral contraceptives" (OCs) without further detail on the type or dose of pill. In these studies, we presume that "OCs" include both combined oral contraceptives (COCs) and progestogen-only pills (POPs); however, we also presume that the proportion of women using POPs is fairly small [10]. We excluded studies that only used ovulation or pharmacokinetic measures as surrogate markers for risk of pregnancy.

2.3. Study quality assessment

The quality of each individual study was assessed using the system for grading evidence developed by the United States Preventive Services Task Force [11]. Evaluation criteria included study design, sample size and representativeness, maintenance of comparable groups, extent of loss to follow up (LTFU), rigor and completeness of exposure and outcome measurements and adjustment for potential confounders.

2.4. Data synthesis

All authors participated in summarizing and systematically assessing the evidence through the use of standard abstraction forms. We did not calculate summary statistics due to heterogeneity between the studies with regard to study population, exposure measurement, BMI or body weight categorization, control selection and outcome.

3. Results

We identified a total of 2874 articles, of which 15 reports met the selection criteria (Table 1). Fourteen studies provided direct evidence for COCs (two pooled analyses and 12 individual studies) [12–25], and two provided direct evidence for patch users (both pooled analyses) [12,26]. No studies reported on specific risks for contraceptive failure among obese or overweight contraceptive vaginal ring or injectable users.

3.1. Pooled analyses of COCs (Table 2)

A recently published Level II-2 fair quality analysis pooled individual level participant data derived from Phase 3 clinical trials submitted to the US FDA between 2000 and 2012 [12]. Eligible studies needed to have a minimum sample size of 200, include at least 10% obese women or 100 obese subjects for analysis and a duration of CHC use for at least six 28-day cycles. When multiple dose levels of the same estrogen/progestin were studied, only results from the lowest dose formula were included. Typical clinical trials were multicenter, open-label and noncomparative; only information from the relevant drug arm was included. Inclusion and exclusion criteria were generally similar and studies enrolled women aged 18–49 years at risk for pregnancy (able to become pregnant, sexually active

with a male partner). Data from seven COC clinical trials were included in the pooled analysis (n=14,024). The pooled pregnancy rate (Pearl index: PI) for obese COC users was 3.14 [95% confidence interval (CI): 2.33–4.22] and for nonobese users was 2.53 (1.88–3.41). For all of the individual studies, no significant association was observed between obesity and pregnancy rates when comparing obese COC users with nonobese COC users, with adjustment for age and race. However, when these data were pooled, obese women had a 44% higher relative risk (RR) for pregnancy compared with nonobese COC users (adjusted hazards ratio: 1.44; 95% CI: 1.06–1.95).

A Level II-2 fair quality prospective pooled analysis of six noninterventional trials conducted in Germany included 60,508 adolescent and adult women users of a COC containing 2-mg chlormadinone acetate (CMA) and 30 mcg of ethinyl estradiol (EE); 2.6% of the sample had a BMI>30 kg/m^2 [13]. Of the 85 pregnancies reported, the authors concluded that 19 were among women with regular COC intake (no missed pills). Obese users had both a low practical (reflecting total pregnancies during treatment) and theoretical (reflecting only pregnancies attributed to method failure) PI, similar to users with a BMI<30 kg/m^2, suggesting no association between BMI and contraceptive failure.

3.2. Individual studies of COCs (Table 3)

Three Level II-2 fair quality large, prospective cohort studies conducted across Europe and the US generally noted little variation in contraceptive effectiveness according to body weight or BMI [14–16]. The Oxford Family Planning Association contraceptive study enrolled 17,032 women of reproductive age between 1968 and 1974, and follow-up ended in 1994 [16]. Ninety-five accidental pregnancies occurred during 48,692 woman–years of COC use (0.20 per 100 woman–years, 95% CI: 0.16–0.24). The investigators reported no association between COC failure rate and increasing body weight, adjusting for age and parity across six body weight categories.

The European Active Surveillance Study on Oral Contraceptives (EURAS-OC) and International Active Surveillance of Women Taking Oral Contraceptives (INAS-OC) shared similar study designs and included 58,674 women initiating COCs (new users, restarters and switchers) recruited from seven European countries (EURAS-OC) beginning in 2000 who contributed 142,475 woman–years of observation and 52,218 women from the US (INAS-OC) beginning in 2005 contributing 73,269 woman–years of observation, respectively [14,15]. In EURAS-OC, authors reported little variation in the crude estimate of contraceptive failure according to BMI categories (BMI<20.0, 20.0–24.9, 25.0–29.9 and≥30) among all COC users. EURAS-OC also presented results for contraceptive failure according to obesity status for individual COC formulations containing desogestrel (DSG), dienogest (DNG), drospirenone (DRSP), levonorgestrel (LNG) and CMA. Only obese (BMI≥30 kg/m^2) users of CMA experienced statistically significant differences in contraceptive failure compared with women of lower BMI (p=.03) [15]. In a US population, INAS-OC noted that women with a BMI≥35 kg/m^2 were at increased risk for contraceptive failure compared to women with a BMI<35 kg/m^2 [hazard ratio (HR) 1.5, 95% CI: 1.3–1.8], when controlling for age, parity and educational level but did not report results separately for each COC formulation by progestogen [14].

Of the six retrospective cohort studies that met inclusion criteria [17–21,23], five Level II-2 fair quality studies reported no association between increasing body weight or BMI and decreasing COC effectiveness. Using survey data from 1916 women, ages 15 to 44 years, who reported using OCs and who completed both the 1993 US National Health Interview Survey and the 1995 US National Survey of Family Growth (NSFG), no significant association between OC failure rate and either BMI or body weight was found, after adjusting for age, marital status, educational level, poverty, race/ethnicity, parity and dual method use [23]. This analysis was subsequently repeated using data from the 2002 NSFG, and no association between BMI and OC failure rates was observed [21]. Nakajima et al. performed a retrospective cohort analysis from a large, multicenter open-label Phase 3 trial of an ultra low-dose COC [10-mcg EE/1-mg norethin-drone acetate (NETA); 24/2/2 dosing regimen with 24 active days, 2 days 10-mcg EE, 2 days ferrous fumarate] and noted that women with a higher BMI did not have decreased COC efficacy [18]. Westhoff et al. performed a retrospective cohort analysis of data from a large, multicenter open-label Phase 3 trial of an 84/7 extended regimen COC containing 100-mcg LNG and 20-mcg EE plus 10-mcg EE and reported a total of 36 pregnancies among 1736 women over a treatment period of up to 1 year [19]. Dichotomous comparisons by weight and BMI as well as distributions across weight and BMI deciles did not show a difference in crude pregnancy rates. Burkman et al. investigated 2810 women participating in a large, randomized, multicenter trial who used either a multiphasic COC [180/215/250 mcg of norgestimate (NGM) and 25-mcg EE] or a monophasic COC (1-mg NETA and 20-mcg EE); there were 39 pregnancies during 6 to 13 cycles of treatment [20]. Overall, there was no significant association between increasing weight or BMI and risk for pregnancy; however, the median BMI in both groups was 23 kg/m^2, and participants with a BMI greater than 32.4 kg/m^2 were excluded from the original study. A poor quality retrospective cohort study reported results referencing only body weight, not BMI [17]. There were 106 reported pregnancies during 2822 woman–years of OC use, for a rate of 3.8 per 100 woman–years among 618 women recruited between 1990 and 1994 as controls for a study on functional ovarian cysts and neoplasms. Women in the highest quartile of body weight (≥70.5 kg) had an increased risk of pregnancy with OC use compared to women in the lower three quartiles [RR 1.6, 95% CI: 1.1–2.4, adjusted for parity]. The authors also reported results when stratified by estrogen dose and noted a dose–response relationship between decreasing estrogen dose and increasing RR for contraceptive failure among women in the highest quartile of body weight.

One poor quality Level II-2 case–cohort study conducted in the US used data from two different population-based surveys [22]. Cases included 153 women with a recent live birth, who indicated OC use at the time of conception and responded to the Pregnancy Risk Assessment Monitoring System survey. The comparison cohort included 205 women using OCs who responded to the Behavioral Risk Factor Surveillance System survey. While the point estimates for the higher BMI groups were slightly elevated [odds ratio (OR) 1.9 for BMI 25–29.9 and OR 1.6 for BMI≥30, with BMI 20–24.9 as the referent group], all CIs included 1.0.

Two Level II-2 fair to poor quality case–control studies reported mixed results [24,25]. One examined 248 cases who became pregnant while using OCs and 533 age-matched controls who were nonpregnant OC users, all of whom were enrolled in a US health maintenance

organization [25]. Women with a BMI>27.3 kg/m^2 were 1.6 times (95% CI: 1.1–2.2) as likely to become pregnant while using OCs as those with lower BMIs. Among consistent users (those who missed no OCs in the reference month), the OR was 2.2 (95% CI: 1.38–3.4). Similarly, consistent OC users with body weight>74.8 kg were 1.7 times (95% CI: 1.1–2.7) as likely to become pregnant while using OCs as women with lower body weights. No interaction was observed between BMI or body weight with the type or dose of OCs.

A second study using data from the UK General Practice Research Database included 1129 cases of women with an unintended pregnancy within 6 months of a prescription for a CHC (various COCs, POPs and patch) [24]. Most cases and controls were prescribed COCs (>75%) and POPs (between 10 and 20%); contraceptive patch users were negligible (<1%). Crude estimates for contraceptive failure were not associated with increasing BMI, the upper limit for comparison across four categories being BMI≥28 kg/m^2, and all methods were analyzed together. When adjusted for age, index year of pregnancy, contraceptive method, prior deliveries, prior abortions, smoking status, prior sexually transmitted disease, prior alcohol or drug abuse, antibiotic use, anticonvulsant use and recent delivery, the point estimates remained unchanged.

3.3. Pooled analyses of CHCs patch, ring and injectables (Table 4)

The previously discussed pooled analysis of Phase 3 clinical trials submitted to the US FDA between 2000 and 2012 included one trial of an EE/norelgestromin (NGMN) patch (n=1523) [12]. When adjusted for age and race, obese women exposed the patch were at increased risk for contraceptive failure [adjusted hazard ratio (aHR): 8.8, 95% CI: 2.5–30.5] [12].

In a Level II-2 fair quality pooled analysis of three multicenter, pivotal open-label studies of the EE/NGMN contraceptive patch (n=3319), 15 pregnancies were diagnosed during 6–13 cycles of follow-up. Five pregnancies occurred among women ≥90 kg; women of this weight constituted <3% of the study population. Ten pregnancies were diagnosed among women <90 kg. [26]. While results by BMI were not provided, the authors noted a significant association between baseline body weight and pregnancy (p<.001).

4. Discussion

The studies included in this review examined different CHC methods and used a variety of measures and cut points to examine associations between obesity status and contraceptive effectiveness, making interpretation across studies somewhat difficult.

A total of four studies of fair to poor quality identified an increased risk of contraceptive failure in obese compared to nonobese women. Two studies by Holt et al. with a high risk of misclassification bias suggested that overweight and obese women using COCs could experience up to a twofold risk of contraceptive failure compared to their normal weight counterparts. However, these studies relied on self-assessment of height and weight, recalled an average of 76.5 months after last OC use, and reported dichotomous outcomes using cut points that included a heterogeneous population of overweight and obese women [17,25]. A recent fair quality pooled analysis of seven Phase 3 FDA trials noted a statistically higher failure rate among obese women, though the magnitude of the difference (PI of 3.14 in obese

vs. 2.53 in normal weight users) may not be clinically important [12]. Likewise, this risk assessment may be biased due to limited control for confounding and pooling of data where women were exposed to different progestogen-containing formulations of COC. One fair quality study found an association between women with more extreme obesity (BMI≥35) and decreased COC effectiveness [14].

By contrast, all 10 remaining studies of fair and poor quality did not show this association. Three fair quality, large, population-based studies did not demonstrate an association with more detailed analyses of weight and BMI classes [15,21,23]. Fair quality observational studies that incorporated more rigorous methods for capturing measures of height and weight, validated pregnancy status and included measures of contraceptive adherence also did not report any increased risk for COC failure [13,18–20].

Two fair quality studies demonstrated a higher risk of contraceptive failure among combined hormonal transdermal patch users [12,26]. Women weighing ≥90 kg reported proportionally more pregnancies compared to those of lesser weight in a pooled analysis [26]. The pooled analysis by Yamazaki et al. noted a significantly increased risk for method failure among obese contraceptive patch users in one trial; however, the point estimate lacked precision [12]. No studies in this review directly compared contraceptive effectiveness among obese and nonobese contraceptive injectable or vaginal ring users.

Though several studies found increased risks of pregnancy with specific COC formulations, overall results were conflicting. One poor quality study found a dose response effect with estrogen dose (higher failure rates among overweight/obese users of pills containing ≤35-mcg EE) [17], while another fair quality study did not find this relationship [25]. One fair quality study found an increased risk of pregnancy with CMA; the authors provided a possible biologic mechanism for this association, noting that CMA is highly lipophilic and accumulates in adipose tissue which could lead to lower levels of systemic hormone in obese women [15]. However, a pooled analysis of six noninterventional trials evaluating contraceptive efficacy among women only using CMA-containing pills found no difference in performance by obesity status over a median of 5 to 6 cycles [13]. Burkman et al. found a significant association with contraceptive failure for COCs containing NETA/EE for women with BMI>25; however, this was not consistent in other subgroup analyses and may have been a chance finding [20]. Further, two other studies evaluating exposure to NETA/EE COC among obese and nonobese users did not find an association [12,18].

If there are true effects for certain subgroups of CHC users, it is important to consider the absolute effect. For example, Dinger et al. observed an overall contraceptive failure rate of 3% in the first year of COC use among a US study population and a significantly increased RR of 1.5 among women with BMI≥35 [14]. This leads to an estimated failure rate of 4.5% among women with a BMI≥35, still lower than typical failure rates for CHCs [36].

This systematic review included all studies of CHCs that reported pregnancy outcomes by BMI categories, including studies which pooled multiple pill formulations. A Cochrane review on hormonal contraceptive effectiveness in overweight and obese women only included studies that reported pregnancy rates for specific CHC formulations, resulting in

the exclusion of many studies that we included in this review, but allowing conclusions for each pill formulation [27]. Progestins may be differently affected by obesity based on their degree of protein binding [28,29, 30, 31, 32]. The pooled analysis by Yamazaki et al. reported a statistically higher failure rate in obese women after grouping data from five progestins [12], but it is possible that the clinical meaning of this difference was diluted by combining progestins with different degrees of sex hormone-binding globulin binding [33]. Likewise, other studies that did not specify pill formulations may have obscured a difference by grouping different pill types. We are unable to determine from current evidence if certain COC formulations or doses may be differently affected by obesity. Future studies in this area should clearly define dose and progestin and may benefit from studying heavily protein-bound progestins such as LNG, which may be more susceptible to clinical differences by body type [29].

All of these studies suffer from similar limitations, including problems in the measurement of the exposure (body weight or BMI), measurement of the outcome (CHC failure) and measurement of potential confounders. In many cases, weight and height were self-reported [14–17,21–23,25]. Studies examining the validity of self-reported weight and height generally show that while there is some underestimation of weight and overestimation of height — leading to underestimation of BMI — the differences in self-reported and actual weight are generally small [34]. However, studies have found that overweight and obese women tended to underestimate their weight more than normal weight women. [34] A larger problem with the assessment of weight and height is the timing of collection of the information. The ideal measurement would be weight and height at the time of CHC failure; however, none of these studies asked women about weight and height at the time of CHC failure. A second limitation is that pregnancies were also self-reported in many studies [14–17,21,23]. Reports of unintended pregnancy are generally underestimated, especially those that end in abortion. While it is not known whether the outcome of unintended pregnancies differs by body weight, this is potentially an important source of bias. Most studies did not have information on adherence to COC regimens [14,17,20–23,25], and none reported the frequency of sexual intercourse. Again, we do not know whether these factors differ by body weight or BMI, but these are also a potential source for bias [35]. Although findings are mixed, it is possible that any effect of BMI on COC users may be limited to women of very high BMI. The majority of efficacy studies excluded women in the highest BMI categories or did not report on the proportion of women in these categories, thus it remains difficult to draw conclusions on contraceptive efficacy for women in the highest categories of obesity. Finally, only three of the included studies were adequately powered to address our primary outcome [14,15,19]; the remainder did not provide power calculations or were underpowered. An ideal study of this topic would be sufficiently powered to address the relatively rare outcome of CHC failure, objectively measure weight and BMI at the time of contraceptive failure, include women with a wider range of weight and BMI, particularly those at higher extremes, and prospectively collect information on contraceptive failure.

5. Conclusion

Current available evidence addressing the risk of CHC failure in obese compared to normal weight women is limited to fair and poor quality studies. Ten of 14 studies of COCs did not

report a difference in effectiveness by body weight or BMI, and the magnitude of difference in COC failure reported in the remaining four studies is small. There is scant and conflicting evidence on the association between contraceptive failure and the highest subgroups of BMI and whether failure rates vary by specific CHC formulations. Based on limited evidence, it appears that increasing body weight and BMI may contribute to decreasing EE/NGMN contraceptive patch effectiveness. No direct evidence regarding the contraceptive ring or injectable was identified.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the World Health Organization or Centers for Disease Control and Prevention.

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Table 1

Summary of evidence.

Author, year	Study design	Exposures	Size*	Outcomes	Result	Quality
Pooled analyses						
Yamazaki, 2015	Pooled analysis of 7 new drug applications submitted to FDA	Various COCs	11,317 nonobese 2707 obese	RR of pregnancy BMI<30 vs. ≥30	aHR 1.44 (1.1–1.95)	Fair
Schramm, 2011	Pooled analysis of 6 trials	COCs with EE/CMA	60,508 women 2.6% obese	PI BMI<30 vs. ≥30	No difference	Fair
Individual COC studies						
Vessey, 2001	Prospective cohort	Various COCs	17,032 women	COC failure per 100 woman–years by body weight	No difference	Fair
Dinger, 2009	Prospective cohort	Various COCs	58,674 women	HR for COC failure by BMI	No difference	Fair
Dinger, 2011	Prospective cohort	Various COCs	52,218 women 23.1% obese	HR for COC failure BMI<35 vs. ≥35	aHR 1.5 (1.3–1.8)	Fair
Brunner, 2005	Retrospective cohort	Various COCs	1916 women	HR for COC failure by BMI and weight	No difference	Fair
Brunner Huber, 2007	Retrospective cohort	Various COCs	1301 women	HR for contraceptive failure by BMI	No difference	Fair
Nakajima, 2016	Retrospective cohort	EE/NETA	1581 women 28.3% overweight 18% obese	PI BMI<25, 25–30, >30	No difference	Fair
Westhoff, 2012	Retrospective cohort	EE/LNG	1736 women 50.6% overweight or obese	Crude pregnancy rate by BMI and weight	No difference	Fair
Burkman, 2009	Retrospective cohort	Various COCs	2810 women 31.2% overweight or obese	RR of pregnancy BMI≤27.3 vs. >27.3 Weight<70 vs. ≥70 kg	No difference	Fair
Holt, 2002	Retrospective cohort	Various COCs	618 women 24.9% over 70.5 kg	RR of pregnancy Weight<70.5 vs. ≥70.5 kg	aRR 1.6 (1.1–2.4)	Poor
Brunner Huber, 2006	Case cohort	Various COCs	153 COC failure pregnancies 205 control COC users	OR for COC failure by BMI	No difference	Poor
Holt, 2005	Case control	Various COCs	248 COC failure pregnancies, 533 control COC users	OR for COC failure BMI<27.3 vs. >27.3 Weight<74.8 vs. >74.8 kg	OR BMI: 2.17 (1.38–3.41) OR weight: 1.71 (1.08–2.71)	Fair
Jick, 2009	Case control	Various COCs	1129 COC failure pregnancies, 4374 control COC users	OR for unintended pregnancy by BMI	No difference	Poor
Individual studies of contraceptive patch						
Yamazaki, 2015	Single study within pooled analysis	EE/NGMN patch	1371 nonobese 152 obese	aHR for pregnancy BMI<30 vs. ≥30	aHR: 8.8 (2.54–30.5)	Fair

Author, year	Study design	Exposures	Size*	Outcomes	Result	Quality
Zieman, 2002	Pooled analysis of 3 studies	EE/NGMN patch	3319 women	Contraceptive failure Weight<90 vs. >90 kg	Association between body weight and pregnancy p<.001	Fair

Abbreviations: aRR: adjusted relative risk.

*If proportion/number of obese subjects is not listed, this information was not reported in the paper.

Table 2

Evidence from pooled analyses regarding body weight or BMI and COC failure.

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Quality
Yamazaki et al., 2015 [12] US FDA US	Various COCs EE≤30 mcg	Pooled analysis of individual participant data from 7 Phase 3 clinical trials from COC New Drug Applications to FDA, 2000–2012	Nonobese=11,317 Obese=2707 Proportion of obese women and average BMI varied across trials (range:8.5–29.9%, p<.001; and 23.7–27.7 kg/m^2, p<.01)	Pooled direct-weighted PI: Obese (BMI≥30): 3.14, 95% CI: (2.33–4.22) Nonobese: 2.53, 95% CI: (1.88, 3.41) Pooled Incidence Direct-Weighted IRR: 1.37, 95% CI: (1.02, 1.84) Pooled Mantel–Haenszel IRR: 1.43. 95% CI: (1.07, 1.92) Effect of obesity on pregnancy rate in COC trials Adjusted HR by fixed effects model: 1.44, 95% CI: (1.06, 1.95) (Nonobese reference group, HR adjusted for age and race) I^2 statistics for seven trials 0% (p<.1), no observed heterogeneity	Large sample size Pregnancy confirmed by urine or serum pregnancy test Conception calculated to time during HC use or within 7 days of stopping	No information on frequency of intercourse or adherence to method Unclear reporting of BMI (median and range or mean and SD) Combined data from multiple progestins Power not addressed	II-2 Fair
Schramm et al., 2011 [13] Support from Grunenthal GmbH Germany	COC containing 2 mg CMA and 0.03 mg EE	Pooled analysis of 6 noninterventional trials conducted 1999 to 2007	60,508 adult and adolescent women 2.6% of the sample was obese (BMI<30 kg/m^2)	**Pearl Index (PI) by BMI (kg/m2)** BMI* / Total pregnancy / Pregnancy regular intake / PI (practical) / PI (theoretical) <20 / 28 / 7 / 0.51 / 0.13 20-25 / 39 / 10 / 0.25 / 0.06 25-30 / 12 / 2 / 0.41 / 0.07 > 30 / 2 / 0 / 0.96 / 0.00 <30 / 79 / 19 / 0.33 / 0.08 ≥30 / 2 / 0 / 0.34 / 0.00 BMI information not available for 4 pregnancies Summary statistics not performed * Report does not indicate which group includes BMI of 25.	Measured height and weight Validated pregnancies 2 of 6 trials provided data on contraceptive adherence	No information on frequency of intercourse Median duration of COC use 5 to 6 cycles Power not addressed	I I - 2, fair

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Quality
				Combined statistics not performed. Heterogeneity assessment not reported.			

IRR = incident rate ratios.

Table 3

Evidence from individual studies regarding body weight or BMI and COC failure.

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit
Vessey et al., 2001 [16] Medical Research Council United Kingdom	Various COCs	Prospective cohort 48,692 woman–years of follow-up Secondary analysis of Oxford Family Planning Association study	17,032 women, ages 25–39 years, recruited between 1968 and 1974 Proportion of overweight or obese women in the sample not stated.	**COC failure rates per 100 women-years (95% CI)** **Body weight (kg)** < 51: 0.24 (0.14-0.38) 51-57: 0.21 (0.15-0.30) 58-64 *: 0.20 (0.13-0.28) 64-70 *: 0.15 (0.08-0.27) 70-76 *: 0.08 (0.01-0.28) ≥77: 0.21 (0.04-0.61) p for trend: 0.14 * Report does not indicate which groups include 64 and 70kg	Cohort study with large sample size and long follow-up Relatively low loss to follow-up (~4 women per 1000 per year) Adjusted for age and parity	Self-report of pregnancy, likely underreporting of pregnancies ending in abortion No information on how body weight was assessed No information on frequency of intercourse or adherence to method Power not addressed	II-2, fair
Dinger et al., 2009 [15] Bayer, Schering Pharma AG Berlin, Germany Europe	Various COCs	Prospective cohort Secondary analysis of EURAS-OC	58,674 women contributing 142,475 woman–years of observation New COC users and switchers to new COC between Nov. 2000 and 2005	Though risk estimates and 95% CI: for oral contraceptive failure by BMI were not stated, the oral contraceptive failure rate per 100 woman–years by BMI depicted graphically across four categories of BMI (<20.0, 20.0–24.9, 25.0–29.9, and ≥30) demonstrated little difference. Crude hazard ratio for contraceptive failure by BMI for all COC formulations: 1.00; 95% CI, 0.98–1.03 Little variation in contraceptive failure and BMI across COC formulations containing DSG, DNG, DRSP or LNG. Contraceptive failure with COCs containing CMA correlated with BMI: obesity (≥ 30 kg/m^2) associated with increased risk of failure (p=.028)	Large, population-based sample Detailed information on contraceptive use Up to 5-year follow up with biannual self-administered questionnaire: 2.4% LTFU Adequately powered	Self-report of pregnancy, likely underreporting of pregnancies ending in abortion Weight and height self-reported Crude risk estimates, no control for confounding No information on frequency of intercourse Contraceptive failures include true failures and those from COC nonadherence.	II-2, fair

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit
Dinger et al., 2011 [14] Bayer Schering Pharma US	Various COCs	Prospective cohort Secondary analysis of INAS-OC	52, 218 women with 73,269 women–years of observation New COC users and switchers to new COC between Aug. 2005 to July 2008 23.1% of study participants were obese.	**Adjusted hazard ratios (95%CI) for OC failure overall** **BMI (kg/m^2)** — **Adjusted HR (95% CI)** <35.0 — Ref (1.0) ≥ 35.0 — 1.5 (95% CI, 1.3-1.8) **Risk of contraceptive failure for 24/4 regimen of drospirenone/EE compared with 21/7 regimen of other progestogens** **BMI (kg/m^2)** — **HR (95% CI)** <25 — 0.7 (0.6-0.8) ≥ 25 — 0.7 (0.6-0.9)	Large, population-based sample Adjusted for age, parity and educational level Up to 5-year follow up with biannual self-administered questionnaire: 7.4% LTFU Adequately powered	Self-report of pregnancy, likely underreporting of pregnancies ending in abortion Weight and height self-reported No information on frequency of intercourse Contraceptive failures include true failures (14%) and those from COC nonadherence (86%).	II-2, fair
Brunner et al., 2005 [23] Support not stated US	Various COCs, presumed to include POPs	Retrospective cohort 1995 US NSFG	1916 women ages 15–44 years, interviewed in 1995	**BMI (kg/m2)** — **n(%)** — **Adjusted HR(95%CI)** < 20 — 398 (25.7) — 0.59 (0.32-1.07) 20-24.9 — 888 (51.9) — 1.0 (referent) 25-29.9 — 337 (15.9) — 0.73 (0.42-1.28) ≥ 30 — 140 (6.5) — 1.51 (0.81-2.82) **Weight (lbs)** — **n(%)** — **Adjusted HR (95%CI)** 80-110 — 203 (13.0) — 0.89 (0.45-1.77) 111-130 — 660 (39.9) — 1.0 (referent) 131-150 — 506 (28.0) — 1.00 (0.55-1.81) 151-170 — 186 (9.4) — 0.99 (0.53-1.83) 171-190 — 127 (5.8) — 1.09 (0.45-2.64) >190 — 81 (3.8) — 1.10 (0.45-2.68)	Large, population-based sample Detailed information on contraceptive use Adjusted for age, marital status, education, poverty, race/ethnicity, parity, dual method use	Self-report of pregnancy, likely underreporting of pregnancies ending in abortion Weight and height self-reported, up to two years prior to pregnancy No information on contraceptive adherence or frequency of intercourse Power not addressed	II-2, fair

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit
Brunner Huber et al., 2007 [21] Support not stated US	Various COCs, presumed to include POPs	Retrospective cohort 2002 US NSFG	1301 women ages 15–44 years, who were using OCs as of January 1999	**Adjusted hazard ratios (95%CI) for OC failure** **BMI (kg/m2) / n(%) / Adjusted HR (95%CI)** < 20 / 145 (12.8) / 1.28 (0.55-2.98) 20-24.9 / 589 (46.3) / 1.0 (referent) 25-29.9 / 321 (23.3) / 0.93 (0.56-1.53) ≥ 30 / 246 (17.6) / 1.35 (0.79-2.30) Note: % are weighted and may not add to 100 because of rounding	Large, population-based sample Detailed information on contraceptive use Adjusted for age, race/ethnicity, parity	Self-report of pregnancy, likely underreporting of pregnancies ending in abortion Weight and height self-reported, up to two years prior to pregnancy No information on contraceptive adherence or frequency of intercourse Power not addressed	II-2, fair
Nakajima et al., 2016 [18] Actavis, Inc. US	1.0 mg NETA/10-mcg EE	Retrospective cohort analysis of large, multicenter Phase 3 trial	1581 participants, 18–45 years Proportion of women of normal weight: 53.7%, overweight: 28.3%, obese: 18.0% Five women had BMI>35, though this was an exclusion criterion for the study	**BMI group / N / Preg / Cycles / Pearl Index (95% CI)** 18-35 yo <25 / 707 / 16 / 6806 / 3.06 (1.75-4.96) 25-30 / 346 / 8 / 3419 / 3.04 (1.31-5.99) >30 / 219 / 4 / 2081 / 2.50 (0.68-6.39) 18-45 yo <25 / 840 / 16 / 8353 / 2.49 (1.42-4.04) 25-30 / 435 / 8 / 4484 / 2.32 (100-4.57) >30 / 279 / 4 / 2753 / 1.89 (0.51-4.83) No pregnancies occurred in 3759 at risk cycles in women 36-45 years of age	Weight measured at baseline and at final visit Pregnancy testing at baseline and follow-up Contraceptive adherence measured by pill count and diaries; reported similar across BMI groups Regular follow-up visits	Height self-reported No information on frequency of intercourse 57% of enrolled sample completed original study Power not addressed	II-2, fair
Westhoff et al., 2012 [19] Duramed Research/ Teva US	84/7 extended regimen COC containing 100-mcg LNG/20-mcg EE+10-mcg EE	Retrospective cohort analysis of large, multicenter, open-label phase III trial	1736 women, ages 18–35 years 44.4% of sample with weight≥70 kg; 50.6% of sample with BMI≥25 kg/m^2.	**Baseline weight / Crude pree rate / 95% CI** <70kg / 1.97% / (1.19-3.05)	Baseline height and weight measured Contraceptive adherence measured by pill count and diaries Pregnancy testing mandatory at baseline and follow-up Ultrasound to	No information on frequency of intercourse Crude pregnancy rates include true failures and those from COC nonadherence.	II-2, fair

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit
					estimate conception date when available. Adequately powered		

Baseline weight	Crude pree rate	95% CI
≥70kg	2.21%	(1.29-3.51)
BMI (kg/m^2)		
< 25	2.22%	(1.34-3.44)
≥ 25	1.94%	(1.13-3.08)

Pregnancy distribution and crude rate of pregnancy across weight and BMI deciles

Weight (kg)	Crude Preg rate	BMI (kg/m^2)	Crude Preg rate
≤ 53.2	1.1%	≤20.2	0.6%
>53.2-57.3	3.1%	>20.2-21.3	1.7%
>57.3-60.9	1.7%	>21.3-22.6	3.5%
>60.9-64.1	1.7%	>22.6-23.8	2.3%
>64.1-67.7	3.5%	>23.8-25.1	2.9%
>67.7-71.8	0.6%	>25.1-26.6	0.0%
>71.8-78.2	1.6%	>26.6-28.7	2.4%
>78.2-85.5	2.4%	>28.7-31.7	2.9%
>85.5-99.5	2.9%	>31.7-36.0	1.7%
>99.5-173.2	2.4%	>36.0-59.8	2.9%

Burkman et al., 2009 [20] Ortho-Mcneil Janssen Scientific Affairs US and Canada	Multiphasic and monophasic COCs 13 cycles	Retrospective cohort	2810 women, ages 18 to 45 years *n*=1671 NGM/EE *n*=1139 NETA/EE 25.3% of sample> 70 kg; 31.2% of sample BMI> 25 kg/m^2, max 32.4. Proportion of obese women not stated.		Baseline height and weight measured Validated pregnancies with serum test and sonography	No information on frequency of intercourse Limited participation to maximum BMI of 32.4 kg/m^2 Underpowered	II-2, fair

Body weight	RR (95% CI)	BMI	RR (95% CI)
< 70 kg	1.0 Ref	< 25	1.0 Ref
≥70 kg	1.25 (0.63-2.46)	≥25	1.84 (0.98 – 3.45)

BMI	RR (95% CI)
All COCs	
≤ 27.3	1.0 Ref

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit
				BMI / **RR (95% CI)**: > 27.3 / 1.18 (0.54-2.57) **NGM/EE** / **NETA/EE**: < 27.3 / 1.0 Ref; ≤ 27.3 / 1.0 Ref; > 27.3 / 1.41 (0.51-3.89); > 27.3 / 0.97 (0.28 – 3.33)			
Holt et al., 2002 [17] NIH US	Various OCs, including both COCs and POPs	Retrospective cohort	618 woman, ages 18–39, recruited between 1990 and 1994 Women weighing>70.5 kg accounted for 24.9% of the sample.	RR of accidental pregnancy ≥70.5 kg vs. <70.5 kg All COCs: 1.6 (95% CI: 1.1–2.4) <35-mcg EE: 4.5 (95% CI: 1.4–14.4) <50-mcg EE or <80-mcg mestranol: 2.6 (95% CI: 1.2–5.9) 50-mcg EE or>80-mcg mestranol: 1.2 (95% CI: 0.4–3.5)	Adjusted for age, parity, race, religion, menstrual cycle regularity	Self-report of pregnancy, likely underreporting of pregnancies ending in abortion Weight self-reported an average of 76.5 months after OC use No information on contraceptive adherence or frequency of intercourse Power inadequately addressed	II-2, poor
Brunner Huber et al., 2006 [22] Support not stated South Carolina, US	Various COCs, presumed to include POPs	Case–Cohort	Cases: 153 women delivering a live-born infant, using OCs at the time of conception Cohort: 205 women between the ages of 18 and 45, using OCs	**Adjusted OR (95% CI) for OC failure** **BMI (kg/m2)** / **Cases** / **Cohort** / **Adjusted HR (95% CI)** < 20 / 31 (18.4) / 39 (20.3) / 1.07 (0.31-3.73) 20-24.9 / 50 (30.1) / 102 (48.3) / 1.0 (referent) 25-29.9 / 44 (35.5) / 45 (22.4) / 1.87 (0.73-4.78) ≥ 30 / 28 (16.0) / 19 (19.1) / 1.58 (0.49-5.10) < 25 / 1.0 (referent) > 25* / 1.90 (0.82-4.41) * Report does not indicate which group includes 25 kg/m2	Adjusted for education, race/ ethnicity, income; dichotomous BMI also adjusted for age	Self-reported prepregnancy weight and height Exclusion of pregnancies not ending in live birth No information on contraceptive adherence or frequency of intercourse Power not addressed	II-2, poor

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit
Holt et al., 2005 [25] NIH US	Various COCs, presumed to include POPs	Case–Control	Cases: 248 women, ages 18 and older who filled OC prescription and experienced pregnancy Controls: 533 women, ages 18 and older who filled OC prescription between 1998 and 2001	**BMI (kg/m2)** / **Cases** / **Controls** Consistent users ≤ 27.3 / 80 (57.9) / 292 (76.6) > 27.3 / 58 (43.1) / 89 (24.4) **Weight (kg)** / **Cases** / **Controls** Consistent users ≤ 74.8 / 90 (65.2) / 299 (78.4) > 74.8 / 48 (34.8) / 82 (21.6) **OR (95% CI) for OC failure:** **BMI (kg/m2)** Consistent users < 27.3 vs > 27.3 / 2.17 (1.38-3.41) **Weight (kg)** Consistent users < 74.8 vs > 74.8 / 1.71 (1.08-2.71)	Validated pregnancies Measured consistency of COC use, excluded women who missed more than 4 pills per month Adjusted for age, reference year, parity	Self-report of weight and height, although validated by medical record reports from an average of 22 weeks from the reference date All data from health maintenance organization database; outcomes may be underestimated if women sought care outside of network Power not addressed	II-2, fair
Jick et al., 2009 [24] Ortho-McNeil Janssen Scientific Affairs UK	Various COCs and POCs, few patch users	Case–Control	Cases: 1129 women with a prescription recorded after Jan. 1, 2003 with unintended pregnancy within 6 months of prescription Controls: 4374 women with at least one prescription recorded after Jan. 1, 2003	**BMI (kg/m2)** / **Cases n(%)** / **Controls n(%)** <20 / 111 (10) / 376 (8.5) 20-23 / 258 (23) / 942 (21) 24-27 / 164 (14.5) / 553 (12.5) 28+ / 123 (11.5) / 484 (11) **Risk of unintended pregnancy according to BMI**	Adjusted for age, index year, HC exposure, prior deliveries, prior terminations, smoking, BMI, prior STD, prior drug use, antibiotic use, anticonvulsant use and recent delivery	Contraceptive failure reflects unintended pregnancy among women prescribed, though not necessarily using, contraceptive method within 6 months of pregnancy. Pills and patch combined for analyses of failure by BMI Power not addressed	II-2, poor

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Qualit

BMI (kg/m2)	Cases n(%)	Controls n(%)
BMI (kg/m2)	**Crude OR (95%CI)**	**Adjusted OR (95%CI)**
<20	1.0	1.0
20-23	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
24-27	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
28+	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)

ORs for BMI reflect risk of pregnancy across all methods.

SD = standard deviation, POPs = progestogen-only oral pills.

Table 4

Evidence regarding body weight or BMI and nonoral contraceptive failure.

Author, year support location	Contraceptive method	Study design	Population	Results	Strengths	Weaknesses	Quality
Yamazaki et al., 2015 [12] US FDA US	EE/NGMN Patch	One study from a pooled analysis. Data from an application for a contraceptive patch to FDA, 2000–2012	Nonobese=1371 Obese=152	Adjusted HR for trial comparing obese to nonobese users (adjusted for age and race): 8.80 (95% CI: 2.54, 30.5)	Pregnancy confirmed by urine or serum pregnancy test Conception calculated to time during HC use or within 7 days of stopping	No information on frequency of intercourse or adherence to method Unclear reporting about BMI (median and range or mean and SD) Power not addressed	II-2, fair
Zieman et al., 2002 [26] RW Johnson Pharmaceutical Research Institute US, Canada and Europe	EE/NGMN Patch	Pooled analysis of 3 studies	3319 women, ages18–45 years	Contraceptive failure by body weight 15 pregnancies: 5 in women>90 kg (<3% of study population); 10 in women<90 kg (97% of study population) Significant association between baseline body weight and pregnancy (p<.001) Stated no association between body weight & pregnancy among women <90 kg	Large sample size	Pooled data from comparative and noncomparative studies Very limited data on efficacy by BMI LTFU unknown Power not addressed	II-2, fair