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Obesity and Oral Contraceptive Pill Failure

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Oral contraceptive pills (OCPs) are the most popular form of reversible contraception in the United States [1]. Most commonly used OCPs contain a combination of estrogen and progestin. However, the efficacy of OCPs is due primarily to the suppression of ovulation that results from the dose of progestin. Changes in the absorption, volume of distribution, metabolism, or excretion of a medication may change its pharmacologic potency. For some medications, the volume of distribution for a given dose in an obese individual is greater than the volume of distribution for a thinner individual. In addition, in obese patients, drugs that undergo phase II metabolism (or a conjugation reaction with glucuronic acid, sulfonates, glutathione or amino acids) tend to be metabolized more rapidly, thus shortening their duration of action [2]. Increasing body weight has been shown to change rates of estradiol metabolism in young women [3]. Time to reach steady state levels of levonorgestrel after ingestion appears to be twice as long among obese women compared with women of normal weight; therefore the interval until hypothalamic-pituitary-ovarian activity is suppressed may be lengthened, placing obese women at higher risk for ovulation [4].

Our goal is to summarize and evaluate the existing literature addressing the question of whether women with increased weight or Body Mass Index (BMI) have an increased risk of OCP failure compared with normal weight women. This is an issue of public health importance both because obesity is reaching epidemic proportions in the United States [5,6] and because pregnancy complications are more likely to occur among obese women than thinner women [7–12].

With the assistance of a trained research librarian, we searched electronic databases (PubMed, Google Scholar) for potentially pertinent articles that were published in English before November 2008. We combined various National Library of Medicine Medical Subject Headings (MeSH) categories (including obesity, and weight) and key words (including oral contraceptive, birth control pill, unintended pregnancy, and failure). To find additional sources of published and unpublished data, we examined the bibliographies of the retrieved articles and also contacted colleagues in the field. We identified eight relevant

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studies (Table 1); we excluded studies that examined only the relationship between BMI and unintended pregnancy without clarifying whether the pregnancy resulted from contraceptive failure [13] or between BMI and contraceptive failure where the type of contraceptive was not known [14].

In 1982, Graham and Frasier published an anecdotal report of a trial of progestin-only pills in which unintended pregnancy occurred only in heavier women [15]. Subsequently, in the United Kingdom, concern was raised that progestin-only OCPs might have lower effectiveness among heavier women. Vessey and colleagues used data from the Oxford/FPA study to address this question [16]. The Oxford/FPA study recruited (between 1968 and 1974) 17,032 married women who were using OCPs, diaphragms or IUDs. Subjects were followed annually until 1994. Failure rates among users of progestin-only OCPs were highest for the heaviest women. However, this study contained only 35 accidental pregnancies during 4,407 woman years of progestin-only OCP use, and the authors concluded that the study was underpowered to identify a decrease in contraceptive efficacy that might be clinically significant.

In 2001, Vessey and Painter published a further analysis of data from the Oxford/FPA study, that showed no association between increasing weight and rates of failure of either progestin-only or combined OCPs, in models that were adjusted for age and parity [17]. They considered social class, tobacco use, and duration of OCP use as possible confounders, but found it unnecessary to include these variables in further models. They examined rates of only “first accidental pregnancy.” Because there were only 38 first accidental pregnancies among women using progestin-only OCPs, power to detect an association between obesity and progestin-only OCP failure was still limited. In contrast, there was more power when considering risk of failure of combined OCPs, as there were 95 failures during 48,692 women years of combined OCP use. However, this study can not be considered definitive as weight, which likely changed over the 20 years women were followed, was measured only once, at recruitment. In addition, many of the combined OCPs used contained 50 mcg estrogen, so the results may not pertain to current low-dose or very-low-dose OCP formulations.

This negative report was followed by a pair of papers by Holt and colleagues, both reporting an increased risk of oral contraceptive failure for women with increased weight/BMI. The first was a retrospective cohort analysis of data from 755 randomly selected female enrollees in a health cooperative in Western Washington State [18]. In multivariate models, many variables were examined for possible confounding effects, including age, smoking status, gravidity, parity, menstrual cycle regularity, race, and religion. The parity-adjusted risk of failure was significantly increased [RR = 1.6 (1.1, 2.4)] for women in the highest weight quartile (>70.5 kg) compared with women of lower weight. In addition, there was evidence of a dose effect as women on low dose OCPs (<50 µg ethinyl estradiol (EE) or <80 µg mestranol) [RR = 2.6 (1.2–5.9) and very low-dose OCPs (<35 µg EE) [RR = 4.5 (1.4–14.4) in the highest weight quartile were at even higher risk of experiencing a contraceptive failure than were women on OCPs with the highest doses of estrogen (50 µg EE or 80 µg mestranol) [RR = 1.2 (0.4–3.5)], after controlling for parity, race, religion, and menstrual cycle regularity. However, this study is limited by a lack of knowledge of the subject’s weight just before becoming pregnant. Weight was self-reported, once, on average 76.5 months after last OCP use. In addition, pregnancies were self-reported, and may have been under-reported if they resulted in an induced abortion. No information was available on adherence to OCPs. Cox regression analysis explicitly controlled for duration of use. Because, with time, less adherent OCP users are more likely to experience an unintended pregnancy, the risk of failure during typical OCP use declines with increased duration of

use. It is therefore very important to control for duration of OCP use when examining the relation between obesity and risk of OCP failure.

The second paper by Holt and colleagues was a case-control study of 248 HMO enrollees in Washington State who became pregnant while using OCPs and 533 age-matched enrollees who did not become pregnant while using OCPs [19]. This study was able to compare women's reported weight to medical record weights which were recorded a median of 22 weeks prior to the reference month. Of note, self-reported weights were on average 2 kg lower than weights recorded in the medical record. Factors examined as potential confounders included race, marital status, education, income, smoking history, pregnancy and birth history, pill-taking behavior in the reference month, and concurrent illnesses and medications. Factors used in matching (age, reference year) or those that altered the estimates by 10% or more were included in the final logistic regression models. The adjusted risk of OCP failure was not significantly higher [OR = 1.4 (0.9, 2.0)] among women in the highest weight quartile (>74.8 kg) but was significantly higher [OR = 1.7 (1.1, 2.7)] among consistent OCP users in the highest weight quartile. The adjusted risk of failure was significantly elevated [OR = 1.6 (1.1, 2.2)] among women in the highest BMI quartile (>27.3) and even higher [OR = 2.2 (1.4, 3.4)] among consistent OCP users in the highest BMI quartile. There are, however, several limitations of this study [20]. More cases than controls had previously been pregnant and had become pregnant while on OCPs, and duration of OCP use, which is negatively related to the risk of OCP failure, was not controlled. Women who missed more than 5 pills in the reference month were excluded. While this exclusion does not affect the consistent-use analyses, it likely affects the results from the typical-use analyses, since those who missed more than five pills and became pregnant might be more likely to report having missed more than five pills than those who missed more than 5 pills but did not become pregnant. Consistent-use results are problematic because they depend on accurate reporting of adherence. Retrospective reports of pill-taking and consistent pill-taking at interview were on average 7 months after the reference month. Yet Potter and colleagues have shown that women cannot accurately recall or report pill-taking, even when they agree to keep a diary of daily pill-taking and transfer that information to a monthly diary card formatted as a calendar page with space for daily entries; [21] comparison with data from an electronic device measuring adherence revealed that the number of women reporting no missed pills was much higher than the number recorded electronically. Arguably, women who became pregnant and who missed pills would be more likely to report having missed pills, and would thus have been more likely to be excluded from consistent-use analyses than those who missed pills but did not become pregnant.

Two retrospective cohort studies based on the 1995 and 2002 National Surveys of Family Growth (NSFG) were completed by Brunner and colleagues [22,23]. In the first study, height and weight were reported by 2,064 women who were interviewed in the 1993 National Health Interview Study (NHIS) and who were using OCPs in January 1993; information on use of OCPs and pregnancy was provided by follow up in the 1995 NSFG. No increased risk of OCP failure was seen in unadjusted or adjusted (for age, marital status, educational level, poverty level, race/ethnicity, parity, dual method use, and fecundity status) models of women in the higher weight categories (171–190 lb and >190 lb) compared to women in the reference category (111–130 lb). The unadjusted risk of failure was significantly higher [RR = 1.8 (1.01–3.20)] among women in the highest BMI group (> 30) than among women in the reference BMI group (20–24.9), but the adjusted RR was not significant. In the second study, the sample is 1,491 women using OCPs in January 1999. In this study, obesity was not associated with increased risk of OCP failure in either unadjusted or adjusted (for age, race/ethnicity, and parity) models comparing women in the highest BMI category (> 30) to women in the reference BMI category (20–24.9). Both of

these studies have several limitations. Height, weight, OCP use (in a month-by-month calendar), and pregnancies were self-reported. Unintended pregnancies which resulted in induced abortions were severely underreported in the 1995 and 2002 NSFG. It has been estimated that only 45% of these were reported in 1995 and 47% in 2002 in the face-to-face interviews [24,25]. Finally, any woman using OCPs in the first month of either of these studies was treated as if she started use in that month. However, many women likely had started using OCPs many months prior to entering the study and the Cox proportional hazards regression models cannot properly account for duration of OCP use.

Brunner and colleagues also conducted a case cohort study in South Carolina [26]. Cases are 179 women delivering infants who reported using OCPs at conception in the 2000 Pregnancy Risk Assessment Monitoring System survey; controls were 223 OCP users in the Behavioral Risk Factor Surveillance Study. Compared with women with a BMI < 25, there was a significantly higher unadjusted risk of OCP failure among those with a BMI of 25 to 29.9 [OR = 2.5 (1.2–5.5)] and those with a BMI ≥ 30 [OR = 2.8 (1.1–7.6)]; however, when adjusted for education, income, and race/ethnicity, these ORs were no longer significant. Limitations of this study include the fact that height, weight and OCP use were self-reported. Cases were pregnancies leading only to live births, so that women who had spontaneous or induced abortions could not be included. Additionally, duration of OCP use was not considered.

Finally, we turn to clinical trials which have several advantages. Height and weight are measured at enrollment, and subjects are prospectively followed, thereby allowing measurement of adherence to pill-taking in real time. Duration of OCP use can be correctly handled in life-table analyses; women enter the analysis in the month they start using OCPs and the trial design could exclude women switching directly from use of another OCP. In one trial, Zhang and colleagues found no significantly elevated pregnancy risk for OCP failure among higher weight or obese women using Ortho Tri-Cyclen Lo [27] either in an analysis that counted all failures or in an analysis limited to pregnancies that occurred in a cycle when no active pills were missed. However, this latter analysis included in the denominator cycles with imperfect use that did not result in pregnancy, and thus it is not a true analysis of rates of failure with perfect OCP use. The sample size was large (N=1,673) and weight ranged from 90 to 240 lb; however, there were not many women in the highest weight category of ≥ 198 lb (N=55). In contrast, there was a good sample of heavier women in a study by Westhoff and colleagues [28] that combined data from five multicenter trials evaluating the efficacy of four different OCPs. Of the sample of 6,465 women, 1005 (15.5%) weighed ≥ 90 kg and 4.4% had a BMI ≥ 40. The crude method-pregnancy rate was 0.7% (7/1,005) among women weighing ≥ 90 kg and 1.0% (54/5,460) among women weighing <90 kg. Unfortunately, duration of use was not considered and the ‘on-drug’ pregnancy rate was computed as the number of pregnancies that occurred during a cycle of perfect use divided by the total number of women; this statistic cannot be interpreted as the pregnancy rate during perfect use. (An unbiased estimate of the pregnancy rate during perfect use can be obtained only by analyzing either all cycles of perfect use or only each woman’s cycles of perfect use before her first cycle of imperfect use [29]). Both of these studies have been published only as abstracts, so a full evaluation is not possible at this time, but perhaps more analyses will be forthcoming.

In our review of the existing literature we found no convincing evidence that very heavy or obese women have a higher risk of OCP failure during perfect use than thinner women, even with the lowest dose formulations. However, we acknowledge that the majority of OCP failures are due to imperfect use. Given the difficulty of collecting reliable data on adherence to pill-taking, this question may never be answered with confidence. It is possible

that OCPs are less forgiving of imperfect use among very heavy or obese women. But even if real, the absolute risk of failure is still likely to be modest:^a

- a 120% increase in risk during perfect use (seen in the second study by Holt and colleagues [19] among consistent OCP users in the highest BMI quartile) implies an attributable risk of 0.28 additional percentage points (from 0.23% to 0.51%) in the first year of perfect use of OCPs in the United States, or
- a 60% increase in risk during typical use (seen in the second study by Holt and colleagues [19] among all OCP users in the highest BMI quartile) implies an attributable risk of 4.3 additional percentage points (from 7.6% to 11.9%) in the first year of typical use of OCPs in the United States.

Therefore, OCPs would remain more effective than barrier methods for obese women during perfect use or during typical use [30]. Sexual behavior, including frequency of sexual intercourse, differs little between women of different BMIs [32]. However, obese women are less likely to use any form of contraception [33]. This is a problem as an unintended pregnancy for an obese woman is more likely to result in adverse health consequences [7–12].

Existing studies addressing the question of whether the risk of OCP failure is increased among heavy or obese women have significant limitations. In our opinion, this question will be answered convincingly only with prospective clinical trial data. The recent recommendation of an FDA advisory committee that subjects in all future trials of hormonal contraceptives must be representative of the population who will actually use the products will ensure that much larger numbers of obese women will be represented [34]. In the meantime, obese women who are concerned about the possibility of decreased efficacy of an OCP can consider using an IUD or Implant as highly effective alternatives, especially as many obese women have hypertension and other risk factors for vascular disease that may be exacerbated by exogenous estrogen.

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^aBoth calculations assume that the first year probabilities of OCP failure are 0.3% during perfect use [30] and 8.7% during typical use [31], that 25% of OCP users are obese, and that the risk of failure is constant over a year. If r is the failure rate among non-obese women during typical use, then we solve for r in the equation $.087 = 0.25 \times (1 - e^{-1.6r}) + 0.75 \times (1 - e^{-r})$. The increased risks in the second Holt study [19] are odds ratios; we apply them here as if they are hazard ratios. The results are not very sensitive to the proportion obese. The attributable risks during typical use are 4.6 percentage points when 10% are obese and 4.0 percentage points when 40% are obese. The attributable risks during perfect use are 0.32 percentage points when 10% are obese and 0.24 percentage points when 40% are obese.

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Table 1

Studies examining the effect on weight/BMI on oral contraceptive failure

Author	Study type	N	OCP use	Weight	Pregnancy	Adjusted for	Adjusted for duration of OCP use	Concludes obesity increases risk of OCP failure?
Vessey 2001 [7]	Prospective cohort	6,779 English and Scottish women-years	Few low-dose users	Measured at enrolment	Self-reported	Age, parity, Other potential confounders examined	No	No
Holt 2002 [18]	Retrospective cohort	618 HMO enrollees in Washington State	Self-reported	Self-reported	Self-reported	Parity, race, religion, and menstrual cycle regularity; many other potential confounders examined	Yes	Yes
Holt 2005 [19]	Case-control	248 HMO enrollees in Washington State and 533 age-matched enrollee controls	Self-reported	Self-reported	Laboratory-confirmed at HMO; pregnancies resulting in abortion obtained elsewhere could be misses	Age, reference year, parity; many other potential confounders examined	No	Yes
Brunner 2005 [22]	Retrospective cohort	2,064 women in the 1993 NHIS using OCPs in January 1993 reported in the 1995 NSFG	Self-reported	Self-reported	Self-reported	Age, marital status, educational level, poverty level, race/ethnicity, parity, dual method use, and fecundity status	Duration measured since January 1993, not since start of OCP use	No
Brunner 2007 [23]	Retrospective cohort	1,491 women using OCPs in January 1999 in the 2002 NSFG	Self-reported	Self-reported	Self-reported	Age, race/ethnicity, and parity; other potential confounders examined	Duration measured since January 1999, not since start of OCP use	No
Brunner 2006 [26]	Case cohort	179 cases in the 2000 PRAMS and 223 controls in the 1999 BRFSS	Self-reported	Self-reported	Only those that resulted in live birth	Age, education, income, and race/ethnicity; other potential confounders examined	No	No
Zhang 2006 (abstract) [27]	Clinical trial	1,673	In trial	Measured at recruitment	Self-reported in trial	Nothing	Yes, but method failure	No

Author	Study type	N	OCP use	Weight	Pregnancy	Adjusted for	Adjusted for duration of OCP use	Concludes obesity increases risk of OCP failure?
Westhoff 2008 (abstract) [28]	Clinical trials	6,465	In trial	Measured at recruitment	Self-reported in trial	Nothing	analysis hard to interpret No, and "on drug" failure rate hard to interpret	No