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The emerging role of obesity in short-acting hormonal contraceptive effectiveness

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1. Introduction

In recent years, regulators and clinicians have become increasingly aware of the limitations of clinical trials conducted in highly controlled settings with very selective populations. The US Food and Drug Administration (FDA) and others have urged drug developers and researchers to increase the diversity of study populations in clinical trials by conducting pragmatic, multi-regional studies to demonstrate contraceptive effectiveness in “real-world” populations who are likely to be future users of the tested products [1,2].

Diversity in body mass index (BMI) is one of many sample characteristics that can influence study outcomes. Specifically related to combination hormonal contraception (CHC), uncertainty exists about the relationship between contraceptive efficacy and BMI, primarily due to lack of data from prospective trials [3]. Obtaining prospective data in broadly

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representative populations with respect to BMI is critically important, especially in light of rising obesity rates among US women [4]. Furthermore, the ongoing uncertainty regarding the extent to which these women are at greater risk of pregnancy while using CHC presents challenges for providers and patients when selecting a contraceptive method.

This commentary summarizes the historical landscape of short-acting CHC trials as it relates to the emerging role of obesity, not only as an important factor in the outcomes of contemporary CHC trials but as a key issue to be considered by potential users and prescribers seeking the most appropriate contraceptive method for each individual woman.

2. Obesity in US Women and Its Potential Impact on CHC Efficacy

Over the past four decades, the prevalence of obesity in the US has increased dramatically. In 2014, approximately 37% of US women of reproductive age (20 to 39 years of age) were obese (defined as a BMI ≥ 30 kg/m²) and approximately 10% were extremely obese (Class 3 obesity defined as BMI ≥ 40 kg/m²) [5]. Thus, obesity represents what may be considered the most common health care problem in women of reproductive age [6].

As early as 1980, clinicians observed that obesity may be a biologic risk factor for oral contraceptive (OC) failure [7,8]. Since then, however, the role of weight and/or BMI as potential risk factors for CHC failure has remained inadequately studied [6].

3. Early Trials of CHC Efficacy Had Low Pearl Indices

The Pearl Index, the measure of efficacy used in contraceptive trials, is defined as the number of pregnancies observed in a trial divided by the number of cycles of product use multiplied by 1300. In general, Pearl Indices generated from trials conducted before the year 2000 to support FDA CHC approvals were approximately 1 per 100 woman-years of use or under [9–15]. Most of these pre-2000 trials did not explicitly exclude obese women (per available inclusion/exclusion criteria), but mean baseline body weights were in the range of 130 to 140 lbs [10,16–18] reflecting a possible selection bias for women of lower body weight. For other trials, eligibility criteria required subjects to be within 25% of “ideal” body weight or not “outside the 80–130% range of ideal body weight” [19,20]. These criteria and potential selection biases may have been guided in part due to concerns for the increased risk of thrombosis in obese women [21]. Additionally, data from trials conducted in Europe, where the prevalence of obesity has historically been lower [22], were generally allowed to be integrated with US data.

4. Is CHC Efficacy Negatively Affected by Obesity?

Product labels were largely silent on the issue of body weight and CHC effectiveness until 2001 [9–15] when the package labeling for the contraceptive patch, Ortho Evra® (Janssen Pharmaceuticals), included this information [23]. The FDA review of this data noted that 33% of pregnancies occurred in a small subset (3%) of the study population whose baseline body weight was ≥ 198 lbs (90 kg). Further, 27% of pregnancies occurred in 17% of the population whose baseline body weight was 74–90 kg [24]. As a result, the original package insert for Ortho Evra included the following statement: “The greater proportion of

pregnancies among women at or above 198 lbs was statistically significant and suggests that Ortho Evra may be less effective in these women” [23]. The FDA review indicated that “acceptable” BMI was among the inclusion criteria for the Ortho Evra clinical trials, but noted that this criterion was not clearly defined [24]. This product labeling is still present in the current label for Xulane® (Mylan Pharmaceuticals, Inc.), the generic equivalent to Ortho Evra (which is no longer available) [25].

The year following Ortho Evra’s approval, research by Holt et al. brought major attention again to the issue of obesity and CHC effectiveness [26]. This retrospective case-control analysis of data from 755 group health cooperative enrollees found a significantly increased risk of OC failure in women in the highest body weight quartile (> 70.5 kg) compared to women of lower weight. A dose-response was also seen with even higher elevations of risk among low-dose and very low-dose OC users. A follow-up study on BMI and body weight by the same authors confirmed the findings, showing that the risk of pregnancy was nearly 60% higher in women with BMI > 27.3 kg/m² and over 70% higher in women with BMI > 32.2 kg/m² [27]. Among consistent OC users, the risk of pregnancy was more than doubled in women with BMI > 27.3 kg/m², over 70% higher in women weighing > 74.8 kg, and nearly doubled in women weighing > 86.2 kg.

Collectively, these studies brought greater attention to the potential interaction of CHC and bodyweight/BMI, but questions still remained regarding whether these findings were real and widely applicable and how they should be managed in clinical trials. It should be noted here that the vaginal ring (Nuvaring®; Merck Sharp & Dohme B.V., a subsidiary of Merck & Co., Inc.), while a short-acting CHC, is not discussed in this commentary due to the exclusion of women with BMI > 30 kg/m² in the registration trials [28], making it difficult to draw any conclusions about the effectiveness of the vaginal ring in higher BMI populations.

5. Evolution of Weight-based Study Eligibility Criteria and Potential Contribution to “The Creeping Pearl”

Before 2002, clinical trials of CHC products continued to use variable inclusion/exclusion criteria with respect to weight and BMI [19,29–34]. Statistical analyses did not include assessment of BMI impact on efficacy or focused only on lower BMI categories. In 2003, FDA recommended that the manufacturer of Seasonale® (Duramed Pharmaceuticals, Inc.) include women with higher BMI in their trial, given data indicating lower efficacy in obese women [29]. Interestingly, FDA’s LoSeasonique™ (Teva Women’s Health, Inc.) review included a decile analysis for weight and found no signal of decreased efficacy in heavier women [32]. The indications sections of CHC labels generally remained silent on BMI, but clinical studies and other label sections began to mention BMI/weight exclusions in the pivotal studies. This change likely reflected increasing awareness by the FDA of a potential BMI effect and the need to provide accurate and complete information to prescribers [30,31,35–37].

This increasing drive for more generalizable clinical trials ultimately stimulated a trend but not an absolute change toward pragmatic, multiregional studies designed to show

effectiveness in a more general population of women reflecting the “real world” [1,2]. At the same time, other aspects of trial design began to change, too, including more frequent and increasingly sensitive pregnancy testing (the original Nordette® trials had no scheduled pregnancy tests) [38], and the use of transvaginal ultrasound to date pregnancies (thus helping to more accurately identify on-study vs off-study pregnancies). Likely as a combined effect of contemporaneous study population and design changes, Pearl Indices for new products were generally higher than those reported in approval studies for older products (Table 1) [10,17,19,29,32–34,39,40]. Further, Pearl Indices for older products included as comparators in these more recent clinical trials have also increased over time (Table 2). For instance, the Pearl Index for Nordette increased nearly 10-fold from 0.48 in its 1982 registration trial to 4.40 as an active comparator in 2006.

The FDA Division of Reproductive and Urologic Products convened the Advisory Committee for Reproductive Health Drugs in 2007 to discuss the evolution of clinical trial design, subject enrollment criteria, and methods of pregnancy assessment for evaluating the efficacy of new oral, transdermal, and vaginal CHCs [41]. Core components of the discussions dealt with common eligibility criteria in contraceptive clinical trials that limit the generalizability of efficacy data as well as the ability to evaluate the product. The Advisory Committee recommended that entry criteria should be more reflective of real-world prescribing with regard to BMI and other risk factors and that product labeling should provide all relevant information to the clinician and patient in an easily understandable format to allow for informed decision-making on appropriate contraceptive methods.

Broader implementation of study designs with representative, real-world patient populations has been gradual since the 2007 FDA meeting. With evolving contraceptive trial design and study populations, estimates of contraceptive failure have continued to increase over time [42–44]. The use of less restrictive weight/BMI eligibility criteria suggests a potential contribution of increased body weight of study populations [38,45], although complex associations among obesity, contraceptive non-adherence and poverty, lack of education, and Hispanic ethnicity complicate the issue [46]. Thus, the relationship among various factors thought to explain the “creeping Pearl” has remained challenging to understand in a setting of increasingly diverse study populations [45,47].

More recently, contraceptive labels have been modified to reflect exclusion of individuals of high BMI and/or weight from clinical trials. For example, the dienogest/estradiol valerate (Natazia®, Bayer HealthCare Pharmaceuticals Inc.) trial excluded women with BMI > 30 kg/m² (overall Pearl Index 1.64), requiring a product statement that “safety and efficacy in women with BMI > 30 kg/m² has not been evaluated” [48]. Similar statements are included in labeling for two other OCs that excluded women with BMI ≥ 35 kg/m², norethindrone/ethinyl estradiol (EE) and ferrous fumarate (Generess® Fe, Allergan USA, Inc.), and norethindrone acetate/EE and EE and ferrous fumarate (Lo Loestrin® Fe, Warner Chilcott Company, LLC) (Pearl Indices were 2.01 and 2.92, respectively) [42,43]. In other cases, weight/BMI criteria are noted in the clinical trials label section, such as the trial evaluating extended cycle levonorgestrel (LNG)/EE (Quartette™, Teva Pharmaceuticals), which had no exclusions for BMI or weight (Pearl Index 3.19). Although the FDA medical review found an effect of BMI on efficacy, this information is not included in the label [44,49,50].

6. Reviews and Meta-Analyses

Several publications have attempted to address the impact of obesity on CHC effectiveness [3,51–54]. A 2009 review by Trussell et al. [3] did not find evidence of lower CHC effectiveness in obese women. However, they pointed to major limitations of available retrospective data, much of which relied on self-reporting of compliance and body weight, both of which are subject to considerable recall and reporting bias. Trussell and colleagues further argued that prospective clinical trial data are the only means of convincingly answering the question about the relationship between BMI and CHC efficacy. They also noted that even if the observed higher risk of contraceptive failure in obese women is real, the absolute risk of CHC failure is probably modest and that CHC would still be more effective than barrier methods for obese women [3,51].

A 2013 Cochrane review that included 9 reports with data from 13 trials of various CHCs and 49,712 women identified 5 reports from 2002 to 2012 that compared BMI groups, including one OC study [52]. The study found more pregnancies among overweight or obese women than normal weight women using the same pills. The review also examined studies from the 1990s, which used weight alone rather than BMI, and again, results were mixed. Consistent with Trussell's statements four years earlier [3], the authors concluded that evidence to implicate obesity in CHC failure was generally lacking and called for future trials to include sufficient numbers of overweight or obese women to answer the question [52]. An update published in 2016 added 8 new studies of various CHCs [53]. Of the 5 studies of combination OCs that evaluated efficacy by BMI, only 2 found a significant difference in efficacy. Again, the authors concluded that overall the evidence generally did not indicate an association between BMI or weight and contraceptive effectiveness. They noted that although more recent studies included larger numbers of overweight and obese women, the overall quality of evidence (for non-randomized comparisons of efficacy by weight/BMI) was low, particularly for older studies. They recommend that investigators consider adjusting for potential confounding related to BMI in studies of contraceptives [53].

In 2015, the FDA published a meta-analysis to further clarify the role of obesity in the effectiveness of CHC [54]. The analysis involved individual participant data from over 14,000 women aged 18 to 35 years; data were derived from Phase 3 trials conducted between 2000 and 2012 for seven OCs and one patch. Among the seven OC trials, the overall Pearl Index for obese women (BMI ≥ 30 kg/m²) was 3.14, compared with 2.53 for non-obese women (BMI <30 kg/m²). Pearl Indices for individual studies ranged from 2.05 to 5.08 for obese women and from 1.84 to 3.80 for non-obese women [54].

For the seven OC studies, the overall adjusted hazard ratio (AHR) for unintended pregnancy in obese women compared with non-obese women was 1.44 (95% CI: 1.06–1.95; $p=.018$), i.e., obese women had a 44% higher pregnancy rate compared to non-obese women, after adjusting for age and race (Figure 1a) [54]. This result is notable considering that women in the highest BMI categories were excluded from three of the seven studies included in the analysis. Individual AHRs for the OC trials ranged from 0.80 to 2.67, the highest from a trial that had no BMI enrollment restrictions and included the greatest percentage of obese

subjects. The AHR for the patch trial was 8.80 (95% Confidence Interval [CI] 2.54 – 30.5), indicating a significantly higher rate of unintended pregnancy for obese women compared to non-obese women. When the patch study was included in the meta-analysis, the difference in pregnancy rates between obese and non-obese women increased to 65% (Figure 1b). The FDA authors called for more data from Phase 3 contraceptive trials to allow for further evaluation, emphasizing that future analyses should assess differences in pharmacodynamics or compliance that could also contribute to observed differences in pregnancy rates.

7. Summary and Conclusions

Emerging prospective data from contraceptive trials suggest that rising rates of obesity in the US population may be an important contributor to the “Creeping Pearl” phenomenon. US contraceptive clinical trials will continue to encompass broader patient enrollment criteria, including elimination of weight or BMI exclusions and greater diversity in race, ethnicity, and age. Results from modern contraceptive trials, including language regarding effects of BMI and other factors on study results, can and should be communicated in product labeling to facilitate informed decision-making by women and providers.

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References

1. Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. *Clin Trials*. 2015; 12:436–41. [PubMed: 26374676]
2. Ford I, Norrie J. Pragmatic Trials. *N Engl J Med*. 2016; 375:454–63. [PubMed: 27518663]
3. Trussell J, Schwarz EB, Guthrie K. Obesity and oral contraceptive pill failure. *Contraception*. 2009; 79:334–8. [PubMed: 19341843]
4. U.S. Department of Health and Human Services. [accessed 08.31.17] Managing overweight and obesity in adults. Systematic evidence from the Obesity Expert Panel 2013 <https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/obesity-evidence-review.pdf>
5. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. *JAMA*. 2016; 315:2284–91. [PubMed: 27272580]
6. ACOG Practice Bulletin No 156: obesity in pregnancy. *Obstet Gynecol*. 2015; 126:e112–e126. [PubMed: 26595582]
7. Boden DC. Unplanned pregnancies and the pill. *Med J Aust*. 1980; 1:391.
8. Stadel BV, Sternthal PM, Schlesselman JJ, Douglas MB, Hall WD, Kaul L, et al. Variation of ethinylestradiol blood levels among healthy women using oral contraceptives. *Fertil Steril*. 1980; 33:257–60. [PubMed: 7364059]

9. Nordette[®]-28 tablets (levonorgestrel and ethinyl estradiol tablets) [prescribing information] Philadelphia, PA: Wyeth-Ayerst; 2000
10. Ortho Tri-Cyclen[®] Ortho-Cyclen[®] (norgestimate/ethinyl estradiol) [prescribing information] Raritan, NJ: Ortho-McNeil Pharmaceutical, Inc; 2017
11. Ortho-Cept[®] tablets (desogestrel and ethinyl estradiol) [prescribing information] Titusville, NJ: Janssen Pharmaceuticals, Inc; Nov, 2015
12. Alesse[™]-28 levonorgestrel and ethinyl estradiol tablets [prescribing information] Philadelphia, PA: Wyeth Laboratories; 2001
13. Levlite[™] 21 tablets (levonorgestrel and ethinyl estradiol tablets, USP) Rx only Levlite[™] 28 tablets (levonorgestrel and ethinyl estradiol tablets, USP) Rx only Tri-Levlen[®] 21 (tablets (levonorgestrel and ethinyl estradiol tablets--triphasic regimen Tri-Levlen[®] 28 tablets (levonorgestrel and ethinyl estradiol tablets--triphasic regimen) Levlen[®] 21 tablets (levonorgestrel and ethinyl estradiol tablets) Levlen[®] 28 tablets (levonorgestrel and ethinyl estradiol tablets) [prescribing information] Wayne, NJ: Berlex Laboratories; Oct, 1998
14. Mircette[®] (desogestrel/ethinyl estradiol and ethinyl estradiol) tablets [prescribing information] Pomona, NY: Duramed Pharmaceuticals Inc; Nov, 2009
15. Yasmin[®] (drospirenone/ethinyl estradiol) tablets [prescribing information] Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; Apr, 2012
16. Drugs@FDA. [accessed 05.18.17] Alesse NDA Medical Review 1997 https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20683_ALESSE%20TABLETS_MEDR.PDF
17. Drugs@FDA. [accessed 05.19.17] Levlite NDA medical review 1998 https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20860_medr_chemr_pharmr.pdf
18. Drugs@FDA. [accessed 05.19.17] Yasmin NDA medical review 2001 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-098_Yasmin_medr_P1.pdf
19. Drugs@FDA. [accessed 05.19.17] Yaz NDA medical review 2006 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021676s000_MEDR_pt1.pdf
20. Drugs@FDA. [accessed 05.19.17] Mircette NDA medical review 1998 https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20713-1.pdf
21. Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. Fertil Steril. 2017; 107:43–51. [PubMed: 27793376]
22. Hruby A, Hu FB. The epidemiology of obesity: a big picture. Pharmacoeconomics. 2015; 33:673–89. [PubMed: 25471927]
23. Ortho Evra[®] (norgestromin/ethinyl estradiol transdermal system) [prescribing information] Titusville, NJ: Janssen Pharmaceuticals, Inc; 2001
24. Drugs@FDA. Ortho Evra NDA medical review 2001 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/021-180_Ortho%20EVRA_medr_P1.pdf
25. Xulane[®] (norgestromin and ethinyl estradiol transdermal system) [prescribing information] Morgantown, WV: Mylan Pharmaceuticals Inc; Apr, 2017
26. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. Obstet Gynecol. 2002; 99:820–7. [PubMed: 11978293]
27. Holt VL, Scholes D, Wicklund KG, Cushing-Haugen KL, Daling JR. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol. 2005; 105:46–52. [PubMed: 15625141]
28. NuvaRing[®] (etonogestrel/ethinyl estradiol vaginal ring) [prescribing information] Whitehouse Station, NJ: Merck & Co. Inc; Aug, 2017
29. Drugs@FDA. [accessed 05.19.17] Seasonale NDA medical review 2003 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-544_SEASONALE_Medr_P1.pdf
30. Seasonique[®] (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets) for oral use [prescribing information] Pomona, NY: Duramed Pharmaceuticals, Inc; Jul, 2010
31. Lybrel[®] (90 mcg levonorgestrel and 20 mcg ethinyl estradiol) tablets [prescribing information] Philadelphia, PA: Wyeth Pharmaceuticals, Inc; 2008
32. Drugs@FDA. [accessed 05.19.17] LoSeasonique NDA medical review 2008 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022262s000_MedR_p1.pdf

33. Drugs@FDA. [accessed 05.17.17] Loestrin 24 FE 2006 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021871s000_MedR.pdf
34. Drugs@FDA. [accessed 05.19.17] Ortho Tri-Cyclen Lo NDA medical review 2001 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/021241_S000_ORTHO-TRI-CYCLEN_MEDR.pdf
35. Ortho Tri-Cyclen® Lo (norgestimate/ethinyl estradiol) [prescribing information] Raritan, NJ: Janssen Ortho, LLC; Aug, 2008
36. Yaz® (drospirenone and ethinyl estradiol) Tablets [prescribing information] Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc; 2010
37. LoSeasonique™ (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets) [prescribing information] Pomona, NY: Duramed Pharmaceuticals, Inc; Oct, 2008
38. Trussell J, Portman D. The creeping pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills? *Contraception*. 2013; 88:604–10. [PubMed: 23683581]
39. Drugs@FDA. [accessed 05.19.17] Seasonique NDA medical review 2005 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021840s000_MedR.pdf
40. Drugs@FDA. [accessed 05.19.17] Lybrel NDA medical review 2007 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021864s000_MedR_P1.pdf
41. U.S. Food and Drug Administration, Advisory Committee for Reproductive Health DrugsFDA Briefing Document. General Meeting; January 23–24, 2007; 2007<http://www.fda.gov/ohrms/dockets/ac/07/minutes/2007-4274m1.pdf>
42. Generess® Fe (norethindrone and ethinyl estradiol chewable tablets and ferrous fumarate chewable tablets) [prescribing information] Irvine, CA: Allergan USA, Inc; Oct, 2016
43. Lo Lestrin® Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) [prescribing information] Rockaway, NJ: Warner Chilcott Company, LLC; Oct, 2010
44. Drugs@FDA. [accessed 05.19.17] Quartette NDA medical review 2013 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204061Orig1s000MedR.pdf
45. Gerlinger C, Trussell J, Mellinger U, Merz M, Marr J, Bannemerschult R, et al. Different Pearl Indices in studies of hormonal contraceptives in the United States: impact of study population. *Contraception*. 2014; 90:142–6. [PubMed: 24813941]
46. Westhoff CL, Torgal AT, Mayeda ER, Shimoni N, Stanczyk FZ, Pike MC. Predictors of noncompliance in an oral contraceptive clinical trial. *Contraception*. 2012; 85:465–9. [PubMed: 22079603]
47. Dinger J, Minh TD, Buttmann N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol*. 2011; 117:33–40. [PubMed: 21213475]
48. Natazia (estradiol valerate and estradiol valerate/dienogest) tablets, for oral use [prescribing information] Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc; Aug, 2015
49. Quartette™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) [prescribing information] Sellersville, PA: Teva Pharmaceuticals USA, Inc; Mar, 2013
50. U.S. Food and Drug Administration Final summary minutes: Advisory Committee for Reproductive Health Drugs meeting; January 23 and 24, 2007; 2007<http://www.fda.gov/ohrms/dockets/ac/cder06.html#rhdac>
51. Trussell J, Aiken A. Effect of obesity on the effectiveness of hormonal contraceptives. *Contraception*. 2015; 92:602.
52. Lopez LM, Grimes DA, Chen M, Otterness C, Westhoff C, Edelman A, et al. Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database Syst Rev*. 2013; (4):CD008452. [PubMed: 23633356]
53. Lopez LM, Bernholc A, Chen M, Grey TW, Otterness C, Westhoff C, et al. Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database Syst Rev*. 2016; (8):CD008452. [PubMed: 27537097]

54. Yamazaki M, Dwyer K, Sobhan M, Davis D, Kim MJ, Soule L, et al. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. *Contraception*. 2015; 92:445–52. [PubMed: 26247330]

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Figure 1. Obesity and Risk of Pregnancy with CHC; AHR for Unintended Pregnancy in Obese Compared to Non-Obese Women in (A) Seven OC Trials and (B) Seven OC Trials Plus Patch Trial (Trial #8) in FDA IPD Analysis*

CHC = combination hormonal contraception; AHR = adjusted hazard ratio; OC = oral contraceptive; FDA = Food and Drug Administration; IPD = individual participant data; EE = ethinyl estradiol; DSG = desogestrel; LNG = levonorgestrel; NET = norethindrone; NETA = norethindrone acetate; NGM = norgestimate.

Trials: 1: Mircette[®], 2: LoSeasonique[™], 3: Quartette[™], 4: Lybrel[®], 5: Generess[®] Fe, 6: Lo Loestrin[®] Fe, 7: Ortho Tri-Cyclen[®] Lo, and 8: Ortho Evra[®] patch (norgestromin/EE).

*Overall AHR of 1.65 indicates a 65% higher rate of unintended pregnancy in obese compared to non-obese women with the inclusion of the Ortho Evra patch data in the FDA IPD analysis. I-squared of 41.0% indicates heterogeneity among the trials after inclusion of Ortho Evra data.

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Table 1

BMI Exclusions, Labeling Language and Pearl Indices in Pivotal CHC Trials for Post-2000 Approvals

Product	Year*	BMI Exclusion in Clinical Trial	Mean Weight/BMI [†]	Pearl Index (UB 95% CI) [‡]	BMI-Related Label Language	
					Indications Section [§]	Clinical Studies or Other Section
NGM/EE (Ortho Tri-Cyclen® Lo)	2002	Within acceptable BMI (<i>within</i> 35%)	23.7 kg/m ² /64.5 kg	2.67	Silent	No exclusions on basis of weight//
LNG/EE (Seasonale®)	2003	None	71.2 kg	1.98 (5.03)	Silent	Silent
NETA/EE (Loestrin® 24 Fe)	2006	> 35	67 kg	1.79 (4.57)	Silent	Silent
LNG/EE (Seasonique®)	2006	None	70.4 kg	1.77 (3.64)	Silent	No exclusions for BMI/weight
DRSP/EE (Yaz®)	2007	> 35	22.4 kg/m ²	1.41 (2.47)	Silent	BMI > 35 kg/m ² excluded
LNG/EE (Lybrel®)	2007	None	70.4 kg	2.38 (3.57)	Silent	No exclusions for BMI/weight
LNG/EE (LoSeasonique™)	2008	None	26.8 kg/m ² /72.4 kg	2.74 (3.78)	Silent	No exclusions for BMI/weight

BMI = body mass index; CHC = combination hormonal contraception; NGM = norgestimate; EE = ethinyl estradiol; LNG = levonorgestrel; NETA = norethindrone acetate; DRSP = drospirenone.

* Year approved.

[†]Weight standardized to kg for comparison; weight and BMI provided if both available.

[‡]Upper bound (UB) 95% confidence interval (CI) provided if available.

[§]Original approved label; some labels updated to include BMI-specific language in indications section.

//Language in current label; not in original approved label; Medical Officer review notes inclusion criterion of “within acceptable BMI (within 35%)”.

Table 2

Select Examples of CHCs; Comparing Original Efficacy Results from Registration Trial(s) to Subsequent Efficacy Results When Used as Comparators in Other Registration Trial(s) *

Product	Trial [†]	Year	BMI/Weight Exclusions	Mean Weight/BMI [‡]	Pearl Index (UB 95% CI) [§]
NET/EE (Loestrin® Fe 1/20)	Original US Registration	1973	n/a [§]	n/a	0.75
	Comparator in Ortho Tri-Cyclen® Lo Registration	2002	Within acceptable BMI (within 35%)	23.6 kg/m ²	3.80
	Comparator in Loestrin® 24 Fe US Registration	2006	> 35 kg/m ²	68.2 kg	3.67 (13.20)
LNG/EE (Levite™)	Original German Registration	1998	None stated	62.7 kg	0.29 (0.91) [¶]
	Original US Registration	1998	None stated	63.0 kg	1.08 (2.34) [¶]
	Comparator in Seasonale® Registration	2003	No restriction	69.7 kg	3.75 (8.60)
LNG/EE (Nordette®)	Original US Registration	1982	n/a	n/a	0.48 (1.04) [¶]
	Comparator in Seasonale® Registration	2003	No restriction	71.0 kg	2.22 (6.38)
	Comparator in Seasonique® Registration [#]	2006	No restriction	71.8 kg	4.40

CHC = combination hormonal contraception; BMI = body mass index; NET = norethindrone; EE = ethinyl estradiol; LNG = levonorgestrel.

* Results for subjects 35 years.

[†] Product used as comparator for trials subsequent to the original registration.

[‡] Weight standardized to kg for comparison; weight and BMI provided if both available.

[§] Upper bound (UB) 95% confidence interval (CI) provided if available.

[¶] n/a = not available on <http://www.accessdata.fda.gov> or package insert.

[¶] Calculated by the authors based on pregnancy and cycle data in FDA Medical Review.

[#] Nordette arm only in smaller supportive trial for Seasonique.