Published in final edited form as:

Expert Rev Clin Pharmacol. 2015 January ; 8(1): 1–3. doi:10.1586/17512433.2015.974558.

How can we improve oral contraceptive success in obese women?

Ganesh Cherala, Ph.D. and Alison Edelman, M.D., M.Ph

Oregon State University/Oregon Health & Science University - Pharm Practice, 2730 SW Moody Ave 2730 SW Moody Ave Portland Oregon 97201, United States, T: 5034180447

Ganesh Cherala: cheralag@ohsu.edu

Summary

A rapid increase in obesity rates worldwide further underscores the importance of better understanding the pharmacokinetic alterations in this sub-population and the subsequent effects on pharmaco-therapeutics. Pharmacokinetics of contraceptive steroids are altered in obese oral contraceptive users which may in turn impact efficacy. Our work has identified several dosing strategies that offset these pharmacokinetic changes and may improve effectiveness for obese OC users.

Keywords

Obesity; oral contraception; pharmacokinetics

Oral contraception (OC) is a mainstay for birth-control in the US with about 12 million users. Although OCs are currently the most popular form of contraception ^[1], they have a significant failure rate resulting in ~1 million unintended pregnancies each year ^[2, 3]. Unintended pregnancies can result in severe burdens on the physical, emotional, and financial well-being of not only the individual woman and her family, but the US health care system as well, costing an estimated \$11.3 billion annually ^[4].

Does obesity elevate the risk of OC failure?

US rates of obesity have increased over time with 50% of reproductive age women meeting the criteria for being obese or overweight ^[5]. OC dosing has always been based on a one-size-fits model all. Holt et al raised the alarm in 2001 that this might be a problem when she demonstrated that obesity might increase the risk for OC failure ^[6]. Studies since this time have varied in their results and this is most likely due to the wide variation in user adherence which may mask the smaller effect of obesity ^[7, 8]. If there is an increased risk for OC

Financial disclosure: Dr. Edelman is a consultant for Gynuity Health Projects, WHO, CDC, Genzyme, and Agile Therapeutics; trainer for Merck & Co.; and author for UptoDate (royalties received). These potential conflicts of interest have been reviewed and managed by OHSU.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

failure among obese women, alterations in pharmacokinetics may explain all or part of the failure.

Understanding OC pharmacokinetics (PK) could reduce failure rate by improving dosing paradigms

We became interested in a potential PK mechanism based on the observation by Holt *et al* that obese women at the highest risk were those on a lower OC doses [very low dose OC [RR 4.5 (1.4–14.4)] or low dose OC [RR 2.6 (1.2–5.9)], compared to high dose OC (very low dose: <35µg EE; low dose: <50µg EE; high dose: 50µg EE) [5]. Given the risk of thromboembolic events associated with ethinyl estradiol (EE) exposure, the EE component has been lowered over time. Holt *et al* speculated that higher body weight is correlated with higher resting metabolic rates, which could result in increased drug metabolism. Interestingly, drug metabolizing enzymes have increases proportional to the total body weight [9]. These same enzymes are predominantly responsible for the metabolism of OCs [10–12]. Another proposed PK mechanism is the increase in fat mass among obese subjects, and given the highly lipophilic nature of OCs one would expect distribution and sequestration in fat tissue. Both of these mechanisms would result in lower blood levels of OCs. However, detailed prospective PK studies of OCs by two research groups, including our own, have shown significant alterations in PK of OCs which are counterintuitive to these proposed mechanisms [13]. The volume of distribution was similar and clearance was decreased by 2-fold in obese women, resulting in a longer half-life as compared to normal body mass index (BMI) women. Subsequently the time to reach therapeutic steady state level was significantly prolonged in obese women opening a “window of opportunity” for OC to fail at the time of pill initiation or following the monthly hormone-free interval.

Contrary to our findings, Westhoff *et.al* [14] only found a small, but statistically insignificant, differences in PK measures of drug exposure namely area under the curve and peak concentration between obese and normal BMI OC users and thus concludes that obesity likely does not impact OC effectiveness. The PK differences in this study was likely blunted due to the shorter sampling scheme which was highlighted to be inadequate study design [15, 16]. Our research group has tested two dosing regimens in an effort to mitigate the obesity related PK changes [10]. As anticipated, a low dose regimen without a pill-free week (i.e. continuous dosing) has eliminated the time to reach steady state when starting the next cycle. Second, a slightly higher but still low dose regimen attains therapeutic levels sooner but the time to reach steady state is still prolonged. Both dosing regimens were effective in reducing follicle-like activity, a surrogate measure of OC efficacy.

Although we have explored alternative dosing regimens to overcome or correct PK alterations in obese women in order to minimize OC failure, a mechanistic understanding of how and why such PK alterations occur is critical to optimization of OC as well as non-OC pharmacotherapies. Based on our counter-intuitive data on volume of distribution and clearance, one theoretical mechanism is that plasma protein binding of levonorgestrel is likely higher in obese women leading to a drastic reduction in free concentrations which is a pharmacologically relevant species. Preliminary data from our group supports this

hypothesis. If proven true, potentially attractive therapeutic strategies could be developed such as drug displacement from plasma proteins, reduction in plasma protein levels, e.t.c.

Biology and Behavior

Our data has proven that obesity causes PK alterations in contraceptive steroid hormones. The actual impact on failure is difficult to ascertain given the significant failure rates due to user non-adherence. However given the type of PK alterations caused by obesity, a longer half-life, an obese woman is likely at greater risk for failure if she does miss a pill. Although strict adherence is recommended, perfect use for anyone taking a daily medication has been shown to be nearly impossible. For obese women that want to use OCs, continuous dosing or skipping the pill free interval appears to be a reasonable alternative. Furthermore, it is important to offer counseling on non-oral contraceptive options such as the long-acting reversible contraception. While obesity induced PK alterations offer potential mechanistic explanation for OC failure, the role of pharmacodynamics (PD) in OC failure is equally important. Given the obesity induced alterations in hypothalamic-pituitary-ovarian axis ^[13], the individual and combined effects of PK and PD on OC failure needs to be teased out in order to develop effective OC pharmacotherapeutic strategies.

Acknowledgments

This work was supported by the grant support from National Institutes of Health [R03 HD053611 NICHD], the office of women's health and the National Institutes of Health [Building Interdisciplinary Research Career in Women's Health - 2K12HD043488 NICHD], the OHSU Oregon Clinical & Translational Research Institute [NIH NCRR 1 UL1 RR024120], and the Bioanalytical Shared Resource/Pharmacokinetics Core at OHSU.

References

1. Mosher WD, Martinez GM, Chandra A, et al. Use of contraception and use of family planning services in the United States: 1982–2002. *Adv Data*. 2004 Dec; 10(350):1–36. [PubMed: 15633582]
2. Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspect Sex Reprod Health*. 2006 Jun; 38(2):90–6. [PubMed: 16772190]
3. McNicholas C, Zhao Q, Secura G, et al. Contraceptive failures in overweight and obese combined hormonal contraceptive users. *Obstet Gynecol*. 2013 Mar; 121(3):585–92. [PubMed: 23635622]
4. Monea E, Thomas A. Unintended pregnancy and taxpayer spending. *Perspect Sex eprod Health*. Jun; 43(2):88–93.
5. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. *Obstet Gynecol*. 2002 May; 99(5 Pt 1):820–7. [PubMed: 11978293]
6. Holt VL, Scholes D, Wicklund KG, et al. Body mass index, weight, and oral contraceptive failure risk. *Obstet Gynecol*. 2005 Jan; 105(1):46–52. [PubMed: 15625141]
7. Dinger JC, Cronin M, Mohner S, et al. Oral contraceptive effectiveness according to body mass index, weight, age, and other factors. *Am J Obstet Gynecol*. 2009 Sep; 201(3):263e1–9. [PubMed: 19481720]
8. Dinger J, Minh TD, Buttmann N, et al. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol*. 2011 Jan; 117(1):33–40. [PubMed: 21213475]
9. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet*. 49(2):71–87. [PubMed: 20067334]
10. Edelman AB, Cherala G, Munar MY, et al. Correcting oral contraceptive pharmacokinetic alterations due to obesity: a randomized controlled trial. *Contraception*. 2014 Jun 27.

11. Madabushi R, Frank B, Drewelow B, et al. Hyperforin in St. John's wort drug interactions. *Eur J Clin Pharmacol.* 2006 Mar; 62(3):225–33. [PubMed: 16477470]
12. Zamek-Gliszczyński MJ, Day JS, Hillgren KM, et al. Efflux transport is an important determinant of ethinylestradiol glucuronide and ethinylestradiol sulfate pharmacokinetics. *Drug Metab Dispos.* Oct; 39(10):1794–800. [PubMed: 21708882]
13. Edelman AB, Carlson NE, Cherala G, et al. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic-pituitary-ovarian activity. *Contraception.* 2009 Aug; 80(2): 119–27. [PubMed: 19631786]
14. Westhoff CL, Torgal AH, Mayeda ER, et al. Pharmacokinetics of a combined oral contraceptive in obese and normal-weight women. *Contraception.* 2010 Jun; 81(6):474–80. [PubMed: 20472113]
15. Fotherby K. Levonorgestrel. Clinical pharmacokinetics. *Clin Pharmacokinet.* 1995 Mar; 28(3): 203–15. [PubMed: 7758251]
16. Kuhnz, W.; Blode, H.; Zimmermann, H. Pharmacokinetics of exogenous natural and synthetic estrogens and antiestrogens. In: Oettel, M.; Schillinger, E., editors. *Estrogens and Antiestrogens II: Pharmacology and Clinical Application of Estrogens and Antiestrogens.* New York, NY: Springer; 1999.