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BODY MASS INDEX AND ORAL CONTRACEPTIVE FAILURE

by

Cristin M. Larder

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

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ABSTRACT

BODY MASS INDEX AND ORAL CONTRACEPTIVE FAILURE

by

Cristin M. Larder

There are suggestions that use of oral contraceptives is related to a higher risk of birth control failure in women with increased weight. However, the few existing studies investigating the association between body mass index (BMI) and oral contraceptive (OC) failure report inconsistent findings. To date, no research has been conducted on the topic using a prospective design, and previous results have been based on self-reported exposure and outcome variables. This thesis is a grant proposal to apply for funding to conduct a prospective cohort study. The objective of the proposed study will be to determine the combined effect of high BMI and OC use on birth control failure. In addition, the study will collect information on exposure and outcome variables from sources other than a self-report and investigate each the following possible confounding variables: OC type and dose, compliance to OC regimen, frequency of intercourse, parity, concurrent contraceptive methods, ethnicity, socioeconomic status, pre-existing diseases and/or medical conditions, and desire for future children. The study proposal includes sample size estimates needed to carry out the investigation, as well as proposed statistical methods of analysis.

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KEY TO ABBREVIATIONS

OC: oral contraceptives

E2: ethinyl estadiol

OB/GYN: Obstetrics/Gynecology

POP: progesterone only pill

NHANES: National Health and Nutrition Examination Survey

BMI: body mass index

HMO: health maintenance organization

COC: combined oral contraceptive

SHBG: sex hormone binding globulin

ALT: alanine aminotransferase

AST: aminotransferase

PCOS: Poly Cystic Ovary Syndrome

WHO: World Health Organization

MEMS: Medication Event Monitoring System

BRFSS: Behavioral Risk Factor Surveillance System

PHM: proportional hazards model

A. Specific Aims

Oral contraceptives (OC) revolutionized family planning in the Twentieth Century by providing a reliable and reversible form of contraception. The typical-use failure rate of the OC has been reported to be between 3.0% and 8.1%.[1-4] However, over the years, the dose of ethinyl estradiol (E2) has been lowered with every new generation of OC in effort to reduce adverse side-effects such as headache, nausea, and risk of venous thrombosis.

Additionally, prospective studies suggest that newer hormonal contraceptives administered through subdermal implants and the transdermal patch are less effective in overweight and obese women.[5-7] Reasons for the reported increase in failure rate are unknown. Retrospective and case-control studies have reported mixed findings regarding the same association with OC's.

Furthermore, studies show that the prevalence of overweight and obesity is rapidly increasing in the United States. As the dose of E2 decreases, and the prevalence of overweight and obesity increases, there are concerns of an increasing prevalence of unintended pregnancies among OC users. Hence, I plan to address this issue in a prospective cohort study with the following hypothesis: overweight and obese women using oral contraceptives will have significantly higher failure rates than normal weight and underweight women using oral contraceptives.

Specific aim 1: I will gain access to the target population through doctor and nurse contacts at local OB/GYN clinics in South Carolina. Four thousand, four hundred, and sixty-six (4,266) women will be enrolled in the study through these contacts after signing an informed consent document.

Specific Aim 2: I will assess compliance with the prescribed OC regimen by obtaining used OC cases at the end of each month. Participants will be offered ten dollars for each case they return. I will also measure compliance using a monthly telephone interview asking how many pills were missed during the previous cycle.

Specific aim 3: In order to identify differences in failure rates among women using high dose, low dose, and very low dose contraceptives, I will determine OC brand from the health care providers' records. I will then classify brands according to the amount of E2 in each: brands containing 50μg or more E2 will be classified as "high dose", brands with 35μg or more, but less than 50μg E2 as "low dose", and brands containing less than 35μg E2 as "very low dose." Progesterone only pills (POP) will be classified as "no estrogen."

B. Background

Unintended pregnancy has an enormous effect on social, financial, and emotional well-being, and it is estimated that half of pregnancies in the United States are unintended.[1] Thirty-two percent of women using reversible contraceptive methods opt for oral contraceptives (OC's),[2] which provide a generally safe and effective method of birth control: typical use failure rates (rates that include failures due to user error) are estimated to be up to 8%, and most failures have been attributed to user compliance issues.[3,4] However, research shows that other hormonal contraceptive methods, such as the subdermal implant and the transdermal patch, are not as effective in larger women.[5-7] Studies examining this effect in oral contraceptives are scarce, and to date, no longitudinal investigations have been published.

Furthermore, obesity in the United States has reached a historically high prevalence rate in women. According to data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES), 62% of American women >19 years of age are either overweight or obese.[8] If the elevated risk of failure for overweight and obese women observed in the implant and patch is indeed present in OC's, the public health consequences would be substantial, particularly if the prevalence of overweight and obesity continues to rise.

Unintended pregnancy has been associated with such adverse consequences as high cost to both the individual and the public and psychological distress. Trussell, et al estimated that compared to the $422 cost of one year of oral contraceptive use, unintended pregnancies cost significantly more for medical services if carried to term--$8619 per pregnancy for individuals,

or $3623 for the public if the individual is on Medicaid.[9] Orr and Miller found that mothers whose pregnancies are unintended are more likely to have depressive symptoms during pregnancy than mothers with planned pregnancies.[10] Additionally, unintended pregnancy is associated with insufficient prenatal care, smoking and alcohol use during pregnancy, low birth weight, elevated infant mortality, and poor health and development of the child.[11] Ultimately, women experiencing an unintended pregnancy not only face an immense financial cost, but are also at risk for increased burdens during and after pregnancy.

B.1. Association between efficacy and weight among subdermal implant and transdermal patch users

The transdermal patch and subdermal implants operate in a manner similar to OC's. Specifically, both use a combination of estrogen and progesterone to prevent pregnancy. Studies have shown that as weight increases, the efficacy of the Norplant® subdermal implant decreases. In a clinical trial conducted in China, Gu, et al found that after 5 years, Norplant users weighing 70kg or more had a 4.58% risk of becoming pregnant, compared to a .77% risk among women weighing less than 50kg.[5] After seven years of use, the percentage of failure grew to 6.62% in women weighing 70kg or more, while the percentage for women under 50kg rose to only 1.18%. Since Norplant® is implanted underneath the skin and does not require daily compliance by the user and thus invites little room for user error, these findings suggest that there may be a biological explanation for the elevated failure rate among women weighing 70kg or more. Similarly, in a trial conducted among 17 countries, Grubb et al reported increasing failure rates with each consecutive 10kg weight group they examined (Figure).[6] Although relative risks were not reported, both studies display a disturbing trend among heavy women.

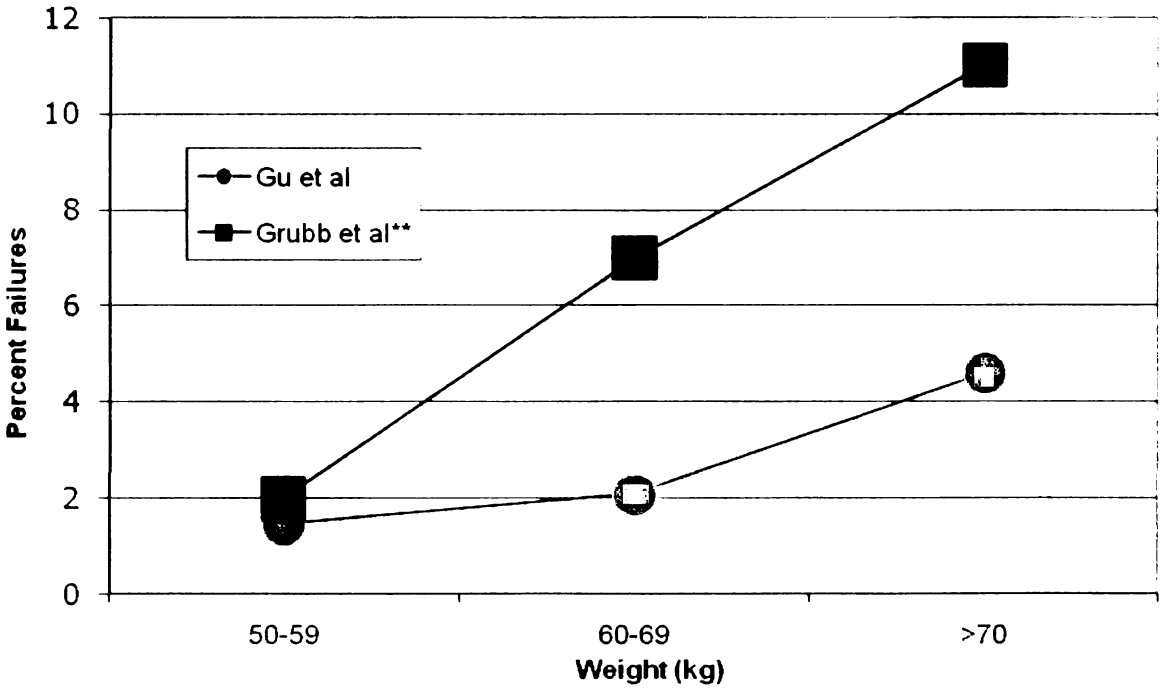
The Ortho Evra™/ Evra™ transdermal patch has also been shown to be less effective in heavy women. Zieman et al pooled data from three clinical trials conducted to determine the efficacy of Ortho Evra™/ Evra™ and found in a post hoc analysis that among 3,319 participants and a total of 22,160 menstrual cycles, 15 pregnancies occurred.[7] Of the 15 pregnancies, 5 took place in women who weighed 90kg or more, a subgroup that represented only 3% of the total

participants. Statistical analysis was not performed on these events, most likely because of the small number of pregnancies that occurred in the pooled data. However, the results of Zieman's analysis did lead to the following warning on the Ortho Evra™/ Evra™ label:

> Health Care Professionals who consider ORTHO EVRA™ for women at or above 198 lbs. should discuss the patient's individual needs in choosing the most appropriate contraceptive option.[12]

Research investigating the efficacy of these hormonal contraceptives in overweight or obese women has consistently shown that the pregnancy rate among larger users is higher than among users weighing less. These findings are suggestive of an association between overweight/obesity and OC failure.

Figure 1. Norplant failure rates by weight group*



*Failures for weight groups below 50kg were less than 1% in both studies.
**Difference between 60-69 and >70 in Grubb et al is not significant (p=.26). All other differences are significant. (P<.01).

B.2. Current studies investigating the association between efficacy and overweight/obesity among oral contraceptive users

Four studies have been published examining the relationship between oral contraceptive failure and either weight or body mass index (BMI), all of which are retrospective cohort or followed a case-control in design (Table 1). Two studies by Holt and colleagues (2002 and 2005) reported an increased risk among women with a BMI ≥27.3 or weighing ≥70.5kg, respectively (Table 1).[13,14] Both studies used a study population of women enrolled in a health maintenance organization (HMO) in Washington state, which may not be representative of women outside of the HMO if these women are collectively different from the general population.

A retrospective cohort study by Brunner & Hougue found a significant crude hazard ratio of 1.8 (CI 1.01, 3.20) for women with a BMI ≥30 compared to women in their 20-29 BMI group, indicating that obese women were 1.8 times more likely to experience OC failure than non-obese women. But, the difference dropped below significance when confounding variables were added to the model (Table 1).[15] The study is a secondary analysis using data from the 1995 National Survey of Family Growth, for which all relevant data was collected by face-to-face interviews where women were asked to recall information from over two years prior to the survey. Therefore, the analysis may be subject to recall bias.

Finally, a retrospective cohort study by Vessey & Painter examined participants in the Oxford Family Planning Association Family Planning Study. The participants were married women who were enrolled between 1968 and

1974.[16] Vessey and Painter reported a non-significant difference in failure between oral contraceptive users weighing ≥82kg compared to those weighing less. However, only 4 women in the sample actually weighed more than 77kg, and the number of women over 82kg was not reported. The lack of significance may be due Type II error since there may not have been enough women in the ≥82kg group to detect a significant difference in the failure rate. Additionally, the study included only *married* women using either combined oral contraceptives (COC's) or POP's. POP's are recommended for use while breastfeeding, so it is possible that POP use is overrepresented among married women. This group of women may breastfeed more often because they have partners to help with household duties, which frees up time for breastfeeding to take place, and they may take pills less diligently than the general population of OC users since they have a family structure that is conducive to caring for children. The formulations of Norplant®, Ortho Evra™/ Evra™ contain both estrogen and progesterone, and are therefore more similar to the combined oral contraceptive.[7] There is no other published research regarding POP efficacy among BMI or weight groups, which contributes to the lack of knowledge about any biological mechanism(s) that may be involved with the association between overweight/obesity and increased risk of OC failure.

Though limited research involving increased OC failure among overweight/obese women exists, there is disagreement between studies as to whether the relationship is significant. The conflicting results may be due to issues involving the design of the existing studies: none use a prospective design to measure pregnancy while using OC's, and the low prevalence of obesity in

Vessey & Painter's study resulted in inadequate statistical power to test the hypothesis.

Table 1. Published research examining the association between BMI/weight and oral contraceptive failure

	Vessey & Painter, 2001	Holt, et al, 2002	Holt, et al, 2005	Brunner & Hogue, 2005
Design	Retrospective cohort	Retrospective cohort	Case-control	Retrospective cohort
Study Population	White, married women, ages 25-39 using COC or POP enrolled in Oxford-FPA Study, England & Scotland, 1968-1994	Women ages 18-39, enrolled in ovarian cyst study through Group Health Cooperative HMO in WA, 1990-1994	English speaking women, age 18+, enrolled in Group Health Cooperative HMO in WA, 1998-2001	U.S. women, ages 15-44, enrolled in the National Survey of Family Growth, 1993-1995
Sample Size	133	618	280 cases 536 controls	1763
BMI/Weight Categories (% of sample)	• <77kg (97%) • Referent: ≥77kg (3%)	• <70.5kg (75%) • Ref: ≥70.5kg (25%)	• BMI <27.3 (65%) • Ref: BMI ≥27.3 (35%)	• BMI <20 (26%) • BMI 20-24.9 (52%) • Ref: BMI 25-29.9 (16%) • BMI ≥30 (7%)
Data Collection Method(s)	Several interviews covering entire reproductive history	One Face-to-Face interview covering entire reproductive history	One Face-to-Face interview covering lifetime history up to month of conception (cases) or randomly matched reference month (controls), medical and pharmacy records	One Face-to-Face interview covering time period from Jan. 1993 to month of interview in 1995
Analysis	Not reported	Cox proportional hazards model	Unconditional logistic regression	Cox proportional hazards model
Findings	• Weight ≥82kg failure rate=0.38 per 100 woman years • Weight <82kg failure rate=0.38 • Change not significant no p-value reported	• Weight ≥70.5kg (<70.5kg=referent) RR=1.6 (CI 1.1, 2.4) • Very low dose RR=4.5 (CI 1.4, 14.4) • Low Dose RR=2.6 (CI 1.2, 5.9)	• BMI >27.3 (≤27.3=referent) OR=1.62 (CI 1.02-2.57) • Among consistent users, BMI ≥27.3 (<27.3=referent) OR=2.17 (CI 1.38, 3.41)	• BMI ≥30 (20-29=referent) crude HR=1.8 (CI 1.01, 3.20) • non-significant in multivariate model HR 1.51 (CI 0.81, 2.82)

B.3. Possible biological explanations for the association between overweight/obesity and increased hormonal contraceptive failure rates

There is more than one potential biological explanation for increased hormonal contraceptive failure among overweight/obese women. First, Edman, et al found that morbidly obese women took 12 times longer to excrete estrone than women of normal weight.[17] Coupled with Lukanova, et al's findings of an inverse correlation between sex hormone binding globulin (SHBG) and levels of free estradiol,[18] this suggests that overweight/obese women may sequester estrogens in their adipose tissue. Notably, overweight/obese women have been found to have lower levels of SHBG than normal weight women.[19,20] Ultimately, overweight/obese women may simply have more fat tissue with which to "trap" estrogens.

Some evidence suggests that SHGB has a positive correlation with estrogen.[21] This relationship is complex, however, and other studies suggest that there are also non-steriodal factors that determine levels of SHBG.[22,23] Bates and Whitworth reported that E2 is "markedly depressed" in obese girls.[24] The relationship between obesity, SHGB, and estrogen levels may provide insight to the BMI/OC failure hypothesis after further research has disentangled the underlying association and causality.

A second possible explanation involves the metabolism in the liver. Oral contraceptives, like many other drugs, go through a "first pass" metabolism. During first pass metabolism, the liver and/or intestinal wall metabolize the drug before it is able to circulate throughout the body. Differences in metabolism may lead to different levels of bioavailability.[25] Overweight/obese individuals have

been shown to have higher levels of liver enzymes than those of normal weight.[26,27] For example, Golik, et al. found that over 28% of their 60 healthy, obese participants had elevated blood levels of the hepatic enzymes alanine aminotransferase (ALT) and aminotransferase (AST).[28] This suggests that overweight/obese women may experience liver damage or dysfunction, which may lead to decreased metabolism of OC steroids; therefore, the OC may be prone to fail more often than in normal weight women.

Additional research by Butte et al indicates that overweight/obese individuals have a higher basal metabolic rate, due to elevated fat free body mass compared to those at a normal weight.[29] In a study designed to determine the energy requirements of women, Jequier found that basal metabolic rate was predicted by height and weight: women with high BMI had a higher basal metabolic rate than those with lower BMI.[30] This difference in metabolism could result in a shortened time in which the OC is functional in the bodies of obese women.

Biomechanisms explaining the relationship between obesity and OC metabolism have not been thoroughly investigated, mainly because research regarding the effect of obesity on OC failure has not been conclusive to date. These potential biomechanisms can be studied further if prospective research confirms the relationship between obesity and OC failure.

B.4. Limitations of current research on the association between overweight/obesity and oral contraceptive failure

The first issue with the current research regarding overweight/obesity and oral contraceptive failure is that, to date, no prospective studies have been conducted. Consequently, the results are susceptible to differential misclassification, the most important example being recall bias.

The four previous studies used mostly questionnaire data to assess important variables, including height, weight, and OC brand, with the exception of Holt's 2005 study, which collected this information from medical records[14]. Their methods could easily be improved upon by using clinic measurements for height and weight and abstracting OC brand from medical records. Moreover, three of the studies only administered questionnaires once, at baseline participation. This is a major shortcoming since many of the covariates that potentially affect the outcome of OC failure are not static, but have the capacity to change over time. For example, a participant may smoke 20 cigarettes per day at baseline, but quit smoking completely by the study's conclusion. Therefore, the effect of tobacco on her risk of OC failure would change over the course of observation. Only prospective study designs can eliminate these types of error by collecting data on exposure and possible confounding variables repeatedly before the outcome (OC failure) occurs.

Furthermore, due to the retrospective design of all but one study among the BMI/weight and oral contraceptive failure publications, many potential confounding variables were not controlled for; hence, the studies could not adjust for these confounders (Table 2). To begin with, frequency of intercourse may

confound the relationship between BMI/weight and oral contraceptive failure; however, only Holt et al (2005) included it in their analysis. Some research suggests that women with a higher waist-to-hip ratio have fewer sexual partners;[31] Rhodes, Simmons, and Peters concluded that body averageness (average body size, as opposed to under or overweight) and symmetry had no relationship with sexual behavior in women.[32] Due to these mixed findings, assessing intercourse frequency may or may not be significantly different in women of different weight categories, and data should be collected and analyzed in future studies to be certain.

OC compliance is also an important covariate in the relationship between overweight/obesity and OC failure. Only Holt et al's 2005 study included compliant behavior. There may be a difference in compliance between different BMI groups, and it is also imperative to determine whether oral contraceptive failures are due to increased BMI or merely an artifact of non-compliance.

An issue closely related to compliance is that of the desire for children. According to Trussell et al, some women using oral contraceptives may actually want children, or feel ambivalent about the possibility.[33] Therefore, carefully designed questions regarding women's intentions to become pregnant would be useful in determining exactly how many accidental pregnancies can actually be considered unintended pregnancies.

Not all oral contraceptives contain the same amount of estrogen, and some use progesterone only. Holt el al (2002) found that the risk of oral contraceptive failure among women ≥70.5kg were elevated in a sub-analysis of women taking oral contraceptives with low and very low doses of estrogen (Table

1).[13] Therefore, results should be stratified according to oral contraceptive type and dose.

Using two contraceptive methods simultaneously undoubtedly lowers the risk of contraceptive failure, yet only two of the four published studies collected data regarding dual contraceptive use and were therefore able to control for this variable. Obtaining information from clinical records or questionnaire data regarding secondary birth control measures would substantially decrease error surrounding this issue.

Caffeine consumption, cigarette smoking, and alcohol use have all been shown to reduce fertility in women.[34-36] As suggested by Sowers et al, smoking, caffeine consumption, and wine drinking can alter the metabolism of estrogen.[37] Smoking was taken into account in two of the four studies examining the association between BMI/weight and oral contraceptive failure (Table 2), but none of the published research includes information on caffeine or alcohol intake. None of the previous studies were prospective in nature, and data was collected for purposes other than investigating the association between BMI and OC failure: it is likely that the information on confounders was not sufficient to adequately measure this association. Questionnaire data requiring information about the use of these substances throughout the study period will provide information that then can be taken into account in by stratification or controlling during statistical analyses.

Table 2. Covariates analyzed in overweight/obesity and oral contraceptive failure research

Covariate	Brunner & Hogue, 2005 (Retrospective Cohort)	Holt et al, 2005 (Case-Control)	Holt et al, 2002 (Retrospective Cohort)	Vessey & Painter, 2001 (Retrospective Cohort)
Frequency of Intercourse		√		
OC Compliance		√		
Type/Dose of OC		√	√	√
Pre-existing Conditions		√		
Desire for Children		√		
Dual Contraception Methods	√	√		
Medication		√		
Marital Status	√	√		
Parity	√	√	√	√
Race	√	√	√	
Socioeconomic Status	√	√		√
Caffeine Consumption				
Alcohol Use				
Smoking		√	√	
Age	√		√	√

C. Research Design and Methods

C.1. Study Protocols

C.1.1. Specific aim 1

I will gain access to the target population through physician and nurse contacts at local OB/GYN clinics in South Carolina. Four thousand, four hundred, and sixty-six (4,266) women will be enrolled in the study through these contacts after signing an informed consent document.

Rationale: The best way to access the target population is by collaboration with clinics specializing in women's health because the proportion of patients using OC's is higher than at general practitioners' offices, which accept a wider spectrum of patients. Recruitment through OB/GYN clinics is also more beneficial than attempting to contact participants directly since practitioners have an established relationship with their patients, and women would be more inclined to participate in research knowing that their practitioners are also involved. Furthermore, communication with OB/GYN clinics will provide access to changes in contact information in the event participants move during the study's follow up period.

Procedures for recruitment: The target population for this study is oral contraceptive users in the state of South Carolina. The study sample will be drawn from a collection of private and publicly funded obstetrics and gynecology (OB/GYN) clinics. The decision to include both private and pubic practices was made in order to increase external validity by recruiting women from a variety of socioeconomic demographics. Subjects will be recruited at their regularly scheduled gynecology appointments. At this time, clinic nurses will use an

eligibility form to determine whether patients qualify for the study. Women of all BMI categories will be included, who have childbearing capacity, desire a prescription for OC's, and have no contraindications to OC use. Eligibility will be also depend on the following criteria:

Age: Patients must be at least 18 years old to participate in the study. Minors will be excluded because they are not old enough to give consent without a parent or guardian's permission.

Duration of OC Use: In order to reduce loss to follow up, women who do not plan to use OC's for at least 12 months will not be included in the study.

Pre-existing Conditions: Chronic diseases may affect women's metabolism or hormone levels. Consequently, patients with diabetes mellitus or any thyroid disorder will be excluded. Additionally, women with polycystic ovary syndrome (PCOS) will also be excluded. The reasoning for this is that research has shown that PCOS is associated with obesity as well as altered glucose and hormone levels.[38] Since the syndrome and its association with reproductive function are complex, and many questions regarding PCOS remain unanswered, including subjects with the syndrome would be beyond the scope of this study.

Pregnancy: An eligibility requirement of the study will be women's intent to return to the clinic where they were enrolled in the case of pregnancy during the course of the study. This purpose of this requirement is to ensure that OC failures will be available for abstraction from medical records.

Pharmacy: Participants in the study must be willing to obtain OC prescriptions at participating pharmacies. Details regarding pharmacy involvement are provided under Specific Aim 2.

Phone: Only women with valid telephone numbers (either landline or cellular) will be eligible for the study since monthly follow up interviews will be conducted via telephone.

After determining eligibility, potential participants will be given a pamphlet describing the study and asked if they would like to participate. All women who answer yes will sign an informed consent document administered by the nurses. The nurses will also provide a study overview with contact information in case of any questions about study procedures.

Clinic records will be abstracted to determine the patient's height and weight without shoes at the time of the initial study visit, as measured by the clinic nurses, as well as the type and dose of OC prescribed. The records will be abstracted by study personnel at a later date.

After the OC's are prescribed, clinic nurses will then inform participants of nearby pharmacies participating in the study. Local pharmacies will be recruited to participate through contacts with pharmacists. The study will offer to pay for participants' OC prescriptions for the duration of enrollment as compensation for their time. When study participants bring their OC prescriptions to be filled, participating pharmacies will bill the cost of the prescription to the study. If a participant has valid health insurance, their co-pay will be billed to the study.

This approach to recruiting participants is ideal for several reasons. Most importantly, collaboration with OB/GYN clinics will afford the opportunity to review participants' medical records in order to confirm information such as height and weight, OC brand, existing medical conditions, and OC failure (i.e. pregnancy). Secondly, women will be able to ask questions and voice any

concerns regarding the study directly to their practitioners, with whom they have an existing rapport. As mentioned previously, study personnel will be able to obtain changes in addresses and phone numbers of participants from clinics in order to successfully complete the follow up period. Additionally, women who visit specialty clinics, rather than their general practitioners, for OC's are likely to be more serious about using OC's for birth control, which would increase the number of participants in the study who comply with the OC regimen.

A possible objection to this approach is the fact that OC users who obtain OC prescriptions from their general practitioners will be excluded from the study. However, since OB/GYN clinics are specialized, they will provide the best environment for recruitment. General practitioners have a broad range of patients to attend, so they may not be as willing to participate in research regarding women's reproductive health and would not have the opportunity to recruit as many women as OB/GYN clinics. Additionally, women who visit OB/GYN clinics for OC's would be more likely to return to the same clinic for pre-natal care than those who see general practitioners: the latter group may be referred to a specialty clinic if a pregnancy is detected. The ability to clinically confirm pregnancies is important in order to acquire accurate information regarding OC failure.

After recruitment, and after their scheduled gynecologic appointment is finished, participants will be asked to fill out a written questionnaire in a private area inside the clinic. Subjects will hand completed questionnaires to the clinic receptionist, who will store them in a locked file until retrieved by study

personnel. The questionnaire will include questions regarding basic demographics and each of the following variables:

Medication: Research suggests that drugs and herbal supplements such as anticonvulsants, antibiotics, and St. John's Wort may affect the efficacy of oral contraceptives.[39-42] Due to these interaction issues, participants' medical records will be reviewed to obtain information on administration of the aforementioned drugs and supplements, and subjects themselves will be asked in the initial questionnaire if they have taken anticonvulsants, St. John's Wort, or any antibiotics, and if so, to write the name of the drug or supplement. Medications will then be reviewed on a case-by-case basis to determine if a possible interaction does in fact exist.

Desire for Children: The importance of participants' desire for children has been described earlier, and this variable will be measured in the proposed study. This will be done by using a Lickert-type scale to assess how burdensome a having a baby would be in participants' life, and how happy they would be to have a child, if they found out that they become pregnant within the 30 days prior to enrollment.

Frequency of Intercourse: As mentioned earlier, intercourse frequency may vary across BMI categories.[31] Furthermore, it is an important variable to consider because a more frequent exposure to sperm will increase the risk of oral contraceptive failure. Frequency of intercourse will be measured by the initial questionnaire, on which participants will check the number of times per week, on average, they engage in sexual intercourse.

Dual Contraception Methods: A monthly telephone interview will ask participants how many times on average they use a second birth control method out of the number of times they reported having sexual intercourse. The rationale for collecting this information is to reduce confounding associated with the added protection against unintended pregnancy that accompanies dual contraception method use.

Marital Status: Given that the National Center for Health Statistics reported that during the time period between 1990 and 2000, pregnancy rates among married women were consistently higher than unmarried women, this factor will be taken into account in the proposed study.[43] The question regarding marital status will include the following response options: married, single and living with partner, single and not living with partner, separated, divorced, and other. Marital status will be measured separately from frequency of intercourse because although married women experience more pregnancies, this may also be due to other factors, such as pregnancy wantedness.

Age, Gravidity, Race, and Socioeconomic Status: As these variables are closely related to pregnancy rates,[43] questions regarding age, pregnancy history, and race and will be included in an initial questionnaire given at enrollment by clinic nurses. Gravidity will be captured in a question asking how many times participants have been pregnant, regardless of the outcomes of the pregnancies. Gravidity will be used instead of parity, which only refers to the number of pregnancies a woman has carried to term, in order to account for pregnancies that ended in spontaneous and induced abortions. Socioeconomic status will be

determined by education level and health insurance coverage, both of which will be included in the questionnaire.

Smoking, Alcohol, and Caffeine: Due to their association with decreased fertility and estrogen metabolism, smoking, alcohol use, and caffeine consumption will be determined. This information will be obtained by asking subjects to record the number of cigarettes, alcoholic and caffeinated beverages consumed on average at the time of enrollment. The monthly telephone interview also includes items on smoking, caffeine, and alcohol consumption to determine any changes in these variables over time.

C.1.2. Specific Aim 2

I will assess compliance with the prescribed OC regimen by obtaining used OC cases at the end of each month. Participants will be offered ten dollars for each case they return to the pharmacy. I will also measure compliance using a monthly questionnaire asking how many pills were missed during the previous cycle.

Rationale: Measurement of compliance to the prescribed OC regimen is essential in order to determine whether differences in failure rates can be contributed to missed pills. The World Health Organization's (WHO) practice recommendation for missed OC pills states that if only one active pill per cycle is missed, the missed pill should be taken as soon as possible, and then the regular one pill per day regimen should be resumed. If more than one active pill is missed, the subsequent missed pills may be discarded. Additionally, the recommendation cautions that the risk of pregnancy is higher when active pills are missed on the day immediately preceding or the day immediately following the 7-day inactive pill interval.[44] This recommendation is central to the following methods of measuring OC compliance.

A monthly telephone interview will be conducted in order to capture new medications and diagnoses, as well as any changes in weight, intercourse frequency, marital status, and tobacco/alcohol/caffeine consumption. Implementation of the monthly interview will allow for more accurate data collection for third variables than with the initial questionnaire alone since information will be available regarding these variables for each menstrual cycle for the entire duration of the study.

Procedures for measurement of OC compliance: Two methods will be used to measure OC compliance--a monthly telephone questionnaire and collection of OC cases at the end of each prescription by the participating pharmacy. The monthly questionnaire will ask how many pills were missed during the previous month, the date(s) missed, and whether the participant took the pill at a later time or skipped it completely. The starting date of the prescription and the starting date of the last menstrual period will also be collected in order to determine which day of the menstrual cycle pill(s) were missed, thereby indicating if the missed pill(s) were during the inactive or high-risk days. The questionnaire will also include questions regarding dual contraception use, new medical diagnoses, medications taken, tobacco/alcohol/caffeine consumption, desire for children, and change in marital status within the past month.

The second method of measuring OC compliance will be the collection of used OC cases at the end of each prescription will be employed. Participants will receive instructions from the pharmacy. They will be advised to leave all missed pills after the first missed one in the case (they will be asked to take the first missed pill as soon as possible after remembering it was skipped per the WHO's recommendation)[44]. The pharmacist will also give participants written instructions on what to do when they miss a pill at this time.

Participants will then be instructed to return the pill case to the pharmacy upon refill of the OC prescription, when they will receive a gift card to the pharmacy as compensation for the time and effort required to keep track of missed pills.

It may be argued that this two-fold method of measuring OC compliance is inferior to electronically monitoring compliance. A study by Potter et al found that women actually missed three times as many pills as they reported on a monthly diary card.[41] Information regarding missed pills was collected using an electronic device called the Medication Event Monitoring System (MEMS). MEMS records the dates and times that the OC case is opened, and the data is transferred to a computer after each prescription runs out. Due to the high cost of the MEMS device and its low success rate (35% of MEMS used by Potter et al were either not returned or the batteries had expired), the device will not be used in the current study. Furthermore, the use of the MEMS device may introduce selection bias. The group of women who failed to return the devices are likely to be non-compliant OC users due to irregular schedules. Collecting electronic data for only compliant OC users would not be helpful since the information would not be generalizable to the entire population of OC users.

C.1.3. Specific Aim 3

In order to identify differences in failure rates among women using high dose, low dose, and very low dose contraceptives, I will determine OC brand from the health care providers' records. I will then classify brands according to the amount of E2 in each: brands containing 50μg or more E2 will be classified as "high dose", brands with 35μg or more, but less than 50μg E2 as "low dose", and brands containing less than 35μg E2 as "very low dose." Additionally, progesterone only pills (POP) will be classified as "no estrogen."

Rationale: Holt, et al (2002) reported higher risks of failure among users of low dose and very low dose OC's than all OC users combined (relative risks 1.6, 2.6, and 4.5, respectively, Table 1)[13] These results indicate that it may be beneficial to carry out a subanalysis with stratification based on the dose of E2 in each OC brand. Furthermore, since POP's provide a slightly different mechanism of avoiding pregnancy than COC's, it is reasonable to anticipate a difference in pregnancy risk between the two types of OC's.

Procedures for data collection: For the purpose of this study, oral contraceptive failure will be defined as a pregnancy occurring while a subject is taking OC's. Non-compliant women will be excluded since pregnancies in this group may reflect user error instead of OC failure for biological reasons. This information will be obtained by two methods: self-report and the health care provider's medical records.

BMI will be determined both by clinic measurements at recruitment and by self-report of height and weight from a monthly telephone questionnaire. Using both sources of information will help gain a more accurate measure of height and

weight, and it will also aid in determining the extent of over and underreporting among oral contraceptive users. BMI will then be calculated using body weight (kg) over height (m) squared. Four BMI groups will be created using the WHO's definition of overweight and obesity: underweight (≤20), normal weight (>20 and ≤25), overweight (<25 and ≤30), and obese (<30).[45] These guidelines were chosen to maximize external validity, as WHO is an internationally established organization. BMI will then be grouped into two categories before statistical analysis—under/normal weight and overweight/obese. If a significant difference in OC failure is detected between the two groups, a sub-analysis will be performed using the four WHO categories to determine whether or not the trend is linear.

C.2. Sample Size and Statistical Power Calculations

C.2.1. Step 1: Calculation of Preliminary Sample Size

A Preliminary sample size was calculated using the survival option in PS: Power and Sample Size Calculation© software.[46] The alpha level was set to .05, and the power to detect a significant difference between groups to .80, which are both standard values in Epidemiologic studies. The relative risk was estimated at 1.6, and the median survival time in the referent group (underweight/normal weight) at 112 months: both were based on the results of Holt et al, 2002.[13]

Accrual time was set to 12 months, in order to keep the recruitment period to a reasonable length for participating clinics and pharmacies. Follow up time was also set to 12 months to allow enough time for women starting OC's at enrollment to become accustomed to the pill taking routine, while avoiding high rates of attrition that are associated with longer follow up periods.

The final parameter, the ratio of the referent group to the experimental group (overweight/obese), was estimated based on data from the 2006 Behavioral Risk Factor Surveillance System (BRFSS), which reported that 60% of South Carolinian women are either overweight or obese and 40% were either underweight or normal weight.[47] By dividing .40 by .60, the ratio of .67 was obtained.

After entering all parameters into the survival option in PS, the resulting sample size estimates were 1,612 for the referent group and 1,080 for the experimental group—a total of 2692 women.

C.2.2. Step 2: Adjustment for Prevalence of Pre-Existing Conditions

The preliminary sample size was then adjusted to account for comorbid conditions that may confound the relationship between BMI and OC failure and render women ineligible for participation. Population based prevalence estimates of the relevant disorders are as follows: PCOS—6.6%,[48] Diabetes Mellitus—4.0%,[49] Hypothyroidism—4.6%,[50] and Hyperthyroidism—1.3%.[50] Adding these percentages gives a total 16.5% of women approached who would be ineligible for the study based on pre-existing medical conditions. After dividing the preliminary sample size estimates by .835 (1 - .165), the new estimates were 1,931 for the referent group and 1,293 for the experimental group—3,224 women total.

C.2.3. Step 3: Correction for Attrition

The next step in calculating the study sample size was to adjust for attrition. Based on previous oral contraceptive research, loss to follow up for a 12 month period per women has been estimated at 25%.[51,52] By dividing the estimates from Step 2 by .75 (1 - .25), the estimated sample size after accounting for attrition were obtained: 2,575 for the referent group and 1,724 for the experimental group—4,299 total.

C.2.4. Step 4: Account for OC Failures

Finally, in order to obtain an adequate sample size, it was necessary to account for loss to follow up due to OC failure. Fu, et al estimated that between 3% and 8% of women using OC's became pregnant within 12 months of use.[2] Using the conservative prevalence of 3%, the referent group sample sizes determined in Step 3 was divided by .97 (1 - .03). The experimental group was divided by .952 (1 - .03*1.6), based on the relative risk estimate of 1.6 from Step 1. The final sample size estimates were 1,811 for the experimental group and 2,655 for the referent group—4,466 women total.

C.3. Statistical Analysis

The main analysis will compare two groups of women: underweight/normal weight women (referent group) to overweight/obese women (experimental group). In addition, two sub-analyses will be performed. The first will use all four of the WHO's BMI groups in order to check for a non-linear trend. The second will include four OC groups based on E2 levels (high dose, low dose, very low dose, no estrogen) to determine whether or not the dose of E2 depicts a linear relationship.

The effect of BMI on risk of oral contraceptive failure will be determined by a Cox proportional hazards model (PHM) for survival analysis, with the hazard ratio between BMI groups as the outcome variable. This model is appropriate for analyzing the data collected from this study for several reasons. It allows variables that change over time to be analyzed as functions of time, so the changes will be captured in the statistical model. Furthermore, the model makes no assumptions about the underlying distribution of the population. The model does assume that the risk of pregnancy in each group is proportional over time.

The following measures will be employed to ensure that the model is appropriate: covariates will be assessed for linearity, the proportional hazards assumption will be checked, and the Wilcoxon test will be used to assess the fit of the PHM.

If the proportional hazards assumption is not met, or if the number of events is small (i.e. zero inflation), which may occur with rare events such as OC failure, one of two other statistical methods can be applied. A zero inflated Poisson regression model may be used as long as the number of events at each

level of the covariates has a variance that equals the mean and the data follows a Poisson distribution.[53] However, overdispersion (when the variance is greater than the mean) often occurs with zero inflation, and although correction terms can be added to Poisson models to adjust the standard error, the correction terms often lack efficiency since they add variability to the model.[54] When this occurs, a negative binomial regression model may be a better fit, as it is a generalization of the Poisson model and can accommodate the overdispersion using a dispersion term.

If the Cox PHM model is not found to be adequate to analyze the study data due to overdispersion or zero inflation, both a Poisson model and a negative binomial model will be executed in order to determine the best fit. The Scaled Pearson Chi-Square test statistic will be used to determine the fit of the Poisson model and Akaike's information criterion will be used for the negative binomial model. The most appropriate model will then be used for the final analysis.

D. Strengths and Limitations

The proposed study has several strengths, most importantly the prospective design, which will help reduce recall bias. Furthermore, the study will analyze third variables that have not been included in previous research and measurement of third variables will be improved through clinic measured baseline height and weight and monthly assessment of changes in third variables. Finally, the study will use two methods of measuring OC compliance, namely the monthly telephone interview and the collection of OC cases by the pharmacy.

Like all research, this study has limitations. First, only OC users attending OB/GYN specialty clinics will be enrolled in the study. However, this limitation is not expected to be a hindrance to the selection of participants since differences between these women and women who obtain OC prescriptions from general practitioners is expected to be negligible.

Since only women with valid telephone numbers will be included in the study, there is a possibility for selection bias; however, this is a concern inherent to longitudinal studies that use telephone interviews for follow up. The percentage of women approached who do not have a phone will be collected in order to quantify the number excluded for this reason.

Although overweight and obese women outnumber the under and normal weight women in South Carolina, there may still be a stigma attached to being overweight. To address this issue, I will name the study "Determinants of Oral Contraceptive Failure" (DOCE Study), which does not specifically target overweight and obese women. This may also help mitigate any hesitation

OB/GYN's may have to prescribe OC's to these women based on the study hypothesis by providing a more general description of the study's aim.

Finally, previous OC research has shown that younger women (under age 20), may have higher rates of failure than older women, most likely due to unstable daily schedules and inexperience with the pill regimen.[2] This should not be a concern in this study since the Alan Guttmacher Institute found that the majority of OC users (73%) are over age 20.[55] Furthermore, the conservative sample size of the study will be able to account for OC failures due to user failure.

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