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Cardiovascular Disease Incidence among Females in South Carolina by Type of Oral Contraceptives, 2000-2013: a retrospective cohort study

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Abstract

Introduction—Certain types of oral contraceptives can produce favorable effects on lipid metabolism and vascular tone, while others have potentially detrimental effects. Endogenous and exogenous hormones exert different effects on high-density lipoprotein (HDL) and low-density lipoprotein (LDL) depending on the type, combination, and dose of the hormone. The estrogenic and progestogenic effects of exogenous hormones on HDL and LDL are inconsistent. Studying surrogate end points (LDL, HDL levels) may provide a misleading picture of OCs.

Methods—Medicaid data from 2000 to 2013 were used to assess the relationship between the type of OCs and CVD incidence. Multivariable logistic regression was used to model relationships between cardiovascular disease and OC use adjusting for potential confounders.

Results—Compared to combined oral contraceptives (COC), progestin-only oral contraceptives (POC) were associated with decreased heart disease and stroke incidence after adjusting for important covariates (OR: 0.74; 95% CI: 0.57, 0.97 and OR: 0.39; 95% CI: 0.16, 0.95,

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Conflict of Interest: None to disclose, and we had control of only secondary data through Medicaid

6.7. Contributions of Authors

Marsha/ Swann: project development

Marsha- data collection, management

Marsha/Zhang- analysis, interpretation

Marsha/ Whitney/ Anwar: writing, editing, other (conceptualize)

James/ Charles/ Swann: writing, editing

6.8. Compliance with Ethical Standards:

* Disclosure of potential conflicts of interest: Not applicable

* Research involving human participants and/or animals: Secondary data analysis only. This article does not contain any studies with human participants or animals performed by any of the authors.

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respectively). However, there was a positive association between POC+COC and both heart disease and stroke incidence (OR: 2.28; 95% CI: 1.92, 2.70 and OR: 2.12; 95% CI: 1.34, 3.35, respectively).

Conclusion—In light of an association between POC use and decreased heart disease and stroke, women's CVD risk factors should be carefully considered when choosing which OC to use. Baseline CVD risk should be a part of the discussion between women and their primary care providers when making choices regarding OCs.

Keywords

heart disease; women's health; oral contraceptives; chronic disease; trends

6.1. Introduction

Cardiovascular diseases (CVDs), including hypertension, stroke, coronary heart disease (CHD), peripheral artery disease, and venous thromboembolism (VTE), are the leading causes of death among females in the United States (US).^{2,3} Heart disease and its complications are the largest contributors to CVD incidence and mortality and disproportionately affect women and African Americans (AA).^{4,5} Over the past decades, there has been an increased use of oral contraceptives (OCs), as well as significant increase in heart disease and stroke morbidity and mortality rates.^{2,7,7} OC use, body fat, and race can lead to lipid and lipoprotein abnormalities and are important contributors to CVD.^{8,9}

OCs modulate lipid metabolism differentially according to the hormone make-up (e.g. progestin-only, combined estrogen+ progestin), delivery route and the particular patterns of use.¹⁰ High levels of low-density lipoprotein (LDL) cholesterol and triglyceride levels increase the risk of CVD in women while high-density-lipoprotein (HDL) may confer considerable protection against CVD incidence.¹¹ Hormones may have both beneficial and harmful impacts on lipids, lipoproteins, and cardiovascular health. Ideally, women should use OCs that reduce their risk of CVDs and protect them from unwanted pregnancies.

Endogenous estrogen, or estrogen produced naturally within an individual, can decrease LDL and total cholesterol by 5-15% and increase HDL by 10%.¹² However, exogenous estrogen, which is introduced to the body from an external source, has a diminished cardioprotective effect.¹³ The relationship between hormones and CVD becomes more complex when accounting for specific types of estrogen and progestin formulations or progestin-only formulations, which vary by country and OC generation.¹⁴ The impact of exogenous progestins and estrogens on LDL and HDL levels have not been studied as extensively and may not influence cholesterol levels.^{15,16} Thus, focusing on surrogate end points alone to predict clinical outcomes may be misleading.¹⁷ Although many pharmacologic agents (e.g., statins, PCSK9 inhibitors) that lower LDL significantly reduce cardiovascular events, other interventions that increase HDL and reduce LDL have no beneficial effect on CVD health.¹⁸

Additional studies are necessary to understand the role of OCs in the cardiovascular system, with a particular focus on progestin-only oral (POC) formulations. Due to the popularity of

estrogen+ progestin, or combined oral contraceptives (COC), studies have focused mainly on these types of OCs and overlooked the action of progestin (or exogenous progesterone) on CHD and stroke incidence. We hypothesize that POC use will be associated with less cardiovascular events than current and past COC users. Studies have shown COC users are more likely to suffer from VTE, stroke, myocardial infarction, cancer, and other chronic diseases compared to never users.^{19–22} The primary objective of the present retrospective cohort study was to compare the association of COC formulations with progestin-only regimens to understand the relationship of OC types and CVD incidence. We also examined potential effect modification by race.

6.2. Methods

Setting

The South Carolina (SC) Medicaid population is ideal for studying CVD incidence among racial/ethnic groups due to the high percentage of chronic disease, females and AAs residing in SC. SC is located in the southeastern part of the US, which is often referred to as both the “Stroke Belt” and the “Heart Failure Belt.” This region of the US is known as such because of the excess incidence and mortality of strokes and heart failure compared to the rest of the nation.^{7,24,25} Furthermore, Medicaid is one of SC's largest insurance providers, insuring 21% of SC residents, of which, 43% are AA.^{25,26} There has been significant increase in POC use among European American (EA) and AA women in SC from 2000 to 2013, which will provide us with adequate sample sizes to study the role of progestin-only contraceptives on CVD incidence.²⁷

Study Design and Participants

We constructed a retrospective cohort from the SC Revenue and Fiscal Affairs Office (RFA) Medicaid administrative enrollment and claims data to examine the relationship between OC type and CVD incidence among low-income populations by race/ethnicity. The SC RFA has information on OC prescriptions and the cardiovascular disease outcome (stroke and HD incidence). All women between the ages of 18 and 55 years (i.e., the usual age range for contraception use) with at least one type of OC prescription dispensed from 2000 to 2013 were included. All data were de-identified. Approval for the usage of this de-identified information was obtained by the University of South Carolina Institutional Review Board, as well as the Office of Research and Statistics/ SC Revenue and Fiscal Affairs Office.

Definition of exposure

OC status was determined from pharmacy claims that included the drug/generic names, dispensed date (month/year), national drug codes (NDC), therapeutic class (681200), age at claim, and days supplied. Women with at least one type of OC prescription dispensed during our study period and between 18 and 55 years of age (i.e., the range for contraception use) were included as OC users in our study. Type of OCs to which women were exposed prior to the event included progestin-only oral contraceptives (POC), oral contraceptives containing both estrogen and progestin, which are also known as combined oral contraceptives (COC), and both POC and COC (POC+COC). POC formulations in our study population included norethindrone only. The POC+COC group represents individuals who received prescriptions

for either a POC or a COC during the study period. These individuals were likely switched from one type of OC to another, but were unlikely to be on both simultaneously, as that would represent therapy duplication. OC types (POC, COC, and POC+COC) are mutually exclusive. Never users, POC and POC+COC users were compared to individuals who used COCs, the most popular OC type. Duration of OC use was calculated in months for each member using OCs.

Definition of outcome

The outcome was classified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, collected from the each patient's enrollment period. A primary diagnosis of HD was classified by the subcategory 414.XX. Major complications, such as myocardial infarction (410.XX), other acute or subacute forms of ischemic HD (411.XX), angina pectoris (413.XX), hypertensive HD, and diseases of pulmonary circulation related to HD, and other forms of HD resulted in a woman being flagged for HD (393- 398 and 420-429). Similarly, primary diagnoses of ischemic or hemorrhagic stroke (ICD-9-CM code of 430-438) were flagged for stroke.

Other covariates

Information on demographics were included, such as race (African American/European American), education (< high school/ some high school/ high school/ > high school), marital status (married/not married), duration of OC use, follow-up time and age. SC Medicaid administrative claims data, included women between January 1st, 2000 to December 31st, 2013, who 1) were permanent residents of SC during the study period, 2) had 12 months of Medicaid eligibility 3) were between the ages of 18 and 55 years and 4) were either African American/black or European American/white. Other races accounted for less than 5 percent of our cohort.

Statistical Analysis

Univariate and descriptive statistics were calculated for all study covariates. Differences in continuous measures were assessed using 2-sample t-tests and categorical measures were assessed using chi-square test. We evaluated the association between OCs and incident CVD using logistic regression analysis. Crude and adjusted odds ratios (ORs) were calculated with their corresponding 95% confidence intervals. There were four levels of exposure (never use, COC, POC, and POC+COC). Each group was compared to COC users, our referent group. Models controlled for important confounders, including year of diagnosis, age, race, duration of use, and education. Potential confounders that changed ORs by > 10% were retained in the final model. Analyses were stratified by race based on *a priori* hypotheses that there may be dissimilar effects by race. All p-values were two-tailed, and a value of less than 0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

6.3. Results

Study Participants

From 2000 to 2013, there were 1,396 incident CVD events (1,219 HD and 175 strokes). The mean age of women experiencing stroke (mean: 28.6 (7.5) years) was higher than those experiencing HD (mean: 30.1 (8.4)) (Table 1). The mean age of HD incidence for all women was higher among POC users (age: 31.4 SD: 8.8) than all other OC age groups (never user: 26.6 (SD: 7.0), COC: 28.7 (SD: 7.6), and POC+COC: 26.6 (SD: 7.0). Similarly, the mean age of stroke incidence for all women was higher among POC (mean: 29.8 (SD: 10.4)) compared to all other OC groups among women experiencing strokes (Table 1).

Table 2 shows that after adjusting for important covariates, certain oral contraceptive habits, specifically never use and POC use were inversely associated with HD compared to COC users (OR: 0.65; 95% CI: 0.52, 0.82 and OR: 0.74; 95% CI: 0.57, 0.97, respectively). POC +COC use was positively associated HD (OR: 2.28; 95% CI: 1.92, 2.70) compared to COC users.

The inverse association between never use of OC and HD compared to COC use, was consistent among women who had strokes, albeit it was not significant (OR: 0.95; 95% CI: 0.57, 1.59). However, there seemed to be differential effects by race. Among AA women the point estimate of the association between never use of OC was positive but non-significant (OR: 1.28; 95% CI: 0.72, 2.27) compared to COC users, whereas for EA women it was negative and non-significantly (OR: 0.46; 95% CI: 0.14, 1.46). Overall, POC use was inversely associated with stroke (0.39; 95% CI: 0.16, 0.95) compared with COC users. Longer durations of OC use was positively associated with heart disease and stroke ($p=0.01$). In addition, After adjusting for important covariates, women using POC+COC had twice the odds of heart disease (OR: 2.28; 95% CI: 1.92, 2.70) and stroke (OR: 2.12; 95% CI: 1.34, 3.35) compared to COC users.

6.4. Discussion

This retrospective analysis sought to examine the relationship between OC types among a population of low-income women and the incidence of heart disease and stroke. Our study findings show that POC users were associated with a significantly reduced risk of heart disease and stroke compared to COC users. Never users were also associated with a significantly reduced risk of heart disease; however, among stroke patients, the associated risk reduction is non-significant. Despite the non-significant association between never users, it is interesting to note that the point estimates for never users were in opposite directions for AA and EA women. Among never users, AA women were associated with a non-significantly higher risk of stroke compared to EA women and women had strokes at a younger age than expected.^{28–30} These results requires additional attention in future studies. The high prevalence of substance abuse in the Medicaid hospital care program, as well as the association between young adults' abuse of amphetamines or cocaine and increased risk of stroke may have contributed to the unexpected results among women.^{31–32}

Other potential explanations for the differential associations among stroke incidence by race may be explained by environmental or genetic factors, as well as medical surveillance bias.³⁴ AA women's positive association with stroke incidence and mortality compared to EA women may be due to their higher BMI, differential lipid modulation, thrombophilia occurrence and the type of OC prescribed.^{35–37} Despite a decline in recent decades of CVD mortality in the US, the rate among younger women has plateaued.³⁸ Therefore, it remains critical for us to investigate risk factors for CVD and to identify sustainable methods to successfully prevent disease.

The current literature examining OCs and CVDs often consider surrogate end points, such as glucose tolerance and lipoproteins to determine if an association exists.^{8,10,16} However, OC type and hormone interactions play an important role in modulating carbohydrate metabolism and risk factors such as lipoprotein levels. Due to the complex nature of this relationship, the role of exogenous progestin and estrogen on HD and stroke risk is still not clearly understood.⁸ Additional studies need to focus on the cardiovascular risk impact of exogenous hormones contained in OCs.

Additional medical encounters may reduce stroke risk for high-risk COC users because physicians may be detecting subclinical cases or precursors of stroke (e.g. hypertension) more frequently than for women who have less frequent clinical exposures.^{6,39} This may be more noticeable among AA women because of the known association between race and stroke.⁴⁰ Increased physician-patient contact may also help explain why women in our sample had such a low mean age of disease incidence and why never users may have had more stroke events.

There are many barriers to women's health services.⁴¹ The Patient Protection and Affordable Care Act (ACA) has many significant implications for women's health that may help reduce costs related to women's preventive care services, and that may improve gynecological and reproductive health of low-income women. Future studies should consider the impact of ACA and Medicaid expansion on women's health.⁴²

Adherence to guideline recommendations in clinical practice is usually variable, as patient-specific factors must be incorporated into decision-making. According to the guidelines set forth by the World Health Organization (WHO) Medical Eligibility Criteria (MEC) for Contraceptive Use, women of age 40 and older are in a lower medical eligibility criteria category regarding use of COCs compared to use of POCs. Use of COCs in women age 40 and older is considered a category 2 recommendation, meaning that it is, "A condition where the advantages of using the method generally outweigh the theoretical or proven risks," whereas, the use of POCs in women aged 40 and older is a category 1 recommendation, meaning that being of age 40 or older is, "A condition for which there is no restriction for the use of the contraceptive method."⁴⁵ COC use is still generally recommended in women of age 40 and older, but POCs are preferable. However, in our sample, the majority of women older than 40 were using COCs.^{40,45} Furthermore, the WHO guidelines do not specifically address women who have switched from COCs to POCs, or *vice versa*.⁴⁵ The POC+COC group is a unique group that includes many women who have had to change from COC to POCs, potentially due to a CVD event, breastfeeding; or women who switched

from POCs to COCs due to irregular bleeding.^{3,21,43} We found that these women were associated with significantly higher incidence of CVD; however, additional research needs to focus on this understudied group.

Strengths and Limitations

Our study has both strengths and limitations. A major strength is the large sample size, which allowed us to investigate racial disparities in CVD incidence among OC users in South Carolina. Since SC has a high representation of AA residents, we were able to assess CVD incidence in a multi-ethnic cohort. Another strength of our study is we did not have to adjust for socioeconomic status because all women in the Medicaid population are low-income.^{44,45} This allowed us to study an underrepresented group. However, a limitation to our study is that we did not have information on important factors that may influence CVD incidence including lipoprotein levels, diet, BMI and tobacco smoking. Furthermore, hemorrhagic stroke would not likely be caused by OC since OCs increase the risk of clots (ischemic stroke), but not bleeding (hemorrhagic stroke).³³ We analyzed the relationship between OCs and both types of strokes.

6.5. Conclusion

Our research indicates POCs are associated with a significantly decreased incidence of heart disease and stroke compared to COCs in our SC Medicaid sample. In accordance with the WHO guidelines, high-risk groups should consider non-hormonal contraceptive methods or POCs as an alternative contraceptive method that may be associated with a lower risk of certain cardiovascular diseases compared to COCs. Careful consideration of should be made when prescribing OCs. Determining which groups will benefit most from using POCs as their preferred contraceptive method may improve clinical CVD outcomes for women.

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Table 6.1
 Characteristics of Medicaid Population with Heart Disease and Stroke, South Carolina Medicaid Population, 2000-2013

Heart Disease										Stroke			
Exposure (Cases)		Never Use (n=84)	POC (n=64)	COC (n=898)	POC+COC (n=173)	Never Use (n=17)	POC (n=05)	COC (n=133)	POC+COC (n=22)				
Total Sample		7,604	3,500	51,901	4,729	8,233	3,792	56,578	5,225				
Year													
2000-2001		05 (6.0)	07 (10.9)	84 (9.4)	09 (5.2)	00 (0.0)	00 (0.0)	05 (3.8)	00 (0.0)				
2002-2003		13 (15.5)	07 (10.9)	97 (10.8)	13 (7.5)	01 (5.9)	01 (20.0)	13 (9.8)	01 (4.6)				
2004-2005		12 (14.3)	07 (10.9)	88 (9.8)	18 (10.4)	01 (5.9)	01 (20.0)	11 (8.3)	02 (9.1)				
2006-2007		7 (8.3)	06 (9.4)	140 (15.6)	32 (18.5)	02 (11.8)	00 (0.0)	14 (10.5)	01 (4.6)				
2008-2009		12 (14.3)	08 (12.5)	140 (15.6)	32 (18.5)	05 (29.4)	02 (40.0)	28 (21.1)	04 (18.2)				
2010-2011		16 (19.1)	14 (21.9)	177 (19.7)	40 (23.1)	04 (23.5)	00 (0.0)	29 (21.8)	06 (27.3)				
2012-2013		19 (22.6)	15 (23.4)	198 (22.1)	40 (23.1)	04 (23.5)	01 (20.0)	33 (24.8)	08 (36.4)				
Race													
EA		28 (33.3)	25 (39.1)	370 (41.2)	67 (38.7)	03 (17.7)	01 (20.0)	57 (42.9)	9 (40.9)				
AA		56 (66.7)	39 (5.4)	528 (58.8)	106 (61.3)	14 (82.4)	04 (80.0)	76 (57.1)	13 (59.1)				
Education													
<HS		26 (31.0)	21 (32.8)	319 (35.5)	56 (32.4)	07 (41.2)	02 (40.0)	47 (35.3)	12 (54.6)				
Some HS		11 (13.1)	06 (9.4)	94 (10.5)	31 (17.9)	00 (0.0)	02 (40.0)	13 (9.8)	02 (9.1)				
HS graduate		11 (13.1)	11 (17.2)	149 (16.6)	24 (13.9)	3 (17.7)	1 (20.0)	28 (21.1)	02 (9.1)				
>HS		36 (42.9)	26 (40.6)	336 (37.4)	62 (35.8)	07 (41.2)	00 (0.0)	45 (33.8)	06 (27.3)				
Marital Status													
Married		22 (26.8)	15 (23.8)	210 (23.8)	49 (28.7)	03 (17.7)	00 (0.0)	24 (18.3)	09 (40.9)				
Not Married		60 (73.2)	48 (76.2)	671 (76.2)	122 (71.4)	14 (82.4)	5 (100.0)	107 (81.7)	13 (59.1)				
Mean (Standard Error)													
Age (y)		26.6 (7.0)	31.4 (8.8)	28.7 (7.6)	26.6 (7.0)	26.1 (5.1)	29.8 (10.4)	27.5 (8.2)	28.9 (7.49)				
Duration (m)		N/A	12.2 (33.2)	12.1 (18.3)	37.8 (76.9)	N/A	49.2 (102.4)	11.9 (14.7)	14.7 (11.7)				

HS: High School; Rounding may cause columns not to equal 100 exactly

Table 6.2

Unadjusted and adjusted Odds Ratios of Heart Disease and Stroke by OC status: Using Combined Oral Contraceptives (COCs) as the Referent Group

	Heart Disease OR (95% CI)		Stroke OR (95% CI)	
	Unadjusted (n=1219 [±])	Adjusted [£] (n=1197 [±])	Unadjusted (n=177 [±])	Adjusted [£] (n=175 [±])
COC	1.00		1.00	
Never User				
EA	0.62 (0.42, 0.91) *	0.64 (0.44, 0.96) *	0.44 (0.14, 1.40)	0.46 (0.14, 1.46)
AA	0.89 (0.81, 0.98) *	0.65 (0.49, 0.87) *	1.13 (0.64, 1.99)	1.28 (0.72, 2.27)
Total	0.63 (0.51, 0.79) *	0.65 (0.52, 0.82) *	0.88 (0.53, 1.46)	0.95 (0.57, 1.59)
POC				
EA	0.95 (0.63, 1.43)	0.74 (0.49, 1.12)	0.25 (0.04, 1.80)	0.19 (0.03, 1.38) ¥
AA	1.13 (0.82, 1.58)	0.75 (0.53, 1.05) ¥	0.81 (0.30, 2.22)	0.55 (0.20, 1.50)
Total	1.06 (0.82, 1.37)	0.74 (0.57, 0.97) *	0.56 (0.23, 1.37)	0.39 (0.16, 0.95) *
POC+ COC				
EA	1.91 (1.46, 2.48) *	2.07 (1.58, 2.72) *	1.63 (0.81, 3.29)	1.98 (0.97, 4.05) ¥
AA	2.36 (1.91, 2.91) *	2.42 (1.94, 3.01) *	1.93 (1.07, 3.48) *	2.21 (1.22, 4.01) *
Total	2.16 (1.83, 2.55) *	2.28 (1.92, 2.70) *	1.80 (1.14, 2.82) *	2.12 (1.34, 3.35) *

Referent group: COC (Combined oral contraceptive); POC (Progestin-only oral contraceptive); POC+COC (Combined progestin-only method and combined oral contraceptive method); Each oral contraceptive group is mutually exclusive; EA (European American); AA (African American); Total (All Races)

[£] Adjusted for age, years, duration of use, marital status, and education

[±] total

* Significant (p < 0.05)

¥ Borderline significant (p < 0.10)