A Population-Based, Case-Control Evaluation of the Association Between Hormonal Contraceptives and Idiopathic Intracranial Hypertension

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• PURPOSE: **To determine if the use of oral contraceptive pills (OCP) and other hormonal contraceptives are associated with a higher incidence of idiopathic intracranial hypertension (IIH).**

• DESIGN: **Retrospective, population-based, case-control study.**

• METHODS: **Setting: Female IIH patients evaluated between January 1, 1990, and December 31, 2016 were identified using the Rochester Epidemiology Project (REP), a record-linkage system of medical records for all patient-physician encounters among Olmsted County, Minnesota, residents. Study Population: Fifty-three female residents of Olmsted County diagnosed with IIH between 15 and 45 years of age. The use of OCPs and other hormonal contraceptives was compared to controls matched for age, sex, and body mass index. Interventions/Exposures: Hormonal contraceptives. Main Outcome Measure: Odds of developing IIH.**

• RESULTS: **Of the 53 women diagnosed with IIH between 15 and 45 years of age, 11 (20.8%) had used hormonal contraceptives within ≤30 days of the date of IIH diagnosis, in contrast to 30 (31.3%) among the control patients. The odds ratio of hormonal contraceptive use and IIH was 0.55 (95% confidence interval [CI]: 0.24-1.23, $P = .146$). The odds ratio of OCP use was 0.52 (95% CI: 0.20-1.34, $P = .174$).**

• CONCLUSIONS: **OCP and other hormonal contraceptives were not significantly associated with a higher incidence of IIH, arguing against the need for women with IIH to discontinue their use. (Am J Ophthalmol 2019;197:74–79. © 2018 Elsevier Inc. All rights reserved.)**

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IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH) IS A condition of unclear etiology that typically occurs in young, obese women in the reproductive years, which causes headaches, papilledema, and possible vision loss.[1–5] Some prior studies, largely consisting of case reports,[6–10] suggest a link between oral contraceptive pills (OCPs) and an increased risk of intracranial hypertension,[7,8,11–15] while other studies have not shown this association.[2,16–19] There are also a few studies suggesting a possible association between IIH and non-OCP hormonal contraceptives, such as the levonorgestrel intrauterine device (IUD), contraceptive implants, and medroxyprogesterone.[6,9–11,15,20,21] The connection between hormonal contraceptives and IIH, therefore, remains controversial among clinicians and the general public. Any study evaluating the connection between hormonal contraceptives and IIH must take into account possible bias from the demographics of the disease, since women of childbearing age are the most likely patients to use contraceptives. The Rochester Epidemiology Project (REP) allows for an unbiased population-based investigation of associations across multiple medical centers, which has significantly contributed to our understanding of the incidence, pathophysiology, and risk factors for many diseases.[22,23] In this study, we used the REP to provide a population-based, case-control evaluation of the association between hormonal contraceptives and IIH.

METHODS

THIS RETROSPECTIVE CASE-CONTROL STUDY WAS CONducted using the REP database, a multicenter medical records database designed to capture data on all patient-physician encounters in Olmsted County, Minnesota.[22,23] The medical records of all female patients diagnosed in Olmsted County with IIH from January 1, 1990, through December 31, 2016, were reviewed. This study was approved by the Institutional Review Board of the Mayo Clinic and the Olmsted Medical Center, in Rochester, Minnesota, and conforms to the requirements of the

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United States Health Insurance Portability and Accountability Act.

During the 27-year study period, 63 women between the ages of 15 and 45 years were determined to have IIH using the modified Dandy criteria, which included signs and symptoms of increased intracranial pressure, no localizing neurologic finding except abducens nerve palsies, normal neuroimaging, lumbar puncture opening pressure > 250 mm H_2O with normal cerebrospinal fluid constituents, and no other apparent cause.[24,25] Four patients with disc edema and borderline opening pressures (200-250 mm H_2O) were determined to have had IIH after a neuro-ophthalmologist (J.J.C.) had reviewed each of their charts, and were also included in the study. Patients without a body mass index (BMI) on record or known contraceptive use status were excluded from this study, which left 53 IIH patients.

Data on the IIH patients' sex, ethnicity, age at diagnosis, BMI, ocular history, risk factors, presenting signs and symptoms, and treatments were obtained from the medical records. Up to 2 female age- and BMI-matched controls were selected for each IIH patient. The controls were selected such that their date of birth was within 3 years, age at diagnosis/point of contact was within 4 years, and BMI was within 4 points of their matched case. The closest BMI within 1 year of diagnosis was used for the matching. If there was no BMI recorded within 1 year of the match date, they were not considered for the matching. Data on use of various hormonal contraceptives in the IIH and the control patients without a diagnosis of IIH were retrieved from the medical records. The contraceptive forms in this study included intrauterine or intravaginal devices, medroxyprogesterone injections, contraceptive patches, and subcutaneous implants. The use of condoms or permanent sterilization was not included. IIH patients whose earliest contraceptive use was after the date of IIH diagnosis were included in the group without contraceptive exposure. For controls, contraceptive use was assessed on a date within a year of the IIH diagnosis date when a BMI was available in the medical record (match date). Continuous data were presented as medians and interquartile ranges, and categorical data were presented as counts and percentages. Univariate comparisons in patient characteristics across case status were performed using a Wilcoxon test for continuous variables and χ^2/Fisher exact tests (where appropriate) for categorical variables. Univariate associations between IIH diagnosis and OCP use were investigated using conditional logistic regression models to account for the matching. $P < .05$ was considered significant. All tests were 2-sided and were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

FIFTY-THREE WOMEN BETWEEN THE AGES OF 15 AND 45 YEARS met the inclusion criteria for IIH in Olmsted County between 1990 and 2016 and were matched by age and BMI to 96 controls. The distribution of age, year, and BMI was evenly balanced across IIH status (Table 1). Of the IIH patients, 11 (20.8%) were using hormonal contraceptives, 8 (15.1%) OCP, and 5 (9.8%) non-OCP. In contrast, among the controls, 30 (31.3%) were using hormonal contraceptives, 22 (22.9%) OCP, and 8 (8.4%) non-OCP (Table 2). OCP use was not associated with increased odds of IIH diagnosis, with an odds ratio of 0.52 (95% confidence interval [CI]: 0.20-1.34, $P = .174$), nor was the use of non-OCP hormonal contraceptives, which had an odds ratio of 1.31 (95% CI: 0.38-4.45, $P = .671$) (Table 2). Hormonal contraceptive use of any kind was also not associated with IIH, with an odds ratio of 0.55 (95% CI: 0.24-1.23, $P = .146$).

TABLE 1. Characteristics of the Idiopathic Intracranial Hypertension and Control Patients

Characteristic	Control N = 96	IIH N = 53	*P* Value
Age			.97[a]
Median (Q1, Q3)	27.0 (23.0, 31.5)	27 (23, 32)	
Range	16-44	16-44	
Year			.67[b]
<2005	23 (24.0%)	17 (32.1%)	
2005-2009	31 (32.3%)	13 (24.5%)	
2010-2014	26 (27.1%)	14 (26.4%)	
2015-2016	16 (16.7%)	9 (17.0%)	
Body mass index			.69[b]
Median (Q1, Q3)	38.0 (33.2, 45.5)	37.9 (34.1, 46.0)	
Range	20.5-61.6	21.4-61.1	

IIH = idiopathic intracranial hypertension; Q1 = lower quartile of interquartile range; Q3 = upper quartile of interquartile range.
Data indicate n (%) unless otherwise noted.
[a]Wilcoxon.
[b]χ^2.

DISCUSSION

BY DEFINITION, IIH IS A CONDITION OF INCREASED INTRACRANIAL pressure of unknown etiology.[16,25,26] In trying to better characterize the disease, IIH studies have investigated several possible associations, ranging from social factors (ie, marital status, education level, and history of insecticide exposure) to medical history information (ie, obesity, endocrine disorders, gravidity, and medication use).[2,17–19] While some medications, such as tetracyclines,[27–33] are commonly accepted to be associated with IIH, there has been no firm consensus among physicians on whether hormonal contraceptive use is associated with intracranial hypertension. Our study revealed that the rate of OCP use

TABLE 2. Associations Between Contraceptive Use and Idiopathic Intracranial Hypertension Status

Characteristic	Control (N = 96) N (%)	IIH (N = 53) N (%)	Odds Ratio[a] (95% CI)	*P* Value[a]
Oral contraceptive pills				.174
Yes	22 (22.9%)	8 (15.1%)	0.52 (0.20, 1.34)	
No	74 (77.1%)	45 (84.9%)	1.00 (ref)	
Medroxyprogesterone acetate				.535
Yes	4 (4.2%)	1 (2.0%)	0.50 (0.06, 4.47)	
No	91 (95.8%)	50 (98.0%)	1.00 (ref)	
Contraceptive patch[b]				
Yes	0 (0.0%)	1 (2.0%)		
No	95 (100.0%)	50 (98.0%)		
Levonorgestrel-releasing intrauterine device				1.000
Yes	4 (4.2%)	2 (3.8%)	1.00 (0.18, 5.46)	
No	91 (95.8%)	50 (96.2%)	1.00 (ref)	
Etonogestrel/ethinyl estradiol vaginal ring[b]				
Yes	0 (0.0%)	1 (1.9%)		
No	95 (100.0%)	51 (98.1%)		
Contraceptive implant[b]				
No	95 (100.0%)	52 (100.0%)		
Any non-OCP contraceptive				.671
Yes	8 (8.4%)	5 (9.8%)	1.31 (0.38, 4.45)	
No	87 (91.6%)	46 (90.2%)	1.00 (ref)	
Any hormonal contraceptive[c]				.146
Yes	30 (31.3%)	11 (20.8%)	0.55 (0.24, 1.23)	
No	66 (68.8%)	42 (79.2%)	1.00 (ref)	

IIH = idiopathic intracranial hypertension; OCP = oral contraceptive pill; ref = reference value.

[a]Odds ratio, 95% CI, and *P* value come from a conditional logistic regression model.

[b]Variables were not included in logistic regression models owing to insufficient numbers.

[c]"Any hormonal contraceptive" includes intrauterine or intravaginal devices, medroxyprogesterone injections, contraceptive patches, and subcutaneous implants.

was 15.1% among IIH patients, which is consistent with CDC reports of 15.9% OCP use among women between 15 and 44 years of age in the United States.[34] The rate of use of long-acting reversible contraceptives, such as an intrauterine device or contraceptive implant, among IIH patients in this population-based cohort was similar at 9.8%, compared to 8.0% nationally in 2016.[34] Our study also showed that there is no association between IIH and the use of OCPs or other hormonal contraceptives, with an odds ratio of 0.55 (*P* value = .146).

The debate on whether the use of hormonal contraceptives is associated with IIH has persisted over the decades. One of the early studies often cited as suggesting there was a connection was by Walsh and associates (1965).[35] Of the 63 patients reported, they had just 4 cases of IIH with OCPs, and their conclusion was ultimately that further study was indicated regarding an association with OCPs. Another source commonly cited as evidence of an association between levonorgestrel and IIH was a letter to the editor by Alder and associates (1995).[20] This included a summary of a review of 2 databases for levonorgestrel use and any intracranial hypertension or disc edema and 2 case reports. The authors again concluded that levonorgestrel "may have contributed to the onset of intracranial hypertension, or it may have had nothing to do with it."[20] Lastly, 2 articles commonly cited by proponents of an association between hormonal contraceptives and IIH are based on the U.S. Food and Drug Administration's (FDA) MedWatch Spontaneous Reporting System,[10] FDA's Adverse Events Reporting System database, and a large health claims database, IMS LifeLink.[21] Wysowski and associates (1995) reviewed reports of adverse events in Norplant users and noted 39 patients with IIH, but 18 out of the 39 were overweight or obese, and no BMI was available for the remaining 21 patients.[10] Etminan and associates in 2015 reviewed both the reported adverse events of Mirena users and records of patients who used any 1 of 3 hormonal contraceptives (intrauterine levonorgestrel, ethinyl estradiol–norgestimate, and norethindrone), but included various types of intracranial hypertension, including cerebral edema and "obstructive hydrocephalus idiopathic normal pressure hydrocephalus."[21]

More recently, Contreras-Martin and associates in 2015 published a retrospective case series showing 10 of 42 (23.8%) IIH patients on OCPs, again suggesting there is an association between the two, but this study did not have a control group.[12] Valenzuela and associates (2017) used a different approach and compared the use of levonorgestrel IUD among IIH patients in the University of Utah and the Glostrup Hospital in Denmark using controls who were found through different methods.[15] At the University of Utah, controls were gathered among female patients without IIH who had undergone levonorgestrel IUD insertion at that center over the same time period.[15] At the Glostrup Hospital in Denmark, the proportion of women without IIH who might have a levonorgestrel IUD was estimated by extrapolation from the number of such IUDs sold in the country in 2014.[15] The prevalence of IIH compared between the groups with and without IUDs revealed odds ratios of 7.70 (95% CI: 3.7-16.0) and 3.91 (95% CI: 1.89-8.06) in the 2 groups, respectively.[15] In addition to the unconventional methods of obtaining the controls, the numbers of IIH patients were acknowledged by the authors to be small (8 patients at each medical center), and there was no adjustment for potentially confounding factors such as BMI and use of other hormonal contraceptives. The authors ultimately encouraged caution in applying their preliminary findings in practice and did not recommend that levonorgestrel IUDs be discontinued in IIH patients.

These findings have been in contrast to 4 earlier case series, each with 27-50 IIH patients, all finding no significant association between IIH and OCP use. Durcan and associates (1988) found that 4 of 27 (17%) of their IIH patients were on OCPs, similar to the 15.6% in the general population at the time.[2] Ireland and associates (1990) reported that among their 40 IIH patients and 39 age- and sex-matched controls, there was no significant association between IIH and OCP use (OR 1.80, 95% CI: 0.42-7.64).[18] Giuseffi and associates (1991) followed up closely with 50 IIH patients and 100 age- and sex-matched controls, also demonstrating no significant association between IIH and OCP use (OR 0.6, 95% CI: 0.2-1.8).[17] Lastly, Radhakrishnan and associates (1993) showed that among their 40 IIH patients and 80 age- and sex-matched controls, OCP use was not significantly associated with IIH (OR 1.39, 95% CI: 0.63-3.04).[19] Our study was designed to address the gaps left in these prior studies by providing a population-based, case-control study with age-, sex-, and BMI-matched controls. It reaffirmed that from 1990 to 2016, there was no significant association between hormonal contraceptive use and IIH.

There are several reasons why the perception that an association exists between hormonal contraceptive use and IIH may have persisted despite evidence to the contrary. First, young female individuals of reproductive age who are at the highest risk for IIH[1–5] are also most likely to be using contraceptives.[36] From 2011 to 2013, 61.7% of the 60.9 million women aged 15-44 years in the United States were using contraception, the most common of which were the OCPs, at 16.0%.[36] Secondly, hormonal contraceptives are known to induce a prothrombotic state[37] and are the most frequent risk factors for cerebral venous thrombosis in women.[38] Although the modified Dandy criteria require normal neuroimaging and no other apparent cause of increased intracranial pressure for the diagnosis of IIH, the use of magnetic resonance venography was not as prevalent in the 1990s. It is also possible that early studies using different criteria may have included undiagnosed cases of cerebral venous thrombosis, reflecting the higher risk of thrombosis in patients using hormonal contraceptives.[39]

Perhaps the most convincing argument against the hypothesis that hormonal contraceptive use increases the risk of IIH is simply that if there were a causal relationship, and approximately 16.8 million women in the United States are using a hormonal contraceptive,[36] we might expect the IIH incidence rate to be higher than 1.8/100 000 persons.[40]

This study's limitations include the retrospective design, the inconsistent reporting of contraceptive use in the medical records, the small number of patients with non-OCP hormonal contraceptive use, the lack of data on the use of other medications known to be IIH risk factors, and the racial homogeneity of the study population. Owing to the retrospective nature of this study, some data points were imprecise or unavailable, some patients were unavoidably lost to follow-up, and there was no prospective masking or randomization. However, this can be expected to affect both the IIH and control cohort equally. If there were a bias from underreporting, the controls should theoretically have less complete medical records because the patients with IIH were likely getting more frequent medical care owing to their disease. Another limitation of this work was the exclusion of patients missing contraceptive use data (n = 10). By excluding patients with missing data, we may have biased our results, as we had assumed the data were missing at random. This assumption was reasonable, however, as the distribution of age, year of diagnosis, and BMI were similar across excluded and included patients. There were also few patients on non-OCP hormonal contraceptives within 30 days of IIH diagnosis, so a larger study population would be necessary to analyze the data by contraceptive subcategories, each with a different type and amount of hormones, to fully exclude a potential link for each non-OCP hormonal contraceptive. In addition, our study included cases of IIH and control patients from 1990 to 2016 and therefore we could not evaluate for a potential connection with the original OCPs that had much higher levels of hormones. Exposure to medications known to be associated with IIH, including tetracyclines or vitamin A derivatives, was not examined in the controls and therefore was not analyzed. Lastly, it may be difficult to extrapolate these findings to more racially heterogeneous populations since the study population was 90% white. Despite these limitations, this study is valuable because it combines population-based data with a case-

control evaluation, which minimizes bias and supports prior non-population-based, case-control studies showing no association between hormonal contraceptives and IIH.

In conclusion, this study provides further evidence against the association between hormonal contraceptive use and the development of IIH.

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