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Original Research Article

Risk of Pseudotumor Cerebri Syndrome (PTCS) with hormonal contraceptive use

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ABSTRACT

Background: Hormonal contraceptives (HC), one of the most prescribed classes of medication in women, have been linked with pseudotumor cerebri syndrome (PTCS). To date, no large epidemiologic study has examined this association.

Methods: A case-control study using the IMS LifeLink Pharmetrics Plus database was conducted. Cases had an ICD-9-CM code for benign intracranial hypertension as well as a procedural code for a CT or MRI and a code for lumbar puncture procedure within 15 days of the PTCS code. Controls were selected from the cohort using density-based sampling.

Results: From a cohort of 9,053,240 subjects, there were 288 cases of PTCS corresponding to 2,880 controls. The adjusted RRs for two or more prescriptions of oral combined contraceptive was 0.62 (95% confidence interval 0.39-0.99). RRs for overall HC use was 0.91 (95% CI 0.39-2.12) for one prescription of HCs and 0.69 (95% CI 0.45-1.05) for two or more prescriptions. The RRs for one and two or more prescriptions of progestin only HCs were 0.75 (95% CI 0.08-7.46) and 1.06 (95% CI 0.42-2.69), respectively.

Conclusions: Overall HC use does not have a significant effect on incidence of PTCS, however harm associated with progestin-only contraceptives cannot be excluded.

Keywords: Benign intracranial hypertension, Case-control study, Estrogen, Hormones, Hormonal contraceptives, Oral contraceptives

INTRODUCTION

Hormonal contraceptive (HC) drugs are one of the most prescribed classes of medications in women. Pseudotumor cerebri syndrome (PTCS) is a rare but serious condition that leads to an increased intracranial pressure in the absence of malignancy or other causes. One clinical feature of PTCS is papilledema or swelling of the optic nerve secondary to raised ICP. If untreated,

this can lead to vision loss. PTCS occurs most often in women of child bearing age. Obesity has also been shown to be highly correlated with the disease¹. The effect of several medications on the risk of PTCS have also been studied including tetracycline and fluoroquinolone antibiotics, vitamin A derivatives, and HC medications.²⁻⁴

The role of HCs on the risk of PTCS has been the topic of much debate and many studies have reported on the

potential association of HCs and PTCS. There is sufficient plausibility that HCs increase the risk of PTCS. Indeed, studies that have measured levels of estrogen analogues (estradiol, estriol, and estrone) in human cerebrospinal fluid (CSF) demonstrated that in most patients with PTCS, CSF estrone levels, not estradiol and estriol, were measurable in most PTCS cases and were significantly elevated versus controls.⁵ In addition, one published case series described five women aged 18-27 who developed symptoms of PTCS, namely headaches, papilledema, and engorged veins of the optic disk, while on combined HCs.⁶ Once these patients were switched to progesterone-only HCs, clearance of headache and return of normal blood flow to the optic disks was observed, thus indicating the potential role of estrogens in PTCS.⁶

A study by Ireland et al undertook a small case-control study of 40 cases and 39 controls that examined potential risk factors for PTCS.⁷ The study found a non-statistically significant increase in risk (Odds Ratio = 2.50, 95% CI: 0.95-6.54) among women who took HCs within 12 months of PTCS diagnosis.⁷ However, with only 40 cases of PTCS, there was insufficient statistical power to draw any conclusions from this study. Another study by Giuseffi et al also examined the relation between HCs and PTCS.⁸ This study found no association between HCs with PTCS (OR: 0.60, 95% CI 0.2-1.8) although the study was also underpowered and relied on patient recall to ascertain HC exposure.⁸

In light of the lack in large epidemiologic studies on the relation between HCs and PTCS we sought to examine the risk of PTCS with HCs using a large health claims database in the United States.

METHODS

Data sources

The IMS LifeLink Pharmetrics Plus database contains health claims comprised of over 150 million unique enrollees, with fully adjudicated medical and pharmacy claims including detailed information on the pharmacy and medical benefit (copayment, deductible) and the inpatient stay and provider details (provider specialty included in all extracts). Specifically, it contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs. This database is generally representative of the under 65 commercially insured population in the US with respect to both age and gender.⁹ The database is a good representation of all geographic areas of the United States.⁹ We had access to a random sample of 9,053,240 million subjects of PharMetrics from 2006-2016.¹⁰

Cohort entry

Subjects entered the cohort with the first enrollment date and were followed to the first physician visit for PTCS (International Classification for Diseases 9th Revision,

Clinical Modification (CM), ICD-9) code 348.2. From the cohort, we omitted those with prior diagnosis of papilledema, as this condition implies raised intracranial pressure secondary to an intracranial mass lesion. We also excluded cases of meningitis and central venous thrombosis, given they are distinct clinical entities that present with papilledema unrelated to PTCS. A one year look back period was required for all subjects to assess study drug and covariate distribution. We restricted our analysis to only women.

Case and control definition

A definition for identifying PTCS cases was derived following consultation with a neuro-ophthalmologist (CAS). All newly diagnosed cases of PTCS (ICD-CM 348.2) were first identified. This date was regarded as the index date. In addition to having the first ICD-CM code for PTCS each case was required to have received a current procedural terminology (CPT) codes for a head computerized tomography (CT) scan or magnetic resonance imaging (MRI) in addition and prior to a code for lumbar puncture (LP) within 15 days of the PTCS code. This definition was used in the primary analysis. As some cases of PTCS may be diagnosed first and confirmed by imaging or LP later, a patient could have received these procedures within 15 days after the date of the ICD-9 code. For each identified case, ten control patients (those without any diagnosis of PTCS) were identified and matched to the cases by calendar time, age, and follow up time. Controls were eligible to become future cases and could have been selected more than once. This density-based sampling approach of control selection has shown to generate odds ratios (ORs) that closely approximate rate ratios (RR).¹¹

Exposure definition and statistical analysis

We ascertained all HC prescription records for cases and controls in the year prior to the index date. We categorized HCs to mutually exclusive groups of one of the following categories:

1. All forms of hormonal contraceptives (HCs) including combination ethinyl estradiol and progestin pills
2. Oral combination pills
3. All forms contraceptive progestins which included intrauterine or subdermal preparations, and injectable progestin HCs
4. All forms of progestins which included drugs in the point above in addition to non-contraceptive progestins used for hormone replacement therapy or gynecological disorders.

Exposure was defined as use of at least one prescription in the year prior to the index. Given that both estrogen and progestin hormonal contraceptives may play a role in PTCS development and studies/case reports suggesting that both estrogen and progestin containing

contraceptives might increase the risk of PTCS, we combined all HCs in one of the analyses. The use of one prescription was used to examine whether the risk of PTCS is an acute event. We further examined the risk of PTCS with two or more prescriptions to observe any dose response effect with the study drugs and also ensured that patients continued taking their medications. Additionally, this category maximized exposure as it examines the risk in women who renewed their prescriptions. The RRs for all categories were compared to non-users of any category.

A conditional logistic regression model was used to estimate rate ratios adjusting for the following covariates: obesity, hypothyroidism and use of tetracyclines, fluoroquinolones, isotretinoin and steroids. In order to assess the effect of obesity in the study we also undertook an analysis excluding obesity in the model. All analyses were done using SAS version 9.3. Ethics approval was obtained from the University of British Columbia Ethics Board.

RESULTS

From a cohort of 9,053,240 million subjects, there were 288 cases of PTCS which were matched to 2,880 controls (Table 1). We excluded all men from the study and the women had a Mean±SD age of 33.6±13.2 years and obesity were greater in cases (35.1% of cases versus 9.3% of controls) (Table 1). Proportion of patients with hypothyroidism was also slightly higher in PTCS cases compared to controls (19.4% versus 8.7%) (Table 1). Additional prescription drug use including tetracyclines, fluoroquinolones, isotretinoin, and steroids was also found to be higher in cases compared to controls (Table 1).

Table 1: Characteristics of pseudotumor cerebri cases and their matched controls.

Characteristics	Cases	Controls
Number	288	2.880
Age in years	33.6±13.2	33.6±13.2
Follow-up in years	3.7±2.9	3.7±2.9
Covariates (%)		
Obesity	35.1	9.3
Hypothyroidism	19.4	8.7
Tetracycline	26.7	11.3
Fluoroquinolone	0.7	0.5
Isotretinoin	16.0	6.7
Steroids	26.0	11.2

The adjusted rate ratios (RR) for one prescription of all HCs was 0.91 (95% confidence interval [CI] 0.39-2.12) and for two or more prescriptions, the RR was 0.69 (95% CI 0.45-1.05) (Table 2).

The RRs for one and two or more prescriptions for oral combined contraceptives were 1.00 (95% CI 0.41-2.45) and 0.62 (95% CI 0.39-0.99), respectively (Table 2). The RRs for one and two or more prescriptions of all forms of progestin HCs including those used for hormone replacement therapy (HRT) was 0.75 (95% CI:0.08-0.46) and 1.06 (95% CI 0.42-2.69). The RR for two or more prescriptions for all forms of progestin HCs was 1.90 (95% CI 0.74-8.72) (Table 2). The results did not change significantly in the obesity excluded analysis other than the category for those taking two or more oral contraceptives where the protective effect was lost (Table 3).

Table 2: Rate ratios and confidence intervals for the risk of pseudotumor cerebri syndrome with different formulations of hormonal contraceptives.

	Cases	Controls	Crude Rate ratio	Adjusted* Rate ratio	95 % CI
Number of subjects	288	2880			
No use of any HC (%)	86.5	83.8	Reference	-	-
All HCs N (%) 1Rx	7 (2.4)	64 (2.2)	1.04	0.91	0.39-2.12
All HCs N (%) ≥2Rx	32 (11.1)	403 (14.0)	0.75	0.69	0.45-1.05
Oral combination pills N (%) 1Rx	6 (2.1)	56 (1.9)	1.01	1.00	0.41-2.45
Oral combination pills N (%) ≥2Rx	23 (8.0)	339 (11.8)	0.64	0.62	0.39-0.99
All progestins+HRT N (%) 1 Rx	1 (0.4)	8 (0.3)	1.20	0.75	0.08-7.46
All progestins+HRT N (%) ≥2 Rx	6 (2.1)	48 (1.7)	1.18	1.06	0.42-2.69
All forms progestin HCs N (%) ≥2 Rx	4 (1.4)	16 (0.6)	2.39	1.90	0.74-8.72

*Adjusted for variables in Table 1 except obesity; Rx: Prescription; HRT: Hormone replacement therapy

Table 3: Rate ratios and confidence intervals for the risk of pseudotumor cerebri syndrome with different formulations of hormonal contraceptives excluding obesity from the analysis.

	Cases	Controls	Crude Rate ratio	Adjusted* Rate ratio 95% CI	
Number of subjects	187	1,720			
No use of any HC (%)	86.1	85.0	Reference	-	-
All HCs N (%)	6 (3.2)	34 (2.0)	1.56	0.64	0.67-4.04
All HCs (%) ≥ 2 Rx	20 (10.7)	220 (13.0)	0.80	0.74	0.44-1.25
Oral combination pills N (%) 1Rx	5 (2.7)	32 (1.9)	1.40	1.47	0.56-3.85
Oral combination pills N (%) ≥ 2 Rx	17 (8.0)	193 (11.8)	0.78	0.71	0.41-1.24
All progestins +HRT N (%) 1Rx	1 (0.5)	2 (0.1)	3.92	4.68	0.42-52.27
All progestins +HRT N (%) ≥ 2 Rx	3 (1.6)	22 (1.3)	1.19	1.23	0.34-4.41
All progestin HCs N (%) 1 Rx	0 (0.0)	1 (0.1)	0.00	0.00	-
All progestin HCs N (%) ≥ 2 Rx	3 (1.6)	5 (0.3)	4.84	5.11	1.19-21.96

*Adjusted for variables in Table 1 except obesity; Rx: Prescription; HRT:Hormone replacement therapy

DISCUSSION

This study is the first large epidemiologic study investigating the effects of all HCs and PTCS.

These results found no association of PTCS with overall HC use. Progestin-only contraceptives were also not associated with an increase in risk, although the upper limit of the confidence interval is high, which does not exclude a harmful association. Subjects with two or more prescriptions of oral combined HCs demonstrated a statistically significant protective effect against PTCS when obesity was adjusted for although the upper limit of the confidence interval was very close to 1.

Since obesity is a major confounder in this study, RRs from the obesity adjusted model are more accurate than the analysis where obesity was not accounted for. Although this may seem contradictory to previous aforementioned case reports, some animal studies provide evidence that highlights a potential protective effect of estrogen. For example, estrogen has been implicated in decreasing brain edema, brain tissue water content, and ICP thus exerting a protective effect, in particular following traumatic brain injury.¹²⁻¹⁴ Furthermore, estrogen has demonstrated a decrease in choroid plexus production of CSF, thus decreasing intracranial pressure (ICP) in rabbits.¹⁵

The cellular mechanism relating estrogen to ICP is unclear. Increased glutamate receptor and excitatory neurotransmission has been found to increase intracranial pressure and antagonizing glutamate receptors has been shown to decrease brain tissue water content¹⁶. Estrogen has been implicated in decreasing severity of glutamate neurotoxicity by upregulating glutamate transporters in astrocytes, which are critical for synaptic glutamate reuptake and preventing excitotoxicity and neurodegeneration¹⁷. In humans, on days of the menstrual cycle when blood glutamate levels are at their lowest, plasma estrogen levels are at their highest and vice versa,

indicating a potential protective role.¹⁸ It has also been speculated that estrogens may promote venous sinus thrombosis, impairing CSF resorption however, in the current study, subjects with cerebral venous thrombosis were excluded from analysis and we are unable to comment on this association.^{19,20}

Future studies are needed to further examine the role of progestin only contraceptives with PTCS, other than case studies.^{21,22}

One recent descriptive study demonstrated an increase in risk with intrauterine levonorgestrel (IL) and PTCS.²³ The study used data from Utah and Denmark and showed an increased odds ratio of 7.70 (95% CI: 3.7-16.0) and 3.91 (95% CI: 1.89-8.06).²³ One limitation of the study was difficulty discerning the timing of the onset of PTCS in relation to IL use.

The present study has a few strengths and limitations. One key strength of our study methodology was in the identification of PTCS. We ensured robust ascertainment of PTCS with the assistance of a neuro-ophthalmologist (C.A.S) and made use of lumbar puncture and brain imaging codes.

One main limitation is the relatively low number of cases. Another limitation of our study is that the database we utilized does not record patient medical records, and thus we did not have details of individual patients' medical history. We did not have complete information on BMI for cases and controls, although the crude and adjusted analyses for obesity did not change the results.

Finally, it is possible that some women may have acquired HCs through other insurance providers which would not be captured in their prescription drug history. However, we do not believe this would have occurred differentially among cases and controls and is unlikely to have affected the results of the present study.

CONCLUSION

Overall use of HCs was seen to have no significant effect on incidence of PTCS, however harm for progestin-only contraceptives cannot be excluded and requires further work to confirm in addition to investigating different HC drug delivery systems. Estrogen containing HCs may be a viable option for women currently taking drugs that may induce PTCS or have comorbidities of PTCS, however further research must be done to determine potential HC benefit or harm.

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Conflict of interest: No conflict of interest

Ethical approval: The study was approved by University of British Columbia Ethics Board

REFERENCES

- Andrews LE, Liu GT, Ko MW. Idiopathic intracranial hypertension and obesity. *Horm Res Paediatr.* 2014;81:217-25.
- Chen J, Wall M. Epidemiology and Risk Factors for Idiopathic Intracranial Hypertension. *Int Ophthalmol Clin.* 2015;54:1-11.
- Johns Hopkins Medicine Health Library: Pseudotumor Cerebri. Available at http://www.hopkinsmedicine.org/healthlibrary/conditions/nervous_system_disorders/pseudotumor_cerebri_134_57/#risks Accessed 23rd June 2017.
- Sodhi M, Sheldon CA, Carleton B, Etminan M. Oral fluoroquinolones and risk of secondary pseudotumor cerebri syndrome: Nested case-control study. *Neurol.* 2017;89(8):792-5
- Donaldson JO, Horak E. Cerebrospinal fluid oestrone in pseudotumour cerebri. *J Neurol Neurosurg Psych.* 1982;45:734-6.
- Soysa ND. The oral contraceptive pill and benign intracranial hypertension. *N Z Med J.* 1985;98:656.
- Ireland B, Corbett JJ, Wallace RB. The Search for causes of idiopathic intracranial Hypertension A preliminary case-control study. *Arch Neurol.* 1990;47:315-20.
- Giuseffi V, Wall M, Siegel PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. *Neurol.* 1991;41:239-44.
- Quintiles IMS real-world data adjudicated claims: USA [QuintilesIMS PharMetrics Plus] Available at <https://www.bridgetodata.org/node/824> Accessed 26th June 2017.
- IMS. IMS LifeLink PharMetrics Plus US. Available at http://www.imstestarea.com/heor_emailer/IMS_Lifelink_PHX_1012.pdf Accessed 26 June 2017.
- Essebag V, Genest J Jr, Suissa S, Pilote L. The nested case-control study in cardiology. *Am Heart J.* 2003;146:581-90.
- Dehghan F, Khaksari M, Abbasloo E, Shahrokhi N. The effects of estrogen receptors' antagonist on brain edema, intracranial pressure and neurological outcomes after traumatic brain injury in rat. *Iran Biomed J.* 2015;19:165-71.
- O'Connor CA, Cernak I, Vink R. Both estrogen and progesterone attenuate edema formation following diffuse traumatic brain injury in rats. *Brain Res.* 2005;1062:171-4.
- Shahrokhi N, Khaksari M, Soltani Z, Mahmoodi M, Nakhaee N. Effect of sex steroid hormones on brain edema, intracranial pressure, and neurologic outcomes after traumatic brain injury. *Can J Physiol Pharmacol.* 2010;88:414-21.
- Lindvall-Axelsson M, Owman CH. Changes in transport functions of isolated rabbit choroid plexus under the influence of oestrogen and progesterone. *Acta Physiologica.* 1989;136:107-11.
- Cao F, Chen M, Li G, Ye K, Huang X, Zheng X. Altered expression of metabotropic glutamate receptor 1 alpha after acute diffuse brain injury. *Neural Regen Res.* 2012;7:119-24.
- Pawlak J, Brito V, Küppers E, Beyer C. Regulation of glutamate transporter GLAST and GLT-1 expression in astrocytes by estrogen. *Brain Res Mol Brain Res.* 2005;138:1-7.
- Zlotnik A, Gruenbaum BF, Mohar B, Kuts R, Gruenbaum SE, Ohayon S, et al. The effects of estrogen and progesterone on blood glutamate levels: evidence from changes of blood glutamate levels during the menstrual cycle in women. *Biol Reprod.* 2011;84:581-6.
- Galzara M, Gazzeri R. Cerebral venous sinus thrombosis associated with oral contraceptives: the case for neurosurgery. *Neurosurg Focus.* 2009;27(5):E5.
- Sasidharan PK. Cerebral vein thrombosis misdiagnosed and mismanaged. *Thrombosis.* 2011;2012:1-11.
- Chan JW. Idiopathic intracranial hypertension associated with depot medroxyprogesterone. *Eye.* 2006;20:1396-7.
- Bahemuka M. Benign intracranial hypertension associated with the use of Depo-Porvera (depot medroxyprogesterone): a case report. *East Afr Med J.* 1981;58:140-1.
- Valenzuela RM, Rai R, Kirk BH, Sanders JN, Sundar S, Hamann S, et al. An estimation of the risk of pseudotumor cerebri among users of the levonorgestrel intrauterine device. *Neuro-Ophthalmol.* 2017:1-6.

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