Irritable Bowel Syndrome and Drospirenone-Containing Oral Contraceptives; A Comparative-Safety Study

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Abstract: Background: Mineralocorticoids are thought to play a role in tissue repair, including fibrous tissue formation. The antimineralocorticoid activity of spironolactone has been linked to an increased risk of gastrointestinal bleeding. Drospirenone is a synthetic progestin approved in combination with ethinyl-estradiol as an oral contraceptive (OC). It is a spironolactone-derivative, and its antimineralocorticoid effects could irritate the gastrointestinal tract leading to symptoms of irritable bowel syndrome (IBS).

Methods: A retrospective cohort study was conducted evaluating women 18-46 years of age in the IMS claims-database. New-users of progestin-based OCs were identified between 1997-2009. Ninety days of OC therapy and one year of prior enrollment with no prior diagnosis of IBS were required for inclusion. Cases were identified using a previously validated method for the diagnosis of IBS. Cox proportional hazards models were used to estimate the hazard ratio (HR) for developing IBS with the different OC formulations using levonorgestrel as a reference.

Results: The cohort included 939,281 women, averaging 29.1 years of age and 247 days of OC therapy. 3,050 incident cases of IBS were detected. The annualized incidence for IBS with drospirenone was 0.77% (1083 cases) while that for levonorgestrel was 0.46% (483 cases). The crude HR for development of IBS with drospirenone compared to levonorgestrel was 1.70 (95%CI 1.53-1.90), while the adjusted HR was 1.63 (95%CI 1.46-1.82). Multiple sensitivity analyses confirmed this association. Other OCs were unassociated with IBS.

Conclusion: Our study found a positive association between drospirenone and a diagnosis of IBS that was not observed with other OCs.

Keywords: Oral contraceptives, irritable bowel syndrome, drospirenone.

INTRODUCTION

Irritable bowel syndrome (IBS) is a condition of the lower gastrointestinal (GI) tract that has been previously estimated to affect between 13 and 19 percent of women [1, 2]. It is a sensory and motility disorder that is characterized by abdominal pain and changes in bowel patterns without any determined diagnostic cause [3]. Symptoms of IBS have a negative impact on health related quality of life [4], activities of daily living, and both work and leisure time [5-6]. Patients with IBS utilize substantially more health care services, are prescribed more prescription drugs [7], and develop more comorbidities and psychological conditions [8]. Irritable bowel syndrome, like fibromyalgia and migraines, leads to chronic pain and disproportionately affects women [1, 9, 10]. Studies have shown that the severity of IBS symptoms fluctuate with the menstrual cycle and worsen during menses [11, 12], suggesting a role of female gonadal hormones in IBS. Females of reproductive age represent the majority of women seeking medical care for IBS [13], while the prevalence of IBS in postmenopausal women is approximately the same as that in men [14]. This suggests that varying levels of estrogen and progesterin may be associated with IBS. It is however unknown how the differing androgenic and estrogenic properties of available oral contraceptives (OCs) affect IBS development and symptomology.

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Drospirenone is a synthetic progestin approved in combination with ethinyl estradiol as an OC, and it is a derivative of spironolactone [15]. It was designed as an antimineralocorticoid steroid that does not possess androgenic effects, but actually exhibits antiandrogen activity [16, 17]. This antimineralocorticoid activity is unique to drospirenone products and not present in other available OCs.

Mineralocorticoids have known endocrine properties and are thought to promote tissue repair, including fibrous tissue formation [18, 19]. An animal study has also shown that antagonism of mineralocorticoid receptors with spironolactone can attenuate the formation of fibrous tissue [19]. Based on the hypothesized mechanism for the inhibition of fibrous tissue formation in the GI tract, cases reports [20-22], two large case-control studies [23, 24] and one cohort study [25] have concluded that spironolactone use leads to a two-fold increase in upper-GI bleed. Spiroalactone also has labeled GI side effects for anorexia, nausea, vomiting, cramping, diarrhea, gastritis, abdominal pain, gastric bleeding, and ulceration [26], and a recent case series linked spironolactone to diarrhea [27]. Based on the similar chemical structure and shared antimineralocorticoid activity of drospirenone and spironolactone, it was hypothesized that long-term administration of drospirenone could have adverse GI effects and may be associated with incident IBS. Drospirenone also has labeled gastrointestinal side effects (>1%) including abdominal pain, diarrhea, dyspepsia, enlarged abdomen, and gastroenteritis. Additionally, antimineralocorticoid activity is also known to affect both electrolytes and water balance which could also affect the GI tract [16, 17]. This study aims to evaluate the association between drospirenone and irritable bowel syndrome.

METHODS

Data Source

The IMS Lifelink™ Health Plan Claims Database contains paid claims data from over 102 managed care plans in the United States. The database contains fully adjudicated medical and pharmacy claims for over 68 million patients, including inpatient and outpatient diagnoses and procedures (International Classification of Diseases, 9th Revision, Clinical Modification format) in addition to retail and mail order prescription records. The data is representative of US residents with private health insurance in terms of geography, age, and gender. The Lifelink™ database is subject to quality checks to ensure data quality and to minimize error rates [28].

Cohort Description

A retrospective cohort was developed, evaluating women in the IMS Lifelink™ claims database between January 1st, 1997 and December 31st, 2009. All women between 18-46 years of age with the first prescription for an OC containing ethinyl estradiol (35 μg or less) and one of the following progestins were included in the cohort: desogestrel, drospirenone, ethinodiol diacetate, levonorgestrel, norethindrone acetate, norethindrone, norgestimate, and norgestrel. Although our intent was to evaluate the association between drospirenone and IBS, all progestin containing OCs were included to provide a full picture for the development of IBS with use of available OC products. Inclusion into the study cohort also required 90 days of continued exposure to an OC, and the index date was defined as day 90 of OC therapy. This was modeled after ROME III criteria, which requires three months of active symptoms before diagnosis of IBS [29].

Women were excluded if they did not have one full year of enrollment in IMS data. They were further excluded if they had a diagnosis for IBS (ICD-9-CM 564.1) or inflammatory bowel disease (IBD: ICD-9-CM 555, 556) during this one year period, or if their index OC prescription (day 90 of OC therapy) was prior to this one year period, creating a cohort of new users. Women were censored from further analysis 90 days after discontinuation of OC therapy or if they switched to another OC, developed IBS during the study period, ended enrollment, or reached the end of the study period. Nearly all women switching to a second OC had at least a 90 day gap in OC therapy. If the development of IBS causes a patient to switch OCs, evaluation for the outcome during the 90 days post-discontinuation will prevent against an informative censoring bias.

Outcome Definition

The primary analysis for incident IBS cases in our study cohort was performed using a previously validated method that found a positive predictive value of 83% [30]. This method required one year of enrollment with no prior claims for IBS. Patients were required to have at least one diagnosis of IBS (ICD-9-CM 564.1) in addition to diagnoses of abdominal pain (ICD-9-CM 789.0) and either diarrhea (ICD-9-CM 564.5, 787.91) or constipation (ICD-9-CM 564.0) to be counted as a case. All three diagnoses were required to occur after the start of OC therapy, and for patients who met these criteria, the date when all criteria were met was used as the index date for development of IBS. Cases were further broken down into constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), and alternating (IBS-A) based on the presence of diagnostic codes for constipation and diarrhea in the case ascertainment.

Statistical Analysis

Cox proportional hazards models were used to estimate the time to first occurrence of IBS. The primary analysis compared OCs containing drospirenone with OCs containing levonorgestrel. Levonorgestrel was chosen as a reference OC based on its high utilization in our study population and its use as a reference in previous comparative-safety studies [31-33]. All estimates were adjusted by potential confounders which included age, calendar time, smoking status, obesity, diabetes mellitus, hypertension, chronic kidney disease, anxiety, depression, acne, premenstrual tension syndrome (premenstrual syndrome, and premenstrual dysphoric disorder), and polycystic ovary syndrome (PCOS). ICD-9-CM codes were used to define covariates during the one year prior to cohort entry.
Sensitivity Analysis

Sensitivity analysis was conducted to determine the effect of changing the reference to 1) norgestimate, which is the most commonly used OC in IMS data and 2) all other study COCs. A second sensitivity analysis was conducted, comparing drospirenone to levonorgestrel and requiring five diagnoses of IBS, each at a separate physician visit, for inclusion as a case. This method has been validated in IBD patients [34, 35].

Because patients with PCOS may have higher rates of gastrointestinal disorders [36] and drospirenone’s antiandrogenic activity is thought to be beneficial for PCOS [37], we quantified the effect of adjustment for PCOS (ICD-9-CM 256.4) on the point estimate in the main analysis using levonorgestrel as a comparator. Further, we developed a second PCOS definition that would likely have a higher sensitivity and evaluated the impact of its adjustment on the point estimate for drospirenone and IBS. The second PCOS definition included women with a claim for PCOS (ICD-9-CM 256.4), a claim for a diagnostic criteria for PCOS [anovulation (ICD-9-CM 628.0) and hirsutism (ICD-9-CM 704.1)], prescription treatment for PCOS (spirolactone), or a procedure for polycystic ovaries [wedge resection of ovary / ovarian drilling (CPT-4 58920), drainage of ovarian cysts (CPT-4 58800, 58805), and ovarian cystectomy (CPT-4 58925)].

In addition, a validation study was conducted to evaluate the ability of this database to determine known associations between medications and IBS. For positive controls, we tested the ability of this database to detect the presence of IBS in patients taking loperamide and alosetron. Because these treatments for IBS, a large portion of patients taking these drugs will have IBS, and a strong association would demonstrate our ability to detect this condition. Two negative controls, not known to cause IBS, were tested for an association with incident IBS: hydrochlorothiazide and amlodipine.

The Rule-out approach was used to measure the magnitude of a residual confounder necessary to mitigate the association found between drospirenone and IBS [38]. All analyses were conducted with SAS version 9.2, and this study was approved by the University of Florida IRB.

RESULTS

The cohort included 939,281 women with 635,323 person-years of follow up time. Patients in the study averaged 29.1 years of age and had a mean follow up time of 247 days of OC therapy. There were 3,050 newly diagnosed cases of IBS. Broken down by subtype, 581 (19.0%) cases were constipation-predominant, 1643 (53.9%) cases were diarrhea-predominant, and 826 (27.1%) cases were alternating-subtype. These cases represent new reports of IBS starting during OC therapy. Baseline characteristics are reported in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Women Included in the Study Cohort by Type of Progestin Oral Contraceptive Used (n=939,281)</th>
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</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>Mean follow up, days</td>
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<tr>
<td>Cases IBS</td>
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<td>IBS-C*, %</td>
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<tr>
<td>IBS-D*, %</td>
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<td>IBS-A*, %</td>
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<tr>
<td>IBS annualized IR, (%)</td>
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<tr>
<td><strong>Covariates (%)†</strong></td>
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<td>Acne</td>
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<td>Anxiety</td>
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<td>Depression</td>
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<td>Diabetes</td>
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<td>Obesity</td>
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<td>PCOS</td>
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<tr>
<td>PTS (PMS/PMDD)</td>
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<td>Smoking</td>
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IBS=irritable bowel syndrome, IR=incidence rate, CKD=Chronic Kidney Disease, PTS (PMS/PMDD) = premenstrual tension syndrome (premenstrual syndrome and premenstrual dysphoric disorder), PCOS=Polycystic Ovary Syndrome.

*All covariates are defined with ICD-9-CM codes.
†IBS subtypes were determined through the presence of a diagnostic codes: Constipation predominant (IBS-C) symptomology was determined by claims for IBS (ICD-9-CM 564.1) and constipation (ICD-9-CM 564.0); Diarrhea predominant (IBS-D) symptomology was determined by claims for IBS (ICD-9-CM 564.1) and diarrhea (ICD-9-CM 564.5, 787.91); Alternating symptomology was determined by claims for IBS (ICD-9-CM 564.1) constipation (ICD-9-CM 564.0) and diarrhea (ICD-9-CM 564.5, 787.91).
The crude HR for the development of IBS with drospirenone compared to levonorgestrel was 1.70 (95% CI 1.53-1.90), while the adjusted hazard ratio was 1.63 (95% CI 1.46-1.82). The adjusted HRs for other OCs were similar and non-significant (Table 2).

**Table 2. Risk for Irritable Bowel Syndrome (IBS)* after 90 Days of Continuous Use of Commonly Used Oral Contraceptives**

<table>
<thead>
<tr>
<th>Contraceptives</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR† (95%CI)</th>
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<tbody>
<tr>
<td>Levonorgestrel</td>
<td>1.0 (reference)</td>
<td>1.0</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>1.07 (0.94-1.22)</td>
<td>1.06 (0.93-1.21)</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>1.70 (1.53-1.90)</td>
<td>1.64 (1.47-1.83)</td>
</tr>
<tr>
<td>Ethynodiol diacetate</td>
<td>0.97 (0.71-1.32)</td>
<td>0.95 (0.70-1.30)</td>
</tr>
<tr>
<td>Norethindrone acetate</td>
<td>0.98 (0.83-1.15)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>Norethindrone</td>
<td>0.73 (0.64-0.85)</td>
<td>0.77 (0.67-0.89)</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>0.78 (0.69-0.89)</td>
<td>0.82 (0.72-0.94)</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>0.79 (0.59-1.05)</td>
<td>0.78 (0.59-1.04)</td>
</tr>
</tbody>
</table>

*Cases of IBS determined by presence of IBS (ICD-9-CM 564.1) and abdominal pain (ICD-9-CM 789.0) and either diarrhea (ICD-9-CM 564.5, 787.91) or constipation (ICD-9-CM 564.0).†Adjusted by age, calendar time, smoking status, obesity, diabetes mellitus, hypertension, chronic kidney disease, anxiety, depression, polycystic ovary syndrome, and premenstrual tension syndrome (premenstrual syndrome and premenstrual dysphoric disorder).

Sensitivity analysis evaluating the association between drospirenone and IBS with norgestimate as a reference, found crude and adjusted HRs of 2.18 (95%CI 1.95-2.43) and 1.97 (95% CI 1.76-2.21), respectively. Using all study COCs as a reference resulted in crude and adjusted HRs of 1.91 (95%CI: 1.77-2.06) and 1.77 (95%CI: 1.64-1.91) for drospirenone and IBS. Additional sensitivity analysis, requiring five diagnostic codes for IBS during OC therapy for inclusion as a case found crude and adjusted HRs of 1.77 (95%CI 1.53-2.05) and 1.58 (95% CI 1.36-1.83), respectively.

Adjustment for a PCOS claim changed the HR by less than 1% when using levonorgestrel as a reference. A second PCOS definition also including diagnostic criteria, treatment, and procedures resulted in PCOS ascertainment representing 5.7% of the total population. This is closer to the known PCOS prevalence of 6% to 10% [39]. Adjustment for this PCOS definition decreased the HR by 2%.

In the validation study, the positive controls had the following HRs: loperamide HR 14.34 (95%CI 8.67-16.41) and alosetron HR 9.85 (95%CI 5.35-15.42). The results of the negative controls are as follows: hydrochlorothiazide HR 0.99 (95%CI 0.66-1.49), and amiodipine HR 1.11 (95%CI 0.60-2.45).

Sensitivity analysis with the rule out approach found that confounding factors with a prevalence of 20% would need a relative odds with both outcome and exposure of 4 to 5 before the hazard ratio for the association between drospirenone and IBS would be reduced to 1.0 (Appendix). The population attributable risk percent [40] was calculated to be 19.25%, when comparing drospirenone to the general OC population. The incidence rate for new cases of IBS with drospirenone is 573/100,000 women years (WY), while that with all other OC users is 262/100,000 WY. The number needed to harm was calculated using these incidence rates to account for contributed time [41], finding one additional incident case of IBS per 322 WYs of treatment with drospirenone compared to other OCs.

Proportionality of hazards were examined graphically by means of log-log survival curves, and no meaningful deviations from proportionality were observed after baseline.

**DISCUSSION**

Our study found an increased risk for development of IBS with drospirenone when compared to levonorgestrel. Sensitivity analysis, changing the reference comparator to norgestimate or to all study COCs, found both stronger crude and adjusted risk for IBS with drospirenone. The non-significant association between all other progestin based OCs and IBS supports the unique nature of this signal with drospirenone.

**Comparison to Previous Publications**

Our literature review did not find any studies reporting the association between OCs and IBS. One study was identified that evaluated severity of IBS in patients taking OCs. The study included 149 patients with IBS and performed a subgroup analysis on 56 of these patients taking OCs [42]. It did not find an association between OCs and severity of IBS. The study however was conducted in a small patient population, included patients only from one source, and did not evaluate the association between OCs and severity of IBS as its primary outcome.

Current evidence supports that IBS symptoms are affected by the menstrual cycle, particularly in the late luteal and early menses phases [43]. Although no study has measured gonadal hormone levels during IBS flares, a study including 46 women with IBS reported that IBS symptomology was significantly (p<0.01) related to the cyclical nature of the menstrual cycle [12]. When stratified by phase of the menstrual cycle, pain sensitivity has been shown to be greater during the luteal phase, when progesterin is at its highest level [44]. Greater levels of thermal pain sensitivity have also been shown with higher plasma levels of gonadal hormones [45]. Further, gonadal hormone levels have been shown to decrease gastric emptying, leading to constipation [46], particularly during the luteal phase of menstruation. These hormones have also been shown to increase expression of 5-hydroxytryptamine3 (5HT3) [47], and the use of 5HT3 antagonists in randomized clinical trials has shown significant reduction in GI symptoms associated with IBS [48]. Because OCs have both estrogenic and androgenic properties, their effect on IBS needs further exploration, particularly with use of drospirenone which contains unique antiandrogen and antimineralocorticoid activity.

Drospirenone’s derivation from spironolactone and unique antimineralocorticoid activity makes it different from
other available OCs [16, 17]. This activity results in increased excretion of water and sodium and retention of potassium. Although drospireNONE contains a bolded warning for hyperkalemia, we did not observe a clinically meaningful increase in hyperkalemia with use of drospireNONE [49].

Drospirenone’s antimineralocorticoid activity has also shown to reduce hirsutism and hyperandrogenism in women with PCOS [37], and we observed selective prescribing of drospirenone in women with PCOS (Table 1). A previous study by Mathur et al. used a gastrointestinal questionnaire to identify IBS and found that 15/36 women with PCOS had IBS compared to 3/30 women without PCOS [36]. In our study, we did find a significant association between PCOS and IBS (HR 1.16, 95%CI: 1.02-1.32); however, its adjustment did not substantially affect our point estimate. Mineralocorticoids are thought to play a role in tissue repair [18-19], and an animal study found the antimineralocorticoid activity of spironolactone reduced fibrous tissue formation in the GI tract [20]. Several large scale observational studies have also implicated spironolactone for a two-fold increased risk of upper-GI bleeding [23-25]. The antimineralocorticoid potency of drospirenone is approximately eight times greater than spironolactone [16], and a 3mg tablet of drospirenone has a similar effect to 20-25mg of spironolactone [50]. This raises concerns for the effect of long term administration of drospirenone on the GI tract. This activity has also been hypothesized to result in an increased risk of gall bladder disease and has fostered recent litigation [51]. Although a clinically meaningful signal for removal of the gall bladder (cholecystectomy) was not seen in IMS data [52], an increased risk for IBS with drospirenone could produce a mechanism for an increased detection of gall bladder disease, resulting in a detection bias [53, 54].

Strengths and Limitations

This is the first, large epidemiologic study to evaluate the effect of different progestin based OC’s on IBS. Our study methodology limited confounding by indication and contraindication by using an active comparator for the analysis. Inclusion into the cohort required 90 days of OC therapy and exposed person time was calculated after this exposure period to prevent an immortal time bias [55]. The use of a validated outcome requiring three types of diagnostic codes for inclusion of cases, in addition to one year of enrollment with no diagnostic codes for IBS or IBD, provides additional assurance that the identified cases are new occurrences of IBS. All positive and negative controls in our validation study provided the expected results. This provides additional assurance in the ability of our cohort and methodology to determine an association between a medication and IBS.

Our case ascertainment was previously validated in the HMO Research Network Center for Education and Research on Therapeutics [30]. This database, like IMS, is comprised of a sample of insurers within the United States. The case ascertainment in our study has been previously shown to have a PPV of 83% for incident IBS and some patients in our study were likely misclassified as having incident cases. It would be expected that any outcome misclassification in our study is non-differential between available OCs, creating a bias toward the null. Because a PPV of 83% in our primary analysis is a potential limitation, an additional sensitivity analysis was conducted, requiring five diagnostic codes for IBS during OC therapy, each at a different physician visit, for inclusion as a case. This more stringent definition was shown to have a 95% PPV when used for inflammatory bowel disease [34]. Its adaption to IBS in the current study likely resulted in a higher PPV than the main study definition, and its use resulted in a similar association between drospirenone and IBS.

Our breakdown of IBS subtype was similar to a previous study that broke down IBS by subtype, finding 19.4% of cases constipation-predominant, 57.3% diarrhea-predominant, 26.4% alternating, and 1.5% unknown [56]. Our subtype classification however could report fewer alternating IBS subtypes if physicians only file a claim for one IBS symptom.

The prescribing of oral contraceptives may be influenced by heavy marketing from manufacturers. By controlling for calendar time, we are attempting to control for secular trends in prescribing of oral contraceptives that may usually favor the prescribing of one oral contraceptive over another. Drospirenone has been shown to benefit in patients with acne, premenstrual dysphoric disorder, and polycystic ovary syndrome, and these covariates were adjusted for in our analysis.

The causal pathways for IBS are poorly understood and there are likely unknown unmeasurable confounders that play a role in IBS. Although anxiety and depression were adjusted for in our regression model, the use of ICD-9-CM codes, during the one year prior to the OC start date, likely underreported these conditions. Two covariates, obesity and smoking, are reported to justify treatment and are used as a best approximate in our regression model. They are specific but underreported. Diet, exercise, alcohol consumption, and ethnicity are other potential residual confounders that could affect our study results. With our large study population and the magnitude of the effect for drospirenone and IBS, it would take a powerful group of confounders to remove the significance of this effect as shown in the rule-out sensitivity (Fig. A1).

FUTURE IMPLICATIONS

With most OCs having similar effectiveness, the comparative safety of OCs has an increasing role for making a treatment decision. Recent studies have shown that drospirenone provides a modest reduction in blood pressure and weight loss due to increased excretion of sodium and water [57, 58]. Risk for venous thromboembolism with drospirenone has received recent attention, and studies have found conflicting results [31, 59, 60]. The positive association between IBS and drospirenone found in this study helps to better refine the safety profile for drospirenone. It however should be considered with respect that the annualized IR for incident IBS with drospirenone was 0.77%. Although physicians should be aware of the potential for adverse GI effects, this should not affect the
initial treatment decision. Further studies are needed to evaluate OCs and incident IBS with the same criteria for case ascertainment. The use of a data source that can more accurately define covariates, especially obesity and depression, would add additional insight into this finding.

CONCLUSION

Our study found a positive association between drospirenone use and a diagnosis of IBS that was not observed with other OCs. The similar efficacy of OCs places additional emphasis on the comparative-safety in the treatment decision. Patients who have IBS or experience IBS while taking drospirenone should carefully evaluate their treatment options when deciding about the continuation of OC therapy.

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Guarantor of the Article

Mahyar Etminan

Specific Author Contributions

All authors contributed to the study concept and design and the analysis and interpretation of data. Steven Bird performed the statistical analysis and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. Mahyar Etminan is the study guarantor, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final draft for submission.

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POTENTIAL COMPETING INTERESTS

Dr. Brophy is a physician scientist who receives peer review financial support from le Fonds de la Recherche en Santé du Québec. Steven Bird is employed by the Food and Drug Administration. This study represents the opinions of the authors and not those of the Food and Drug Administration. The authors have no other competing interests.

APPENDIX

In this sensitivity, the association between the residual confounder and IBS (RRCD) was varied between HR 1.0 to 10.0. The prevalence of the confounder (Pc) was set at 20% and the prevalence of drug exposure was set as the prevalence of drospirenone use in our cohort (20.13%). The absolute relative risk (ARR) was set as the association between IBS and drospirenone (HR 1.63). A second ARR was set as the lower end of the 95% CI (HR 1.46).

Fig. (A1). Sensitivity analysis of residual confounding: Rule-out approach.

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