Gynecologic Conditions in a Cohort with Inflammatory Bowel Disease: A Descriptive Analysis

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Objective: Past studies have demonstrated that women with inflammatory bowel disease (IBD) have a higher risk of gynecological conditions than do women without it. We aimed to characterize the gynecological histories of Hispanic Women living in Puerto Rico with IBD.

Methods: We identified women, aged 21 to 55 years, with a confirmed IBD diagnosis and receiving follow-up care from the University of Puerto Rico IBD clinics from 2017 through 2020. A questionnaire was administered to acquire sociodemographics, family history, past medical history, IBD diagnosis, and gynecologic aspects.

Results: One hundred eighty-six women were recruited. Fifty-three (28%) patients had ulcerative colitis, while 133 (72%) had Crohn's disease. Fifty-six percent of all the participants had a chronic illness in addition to than their IBD. Seventy-four out of 186 patients reported having had at least 1 late period within the last 12 months. Fifty-three (28%) described their period patterns as irregular. Thirty-nine (21%) of the patients reported having been vaccinated against human papillomavirus (HPV), and 8 (4%) had been infected by it. Nine out of 186 (5%) patients reported suffering from infertility.

Conclusion: The results showed that our Hispanic patients (living in Puerto Rico) had a prevalence of irregular menstrual cycles that was similar to that observed in other populations. On the other hand, the presence of HPV, infertility, and cervical cancer were lower and the frequency of Papanicolaou smears performed higher than what has been seen in the continental United States, suggesting that this topic should be investigated in future studies. [*P R Health Sci J 2023;42(3):226-232*]

Key words: IBD, Crohn's disease, Ulcerative colitis, Gynecological conditions

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are conditions of unknown etiology associated with chronic inflammation of the digestive tract. Although they affect men and women equally (1), special attention has been paid to women's health and the possible associations of IBD with the reproductive system. Studies have shown that female IBD patients are at a higher risk of gynecological conditions than are their non-IBD counterparts (2). Inflammatory bowel disease commonly affects women during their reproductive years (3), making the interaction between fertility, pregnancy, and IBD a critical issue (4). These associations and interactions have rarely been addressed in Hispanic Women living in Puerto Rico with IBD.

Two of the most frequent areas of interest to the scientific community are endometriosis and menstrual disorders, including dysmenorrhea, menorrhagia, and abnormal menstrual patterns. According to Kane et al. (5), there is a significantly higher incidence of menstrual-related symptoms in patients with IBD compared to the normal population. Prior research has concluded that IBD impacts the onset of menarche and menstrual-cycle frequency (polymenorrhea, oligomenorrhea, and amenorrhea) (6). In turn, hormonal fluctuations associated with menstruation provoke gastrointestinal symptoms in these patients (1). In a retrospective study of 37,000 Danish women by Jess et al. (7), endometriosis was associated with a higher risk of developing IBD when compared to women without endometriosis in the general Danish population. Moreover, past studies have described an increased risk of spontaneous abortion as well as preterm and cesarean section (C-section) delivery in women with IBD, especially during active disease (8). Patients who suffer from IBD may be chronically immunosuppressed by medications which may dramatically increase their risk of developing abnormal results in Papanicolaou (Pap) smears

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The authors have no conflict of interest to disclose.

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(9–11). A study by Bhatia et al. (10) found that patients with IBD had a higher rate of abnormal Pap smears (18%) than did healthy controls (5%), with no association found between the type of IBD, exposure to immunosuppressants, and having an abnormal cervical histology. Another study, this one by Kane et al. (9), found a similarly high incidence of abnormal Pap smears in women with IBD associated with immunosuppression, in which study all the abnormal samples were positive for high-risk human papillomavirus (HPV) strains 16 and 18. In a Puerto Rican population of women with IBD, HPV and HPV vaccine knowledge were high, but compliance with and adherence to HPV vaccination were poor (12,13).

Though several studies have not demonstrated significant differences in fertility frequency compared with the general population (3,14–16), the data show a higher rate of voluntary childlessness and fewer children in women with IBD (17,18). According to several studies, this is primarily associated with misconceptions and misunderstood clinical considerations about the possible effects of IBD on pregnancy and vice versa (18–20). However, it has been reported that some patients can be at a higher risk of infertility due to medication, nutritional deficiency, weight loss, the presence of fistulae, and surgery (1). The literature suggests that women who have undergone a restorative proctocolectomy with an ileal pouch–anal anastomosis (IPAA) have an overall higher infertility rate compared to those who have not undergone this surgery (1). Additionally, a recent cross-sectional study describing sexual function in Puerto Rican women with IBD concluded that significant sexual dysfunction was present in the cohort (21).

Although women with IBD generally experience safe pregnancies, disease activity can have a negative impact on childbearing and is associated with complications for the mother and fetus. For this reason, it is recommended that patients plan their pregnancy to coincide with the remission of the disease (22). The literature indicates that patients in remission have pregnancies similar to those of women without IBD (23). However, studies report that women with IBD use contraceptive methods to a lesser extent than does the general population (24). A study conducted on Puerto Rican women with IBD reported that 86% of the participants denied the use of contraceptives. Out of those who reported using some type of contraception, the only 2 disclosed were the condom and coitus interruptus (25).

Our study aimed to characterize the clinical and gynecological history of a female Puerto Rican cohort with IBD. The results will aid in the understanding of how a Hispanic population varies from populations of North American heritage and will allow the provision of better health care and treatment addressing the needs of said Puerto Rican population.

Materials and Methods

We conducted a cross-sectional study of females with an established IBD diagnosis (CD or UC), aged 21 to 55 years, and being attended at the University of Puerto Rico IBD clinics from 2017 through 2020. The target sample size was 200. Data were obtained using a questionnaire (created by the investigators) that addressed sociodemographic information, family history, past medical history, IBD diagnosis, and certain female health concerns. The town of residence was classified as either rural or urban using the Puerto Rico Municipalities and Urban Areas map published in the 2013 Puerto Rico Community Survey, 1-year estimates (26). The gynecologic aspects of the disease were evaluated with questions regarding menstrual cycles, sexual experiences, and fertility status, contraceptive use was classified as low effectiveness: male condoms, female condoms; medium effectiveness: pills, vaginal hormonal ring, hormonal patch, medroxyprogesterone; and high effectiveness: intrauterine devices, and etonogestrel contraceptives, Pap smears, lifestyle, history of sexually transmitted diseases (STDs), surgical interventions, and pharmacological interventions. The medications used included aminosalicylates (sulfasalazine, mesalamine, balsalazide), antibiotics (metronidazole, ciprofloxacin, tetracycline), immunomodulators (azathioprine, mercaptopurine, methotrexate), tumor necrosis factor blockers (infliximab, adalimumab, certolizumab pegol), antidiarrheals (loperamide, codeine, cholestyramine), anti-integrins (natalizumab, vedolizumab), and interleukin inhibitors (ustekinumab). The American College of Obstetricians and Gynecologists' definition of infertility (not being pregnant after a year of having unprotected sexual intercourse) was used (27). An infertility questionnaire was used to validate the diagnoses of those in our cohort who reported being infertile.

Descriptive statistics, including mean, standard deviation, and median, were used for continuous variables, and frequency distribution and percentages were performed to describe the participants' demographic traits, medical histories, gynecological histories, STDs, and IBD characteristics. Data analysis was performed using Stata Statistical Software: Release 14 (StataCorp LP, College Station, Texas).

As a part of the medical history, we evaluated the participants for current comorbidities and sought the most prevalent in the cohort. These included chronic illnesses such as psoriasis; rheumatoid arthritis; osteoarthritis, osteoporosis and osteopenia; asthma; thyroid disease; anemia; dermatologic diseases; and others. The frequency and results of Pap smears were studied and compared to the prevalence of cervical cancer in our population. The prevalence of HPV vaccination and the rate of HPV infection were also calculated. The regularity of menstrual periods for the previous 12 months was assessed. The study was approved by the UPR-MSC IRB, protocol 105011.

Results

One hundred eighty-six Hispanic women aged 21 to 55 years, living in Puerto Rico, and having a confirmed IBD diagnosis (CD or UC) were recruited. The mean age of the participants was 35.01 (±9.80) years. The demographic characteristics are

shown in Table 1. Most (72%) had CD. A few reported having relatives with a history of CD or UC.

A total of 105 out of the 186 (56%) participants in the study had another chronic disease. These included 14 patients with psoriasis,16 with rheumatoid arthritis, and 19 with osteoporosis. Other chronic conditions reported included asthma, osteopenia, thyroid disease, arthritis, anemia, and dermatologic diseases, among others. The prevalence of cancer among the participants was 4% (7/186).

Regarding gynecological manifestations, 74/186 (40%) of the patients reported having had at least 1 late period in the last 12 months; 53 (28%) described their period pattern as irregular and 131 (70%), as regular; 2 were postmenopausal. For menstrual cycle duration, 16% reported that their cycle lasted 1 to 3 days, 49%, 4 to 6 days, 27%, 7 days, and 8%, more than 7 days. Dyspareunia was reported by 61 (33%) participants, while 102 (55%) reported having no such pain; 41 (22%) were not sexually active. Of the 61 participants with dyspareunia, 27 (44%) reported visiting their physician for pain/bleeding during sexual intercourse, while 23 (37%) made no such report, and 11 did not reply to this question.

One hundred and twelve (60%) of the 186 women reported history of pregnancy, 54 (29%) indicated no pregnancy and 20 (11%) did not respond to this question. A quarter (25%) of pregnancies have been premature births and 52% had undergone a C-section. Live births were reported by 101 (54%) of the participating women, with a 1.9 average, whereas stillborn births were reported by 20 (11%) of them, with a 1.1 average. In addition, 42% of the patients had undergone an abortion, 87% of which were spontaneous.

Only 9/186 (5%) of our patients reported being infertile, which was confirmed by the infertility questionnaire.

Seventy-eight percent of our patients were sexually active at the time of their recruitment. Addressing the use of contraceptives, 29 (16%) of the patients answered that they currently used contraception, including condoms, intrauterine devices (IUDs), Depo-Provera injections, and the withdrawal method, revealing that most of these sexually active women apparently did not use contraception. One hundred and fifty-one (81%) of the patients had had at least 1 Pap smear performed in their lifetime, as can be seen in Table 2. Of those 151 subjects, 117 (75%) reported undergoing the Pap test every year, while the other 34 (23%) patients reported having it performed every 2 years or more. Only 39 (21%) reported having had an abnormal Pap test. Out of those 39 patients with abnormal Pap smears, 22 (56%) received treatment, with the most common treatment being cryotherapy (10 patients). These findings show a high percentage of patient compliance with screening protocols in our population.

Thirty-eight (20%) of the patients reported having been vaccinated against HPV, 29 when they were from 21 to 29 years of age, 6 when they were from 30 to 39, and 3 when they were from 40 to 44. Only 8 (4%) of our subjects reported ever having been infected with HPV. One hundred and twelve patients (60%) had undergone a surgical procedure for an abscess or a fistula, with 89 (48%) of them having had a fistula. As for bowel surgeries, 14 had had a total colectomy, 40 had had a small bowel resection (21%), 18 had had a partial colon resection (10%), 45 had had an ileostomy (24%), 24 had had a colostomy (13%),11 had had an IPAA (6%), and 4 had had a proctectomy (2%). The IBD medications used by the participants are shown in Table 3.

Table 1. Demographic characteristics

Characteristic	N = 186	%
Age (years)		
Median + SD	35.01 + 9.8	
Marital status		
Single	87	46.77
Married	66	35.48
Consensual union/lives with partner	19	10.22
Separated	3	1.61
Divorced	8	4.3
Refused to answer	3	1.62
Highest level of education		
Middle school or less	2	1.08
High school	25	13.44
Vocational/technical school	4	2.15
Currently attending university	11	5.91
Some university studies	9	4.84
Associate degree	31	16.67
Undergraduate degree	80	43.01
Graduate or professional degree	23	12.37
Refused to answer	1	0.54
Place of birth		
Puerto Rico	168	90.32
United States (not including Puerto Rico)	13	6.99
The Dominican Republic	4	2.15
Other country	1	0.54
Area of residence		
Urban	110	59
Rural	41	22
Doesn't apply	35	19

Table 2. Self-reported gynecological variables

Gynecological variable	Yes n (%)	No n (%)	Does not know or does not apply n (%)
Dyspareunia	61 (33)	102 (55)	23 (12)
History of pregnancy	112 (60)	54 (29)	20 (11)
Pap smear performed in their lifetime	151 (81)	29 (16)	N/A
Pap smear performed within the last year	107 (58)		31 (16)
Pap smear performed within the last 1–3 years	33 (18)		
Pap smear performed within the last 3–5 years	8 (4)		
Pap smear performed more than 5 years ago	7 (4)		
Abnormal Pap smear in their lifetime	39 (21)	119 (64)	28 (15)
HPV vaccination	39 (21)	133 (72)	14 (8)

Pap: Papanicolaou

Table 3. Self-reported inflammatory bowel disease medications

Medication for IBD	Number of Patients n Percentage of use (%)
Aminosalicylates	91 (49)
Antibiotics	62 (33)
Immunomodulators	69 (37)
Anti-TNF	108 (58)
Antidiarrheals	42 (23)
Anti-integrins	22 (12)
Anti-IL	12 (6)
Other IBD medications	39 (21)

IBD: inflammatory bowel disease; TNF: tumor necrosis factor; IL: interleukin

Discussion

The results of our study of Hispanic women with IBD in Puerto Rico were similar to those reported in other Western societies, such as the United States (excluding Puerto Rico), Europe, and Australia, in terms of some of the variables and differences with others. Since our study was purely clinical, we will attempt to provide possible explanations for these observations, based on the patterns that are present.

Studies of the effects of IBD on the menstrual cycle have been limited to clinical observations, but a clear mechanism at the molecular level remains unknown, consequently preventing researchers from concluding that any effects on menses are attributed to IBD and not to some other cause. Of our study subjects, 74 (38.7%) had had a late period in the 12 months prior to their participation in the study, with 53 of them (28.5%) stating that their periods were irregular. For the past 2 decades, it has been said that females with IBD have an increased risk of developing irregular menstrual cycles. This is supported by a study conducted by Weber et al., in which 58% of the recruited females with IBD were shown to have irregular menses compared to the non-IBD controls (3). However, this study was carried out in 1995, before the development of contemporary medical protocols that could substantially decrease the incidence of irregularities in the menstrual cycle. Furthermore, a more recent (2014) study by Saha et al. showed that patients with IBD are at increased risk of developing menstrual irregularities in the first years of IBD diagnosis but also showed that these women regain menses regularity with prolonged disease duration (28). These more recent findings suggest that the association between IBD and irregular menstrual cycles requires further research. Longitudinal studies that evaluate the individual progression of patients from the time of diagnosis to menopause and assess additional symptoms such as dysmenorrhea and menstrual flow would help clarify this issue. The data of our patients support the position that IBD negatively affects the menstrual cycle in some way, while the data of other studies show that the influence of neither UC nor CD over the menstrual cycle is clear. However, we did not study the effects of IBD severity on the menstrual cycle, and there is scant literature on this topic. Hence this relationship should be investigated further in both North American and Hispanic populations to determine the true effects of IBD on, and its levels of severity regarding, the menstrual cycle.

Furthermore, a more extensive comparison between the effects of IBD on menstruation in Hispanics living in Puerto Rico and Hispanics living in the continental United States would probably be of interest in future evaluations. By excluding other ethnicities in this potential study, we would be able to evaluate whether living in Puerto Rico is a potential risk factor that induces disparities in the menstrual cycle. However, the literature evaluating the latter population—Hispanics living in the continental United States—is sparse, which is why that comparison was not made in our study. On a similar note, it is necessary to compare how the menstrual irregularities observed in this study vary from those that may or may not exist in Hispanic women without IBD living in Puerto Rico. Doing so would be useful to proving that the association proposed exists as a result of extraintestinal manifestations of IBD or because, again, living in Puerto Rico is a factor that correlates with these irregularities.

Male condoms and the pill were the most used methods of contraception in our cohort. However, the more effective methods of contraception—IUDs and etonogestrel, for example—are underrepresented in our cohort, increasing the risk of unplanned pregnancy in the members of this population. Further studies are needed to evaluate the reasons for both choosing specific contraceptives and the low use of highly efficacious contraceptive methods by Hispanic females with IBD living in Puerto Rico, as well as compare the rates of usage with those of the general population. The importance of evaluating the contraceptive methods favored by this population lies in the fact that their use affects fertility rates. Thus, the high usage of low-efficacy contraception and the decreased usage of highly efficacious long-acting contraceptives serve as an additive effect to the increased fertility observed in these females with IBD. It would be helpful for further studies to include Hispanic and non-Hispanic females with IBD to assess their use of contraceptive methods as a possible confounding variable so that any fertility rates reported could be correctly attributed to the effects of IBD, if such should be the case.

It has been previously reported that females with IBD in North America have a low rate of Pap smear testing and a substantially elevated incidence of cervical cancer. In 2009, Kane et al. reported an increased prevalence of abnormal Pap smears in IBD patients compared to controls (29), while Long et al. reported in another study that IBD patients compared to healthy women had a suboptimal screening rate (intervals of more than 3 years between testing) for cervical cancer (30). Another study, this one by Singh et al. in 2009, concluded that IBD, alone, was not a risk factor for the development of cervical cancer but that the concurrent use of immunosuppressants and steroids for IBD treatment was a significant one (31); this same relationship is observed in a more recent study by Allegretti et al. (32). On the other hand, our population showed contrary results, with

154 (84%) of them having had a Pap smear performed. In addition, all these patients undergo their Pap either annually or biannually, establishing an optimal level of screening in our population. Of these patients, only 39 reported having had an abnormal Pap smear, with an even smaller number reporting having had cervical cancer in the past (2 patients). The CDC reported in December 2021 that 91% of cervical cancer cases are attributed to HPV, which is an STD (33). However, in spite of the low prevalence of HPV vaccination, only 8 patients in our study reported ever having had an HPV infection (4%). A potential explanation for this could be a decreased frequency of sexual relations due to IBD causing emotional distress and sexual dysfunction, which is supported by the fact that 61 (32.8%) of our subjects reported that they suffered from dyspareunia. Thus, it makes sense that, with such a low incidence of HPV infections in our subjects, cervical cancer cases in our study would be few. Our Hispanic Women living in Puerto Rico population with IBD had a diligent screening practice for cervical cancer that may ultimately play a crucial role in preventing this malignancy, something that was not observed in the populations of previous studies.

Infertility is the main concern of many females with IBD, although its mechanism is still not fully comprehended. A study by Mountfield et al. (19) suggests that patient perception about the possibility of having children is significantly skewed toward thinking that IBD is a contraindication to conception, leading to widespread "voluntary childlessness." Another potential explanation is the anatomical changes and tubal scarring caused by surgeries for IBD, with IPAA causing the greatest damage, according to Waljee et al. (34). These studies were all of populations from the continental United States. In our Hispanic Women living in Puerto Rico sample, however, only 9 patients reported suffering from infertility, making its prevalence in our IBD patients substantially lower than what has been observed in the general population, in which fertility rates have been decreasing in the past 10 years. Along these lines, our participants also presented with slightly higher fertility rates (lifetime average of 1.9 live births) than are found in the general population of Puerto Rico (estimated to be 1.3 in 2022, according to the United Nations) (35). This can be explained by the formation of good physician–patient relationships within our cohort of women with IBD, allowing the open discussion of sensitive topics. Our population was selected from a highly specialized clinic, which may have resulted in a better educated sample regarding the knowledge of fertility and pregnancy with IBD and that may have minimized the practice of "voluntary childlessness." Another explanation could be that Puerto Rico's being a developing country may limit contraceptive access, especially for patients living in the western and central parts of the island (which tend to be rural, making easy access an issue). Additionally, only 11 (6%) of our patients underwent an IPAA, which could further explain the relative absence of infertility; of these 11 subjects, who ranged in age from 25 to 40 years, all had had children before completing their IPAA and none had had children after their having done so. Once again, our population deviated from the North American trend, showing a unique pattern.

Our study had certain limitations that could have potentially altered the results. The study was carried out in the 3 years after a category 5 hurricane (Hurricane Maria, September 2017) affected all of Puerto Rico, and the reconstruction and restoration of all the services lost during the storm was still ongoing. Widespread anxiety and limited access to health services may have altered the results by increasing the stress of the patients, which increase can itself cause menstrual cycle irregularities and even lead to spontaneous abortion. The time spread of the study related to this catastrophic event introduced external factors that changed over time. However, only 1/4 of the recruitment occurred before the hurricane and during the immediate aftermath (a period of 2 months in which the basic services normally provided by the government were unavailable for the population, leading to widespread panic and death), while the rest was done after this period, meaning that the majority of the patients were not subjected to the potential effects that this event may have had on the study. In addition, we collected lifetime data for some of the variables from all the subjects, so we expect these factors to decrease the possible bias introduced by the catastrophic event.

In conclusion, this study revealed that the prevalence of menstrual irregularities in Hispanic Women living in Puerto Rico with IBD was similar to that in the United States, while simultaneously differing from the North American population in fertility rates, screening, and cervical cancer. Puerto Ricans comprise an admixed population, with European, African, and Native American genes, which heterogeneity may impact the prevalence and manifestations of diseases. Health education and access to specialty care are other factors that may result in improved gynecological health, screening, and cancer rates. These were not explored in our study. This study did not examine the interaction between menstrual cycles and IBD. We would like to encourage other researchers to direct longitudinal studies that evaluate the long-term effects of IBD in Puerto Rican females. Strategies to improve the health of our population benefit from well-collected and analyzed data from larger studies.

Resumen

Objetivos: Estudios anteriores han demostrado que mujeres con Enfermedad Inflamatoria Intestinal (EII) tienen un mayor riesgo de padecer afecciones ginecológicas. Nuestro objetivo es caracterizar la historia ginecológica de mujeres hispanas viviendo en Puerto Rico con EII. Métodos: Identificamos mujeres con un diagnóstico de EII entre 21 y 55 años que recibieron seguimiento en las clínicas de EII de la Universidad de Puerto Rico desde el 2017 hasta el 2020. Se administró un cuestionario para adquirir datos sociodemográficos, antecedentes familiares, antecedentes médicos, diagnóstico de

EII y aspectos ginecológicos. Resultados: Se reclutaron 186 mujeres. Cincuenta y tres (28%) pacientes tenían colitis ulcerosa (CU), mientras 133 (72%) tenían enfermedad de Crohn (EC). El 56% de todas las participantes tenían una enfermedad crónica distinta de la EII. Setenta y cuatro de 186 pacientes informaron un período de menstruación tardía en los últimos 12 meses. Además, 53 (28%) describieron sus patrones menstruales como irregulares. Treinta y nueve (21%) de las pacientes reportaron estar vacunadas contra el Virus de Papiloma Humano (VPH) y 8 (4%) habían sido infectadas por el mismo. Nueve (5%) pacientes reportaron tener infertilidad. Conclusión: Los resultados muestran que nuestras pacientes hispanas viviendo en Puerto Rico tenían una prevalencia de ciclos menstruales irregulares similar a la observada en otras poblaciones. Por otro lado, la presencia de VPH, infertilidad y cáncer de cuello uterino es menor y la frecuencia de las pruebas de Papanicolaou realizadas es mayor de lo observado en los Estados Unidos, sugiriendo que este tema debe investigarse prospectivamente.

Acknowledgments

This project was supported by award numbers 5S21MD000242 and 5S21MD000138 from the National Center for Minority Health and Health Disparities of the National Institutes of Health (NCMHD-NIH).

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