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Original Research

Effect of COVID-19 Vaccine in Women with Adenomyosis and Endometriosis

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Abstract

Background: It has been reported that coronavirus disease 2019 (COVID-19) vaccines could provoke flu-like symptoms and changes in menstrual cycles in some women, probably as a result of the immune response caused by the vaccination itself. Altered local immunity and inflammatory processes are found in women suffering from adenomyosis and endometriosis, this having a role in the typical symptomatic manifestations. This study aims to investigate the prevalence of side effects like abnormal uterine bleeding (AUB) or pain following the administration of COVID-19 vaccines in women with adenomyosis or endometriosis. **Methods**: A retrospective cohort study was performed on 172 patients referring to our Chronic Pelvic Pain Center, who underwent COVID-19 vaccination. A hystorical cohort of sixty-three non-vaccinated women was used as control. We collected anamnestic data and each woman scored menstrual pain, chronic pelvic pain, and the occurrence of AUB before and after vaccination. **Results**: Among control women, no one showed AUB, and only 2 women experienced a slight worsening of menstrual pain. Side effects were observed in 29/172 (16.8%) of COVID-19 vaccinated women, independent of whether they were on hormone therapy. In comparison to asymptomatic, symptomatic women had a higher prevalence of adenomyosis (82.7% *vs* 63.6%), adenomyosis being present in 100% of the 6 women with intermenstrual bleeding, in 79% of the 19 women with heavy menstrual bleeding and in 81% of the 16 women with pain worsening. Nine out of 55 (16.3%) women with endometrioma experienced side effects. Among these, the 3 women that were not on hormone therapy experienced a huge increase in endometrioma volume from +208% to +806%. In one case emergency surgery was necessary for endometrioma rupture and hemoperitoneum. **Conclusions**: In our sample, adenomyosis appears strictly related to the manifestation of post-vaccine side effects. Hormone therapy seems to be insufficient to protect from post-vaccine symptoms, but the increase in endometrioma volume was observed only in cases without hormone therapy.

Keywords: adenomyosis; COVID-19; dysmenorrhea; endometriosis; vaccine

1. Introduction

Following all types of coronavirus disease 2019 (COVID-19) vaccination (Moderna, Pfizer/BioNTech, AstraZeneca) more than 1 in 10 people reported flulike illness such as fever, fatigue, headache, pain at the injection site (sore arm) and myalgia. Symptoms were usually mild in intensity and solved spontaneously within a few days after inoculation [1]. Several anecdotal reports indicated that vaccination could also result in menstrual cycle changes [1], even though there is no evidence that COVID-19 vaccination adversely affect fertility [2]. These effects were independent from type and components of vaccines, hinting that likely they are the result of the immune response to vaccination [3]. No study has investigated the effect of immune activation by COVID-19 vaccine in women with an already altered local immune activation as women with adenomyosis or endometriosis [4–6]. Adenomyosis is the proliferation of endometrial glands and stroma within the myometrium and its prevalence ranges from 10% to 40%. Local immunity is altered in adenomyotic lesions with enhanced innate and acquired immune activity and is involved in disease development, progression and symptoms as pain and abnormal uterine bleeding (AUB) [4]. Endometriosis that affects approximately 10% of women of reproductive age, is a chronic, inflammatory, and estrogen-dependent disease characterized by endometrial tissue outside the uterine cavity and it is associated with chronic pelvic pain, AUB and infertility [7,8]. Endometriotic lesions are associated with inflammatory molecules responsible for the progression of the disease and pain [5,6]. The aim of this study was to evaluate whether immune activation induced by COVID-19 vaccination impacts on symptoms as AUB or pain in women with an already altered local immune activity as those suffering from adenomyosis or endometriosis.

2. Materials and Methods

This is a single-center retrospective observational study on gynecological side effects (AUB and increased pelvic pain) following COVID-19 vaccine inoculation to women suffering from pelvic pain, with adenomyosis, or endometriosis. The study was approved by the local Ethics committee (Comitato Etico Regione Liguria N 260/2022).

2.1 Subjects

The study was performed in a cohort of 172 premenopausal women at the outpatient Clinic for Endometriosis and Chronic Pelvic Pain at San Martino University Hospital in Genoa from March 2021 to May 2022. Women were included whether within a maximum period of 60 days from COVID-19 vaccination, performed according to the national vaccination campaign. A cohort of 63 women attending the same outpatient facility in the period immediately preceding the campaign of COVID-19 vaccination and with two evaluations performed six months apart, were evaluated as control group. Women participating to the study signed a written informed consent for the anonymous use of their clinical data. Data were recorded in an electronic database, available for retrospective analyses, as necessary.

2.2 Vaccination

We recorded the type of vaccine women received and the pharmaceutical company who prepared the vaccine.

The site of vaccine inoculation was recorded as well as the dose, i.e., first, second or third dose. Presence of side effects was categorized on the dose woman received. The elapsed time between last administration and symptoms onset were properly saved.

2.3 Data

We collected the following data: age, parity, body mass index (BMI), presence of gynecological pathologies, previous abdominal surgery, presence of AUB, intensity of menstrual and chronic pelvic pain via a 10 cm visual analogue scale (VAS) [9], ongoing hormone therapy, worsening of pain or AUB manifestation in the period between the two evaluations, time and length of symptom manifestation.

Sonographic uterine features, presence of adenomyosis, ovarian and pelvic endometriosis implants were also recorded.

2.4 Sonographic Evaluation

Ultrasound investigations were performed by experienced sonographers using a GE E6 (GE Medical Systems, Zipf, Austria) ultrasound machine and a transvaginal wideband 5–9 MHz transducer. The International Deep Endometriosis Analysis group (IDEA) [10] and Morphological Uterus Sonographic Assessment (MUSA) [11] criteria were used for the diagnosis of endometriosis, adenomyosis, and myomas. The International Endometrial Tumor Analysis (IETA) was used to describe the sonographic features of the endometrium [12]. The International Ovarian Tumor Analysis Consensus (IOTA) [13] was used to describe characteristic of ovarian masses [14].

2.5 Satistical Analysis

Statistical analysis was performed using the StatView 5.1 (SAS Institute, Cary, NC, USA) statistical program. Frequency distribution, prevalence and averages were used to describe data. The Student's t test was used to compare averages and the chi-squared was used to compare frequencies. Multiple logistic regression was used when necessary to define the presence of factors independently related to the presence of symptoms. A p value < 0.05 was considered statistically significant.

3. Results

Vaccinated women and women included in the control group were similar in term of age, BMI, parity, gynecological conditions, use of hormonal therapies and VAS scores of menstrual and intermenstrual pain (Table 1). Vaccinated women had a mean age of 36.8 ± 9.0 years. a mean BMI of 23.1 ± 4.2. 41.3% were nulliparous and 40.1% had a previous abdominal surgery. 67.4% (116/172) had adenomyosis, 32.0% (55/172) ovarian endometriosis and 40.1% (69/172) deep infiltrating endometriosis (DIE). In vaccinated women myomas and endometrial polyps were present in 17.4% and 11.0% of women, respectively. About 36% of vaccinated women were taking hormone (either combined contraceptives or progestins only) for the treatment of their symptoms, and 38.3 % were multiparous (Table 1). In almost all cases women received mRNA vaccines (Pfizer or Moderna).

Table 1. Characteristics of the 172 COVID-19 vaccinated women and of the 63 control women included in the study.

	Cases	Controls	p value
	N = 172	N = 63	
Age (years)	36.8 ± 9.0	34.9 ± 8.8	0.150
BMI (kg/m^2)	23.1 ± 4.2	24.2 ± 5.4	0.102
Pregnancy	38.3%	41.3%	0.677
Abdominal surgery	40.1%	41.0%	0.901
Adenomyosis	67.4.%	60.9%	0.401
Myomas	17.4%	21.3%	0.495
Ovarian endometriosis	32.0%	30.1%	0.727
DIE	40.1%	42.8%	0.709
Polyps	11.0%	12.5%	0.749
Hormonal therapy	36.2%	41.0%	0.501
Menstrual pain	5.8 ± 3.6	5.2 ± 4.0	0.273
Intermenstrual pain	2.8 ± 3.3	3.4 ± 3.5	0.225

BMI, body mass index; DIE, deep infiltrating endometriosis.

At the second evaluation only 2 (3.1%) women of the control group showed a slight persistent increase of menstrual pain. In vaccinated women worsening of pain or AUB appeared in 16.8% (29/172) women, independent of age, BMI, parity, hormone therapy (Table 2). Side effects appeared 15 times following the first (n = 6) the second (n = 3) or the third (n = 6) dose of Pfizer vaccine and 14 times following the first (n = 11) the second (n = 2) and the third (n = 1) dose of Moderna vaccine. The average period between inoculation and symptoms appearance was 14.9 ± 10.1 days and the mean time to resolution was 25.6 ± 20.4 days.

Table 2. Characteristics of women who developed (Symptomatic) or did not develop (Asymptomatic) AUB or pain worsening in the period following COVID-19 vaccination.

	Symptomatic	Asymptomatic	*p* value
	N = 29	N = 143	
Age (years)	37.2 ± 8.9	36.7 ± 9.0	0.783
BMI (kg/m^2)	23.6 ± 4.5	23.0 ± 4.3	0.448
Pregnancy	41.3%	37.7%	0.717
Adenomyosis	82.7%	63.6%	0.047
Myomas	24.1%	16.0%	0.295
Ovarian endometriosis	31.0%	32.8%	0.850
DIE	13.7%	45.7%	0.002
Polyps	20.6%	9.0%	0.069
Hormonal therapy	31.0%	37.3%	0.521
Menstrual pain	4.9 ± 3.4	6.0 ± 3.6	0.147
Intermenstrual pain	2.0 ± 3.7	3.0 ± 3.3	0.178

AUB, abnormal uterine bleeding.

About 14.5% women (25/172) experienced AUB either as heavy menstrual bleeding (n = 19) or as intermenstrual bleeding (n = 6). We did not specifically investigate modifications of menstrual cycle length. Worsening of pain occurred in 16 women (9.3%). Beforehand, these women had menstrual and intermenstrual pain similar to those women not experiencing vaccine-related side effects but had a higher prevalence of adenomyosis (82.7% *vs* 63.6%; $p = 0.047$) and a lower prevalence of DIE (13.7% *vs* 45.7%; $p = 0.002$) (Table 2). Overall, DIE was present in 44 of the 115 women with adenomyosis. Upon multiple regression analysis when corrected for concomitancy, symptom manifestation was significantly related to the presence of adenomyosis (hazard ratio (HR) 4.93, 95% confidence interval (95% CI) 1.57–15.5; $p = 0.006$) but not to the presence of DIE ($p = 0.972$).

Adenomyosis was present in 100%, 79.1% and 81.2% of women developing intermenstrual bleeding, heavy menstrual bleeding or worsening of pain, respectively (Table 3). In women with vaccine-related side effects 9 had endometrioma. Six patients were under treatment with hormone therapy and 3 were not.

In the 3 women without treatment endometrioma's size markedly increased. In the first case endometrioma's volume increased from 78 cm^3 to 537 cm^3 (+688%). This patient underwent to emergency surgery 30 days after vaccine inoculation due to acute abdominal pain and hemoperitoneum. In the second patient endometrioma's volume increased from 36 cm^3 to 75 cm^3 (+208%) and in the third case endometrioma volume increased from 33 cm^3 to 266 cm^3 (+806%). In the 6 patients on hormone therapy endometrioma's volume did not change. No other women required urgent surgery for vaccine related side effects. Uterus volume measured after COVID-19 vaccination did not differ from that the historical volume found in our database. Nine out of the 29 women (30%) who developed symptoms underwent surgical treatment because of uncontrolled bleeding and pain, regardless of medical therapy. One patient spontaneously conceived 3 months after vaccination.

4. Discussion

In this study we investigated the manifestation of gynecological side effects following COVID-19 vaccination in a cohort of women with adenomyosis or endometriosis. Manifestation of AUB or pain worsening differs from that observed in a 6 months follow-up period of non-vaccinated women with endometriosis or adenomyosis. The data indicate that about 16.8% of these women experience gynecological side effects, and add evidence to two recent studies performed in women with endometriosis [15,16].

In a sample of unselected women COVID-19 vaccination was followed by an increase in the length of the cycle but not of the menstrual period [17]. This was subsequently confirmed in another study, showing that only injections performed during the follicular phase of the menstrual cycle prompted modifications of cycle length [18]. In an online survey, menstrual irregularities were reported by 50–60% of women without gynecological disease and not taking any hormone therapy [19]. Similarly, in another web-based survey, a high rate of post-vaccine menstrual abnormalities including menorrhagia, was reported. Respondents with side effects had a higher prevalence of endometriosis (51.1%), fibroids (49.1%), polycystic ovarian syndrome (PCOS) (46.2%), and adenomyosis (54.9%) than women without these gynecological conditions (40%) [20]. A systematic review [19] including 78,138 patients, from clinical and web-based studies showed that after COVID-19 vaccination a significant number of women (52.05%) experiences short-term self-limited heterogeneous menstrual abnormalities (i.e., menorrhagia, oligomenorrhea and dysmenorrhea). Based on the type of study, menorrhagia varied from 0% to about 40%. Recent studies specifically performed in women with endometriosis were not consistent in reporting modifications of bleeding pattern, but worsening of pain symptoms was clearly documented [15,16]. Many of our women were on hormone therapy, and this did not al-

Table 3. Presence of gynecological factors in women with different side effects following COVID-19 vaccination.

	Adenomyosis	Myomas	Endometriosis	Polyps
Intermenstrual bleedings (N: 6/29)	100.0%[a]	16.6%	0.0%	33.3%
Heavy menstrual bleeding (N: 19/29)	79.1%[b]	31.6%	42.0%	21.1%
Pain worsening (N: 16/29)	81.2%[c]	25.0%	56.5%	18.7%

a, $p < 0.0001$ *vs* others; b, $p = 0.005$ *vs* endometriosis and $p = 0.003$ *vs* myoma; c, $p = 0.0001$ *vs* myomas and $p = 0.04$ *vs* endometriosis.

low an appropriate evaluation of modifications of menstrual cycle length [17–21]. Yet an increase of bleeding problems was documented particularly in women with adenomyosis, that were investigated only in our study. All women with intermenstrual bleeding and about 80% of women with heavy menstrual bleeding suffered from adenomyosis. This is consistent with our recent observation that adenomyosis is the most frequent conditions leading women of reproductive age to the emergency service for excessive bleeding [22]. Inconsistencies on bleeding side effects due to COVID-19 vaccine found in other studies may be the consequence of a not adequately evaluated presence of adenomyosis in the cohorts under investigations [15,16].

Different theories may provide an explanation for what is happening in response to COVID-19 vaccine. The female reproductive tract (vagina, cervix, uterus, and endometrium) is a unique environment that balances epithelial and stromal cells protective immune responses against microbial challenge and immune tolerance for reproductive purposes [23]. Infections and external factors like vaccine stimulations can disrupt the system thus affecting the menstrual cycle [24,25]. The endometrium itself is an important site of innate immune defense which vary cyclically according to the phase of menstrual cycle [26], and stimulation of endometrial immune response consequent to vaccine inoculation may cause bleeding. New-onset autoimmune manifestation following COVID-19 vaccination are being reported extensively [26,27], and the trigger factors include molecular mimicry, production of autoantibodies and the role of certain vaccine adjuvant [28,29]. The process appears not to be unique for COVID-19 vaccines. It has been described for many other vaccines, (measles-mumps-rubella (MMR), hepatitis B, diphtheria-tetanus-acellular pertussis (DTaP), varicella and influenza), that via an induced immune thrombocytopenia have resulted in menstrual irregularities [30]. The COVID-19-related spike protein may also play a pathogenetic role considering that menstrual cycle changes have been reported during COVID-19 infection [31]. Hormone therapy is used in women with adenomyosis or endometriosis for the management of pain and AUB [32–34]. In our study hormone therapy was not capable to reduce post-vaccine side-effects, as it was instead recently reported in another study [15]. Yet a rapid increase of endometrioma volume was observed only in the 3 women with endometrioma that were not under treatment. Although this may represent a natural evolution of the disease, the so high rate of sudden endometrioma increase seems to suggest a complications linked to vaccination. Likely an intra cystic bleeding developed in these subjects leading to a marked volume increase of the cysts and in one case to its rupture. The possible protective effect exerted by hormone therapy in the other vaccinated individuals with endometriomas that did not show modification of cyst volume, needs to be evaluated in more extensive studies.

In contrast to adenomyosis, DIE was less prevalent in symptomatic women. Multiple logistic regression analysis showed that the presence of DIE did not affect symptoms manifestation following COVID-19 vaccination. In contrast to adenomyosis or ovarian endometriosis, DIE is mostly composed by a stiff highly fibrotic scar tissue [35], with little residual immune and inflammatory activity. Accordingly immune activation following COVID-19 vaccination, is presumably too little represented in DIE to play a significant role on symptom manifestation.

All our women were followed by our outpatient service for chronic pelvic pain and endometriosis, and all had an appropriate ultrasonographic evaluation. Accordingly, the calculation of the side effects following COVID-19 vaccination in women with these gynecological conditions is rather accurate. A drawback in our study is the limited number of patients that should be increased to have more consistent results. The study was performed in a single center, mainly in a white population. In addition, we evaluated the side-effects induced only by two mRNA vaccines. The data may not apply to other ethnic and other vaccines and need to be replicated in other clinical settings.

5. Conclusions

In the presence of a chronic inflammatory condition associated with adenomyosis or endometriosis, COVID-19 vaccination induced in 16.8% of cases a transitory exacerbation of gynecological symptoms. In few patients, vaccination induced a marked increase of endometriomas' volume. Hormone therapy was insufficient to prevent post-vaccination side-effects but the huge volume increase of some endometriomas was not observed in women who were under hormone treatment.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

AX, AC, APL: design, planning, conduct, revising critically the manuscript for important intellectual content. MGS, IV, FM, EC, US, MJ, FO: conduct, manuscript writing. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the local Ethics committee (Comitato Etico Regione Liguria N 260/2022). Women provided an informed written consent for the anonymous use of their clinical data.

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Conflict of Interest

The authors declare no conflict of interest. Ambrogio Pietro Londero is serving as one of the Editorial Board members and Guest editors of this journal. We declare that Ambrogio Pietro Londero had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Andrea Tinelli.

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