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Clinical and endocrine features of Brazilian infertile women with or without endometriosis: A comparative cross-sectional study

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ABSTRACT

Objective: To compare the clinical and endocrinological features of infertile Brazilian woman with or without endometriosis. **Methods:** This is a cross-sectional comparative study including infertile patients without an established indication for *in vitro* fertilization or intracytoplasmatic sperm injection at a tertiary center for reproductive medicine. A complete investigation of the cause of female infertile included videolaparoscopy for pelvic cavity and peritoneal factor evaluation. **Results:** Average patient age was (31.6±4.6) years. Sixty-nine percent patients presented with dysmenorrhea, 38% with bowel disturbances, and 21% with deep dyspareunia. Endometriosis was found in 76% of patients, and 91% had primary infertility. Dysmenorrhea was the only symptom that was more prevalent in infertile women with endometriosis. Compared to those without, patients with endometriosis had higher levels of follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), and carcinogen antigen-125 and lower levels of luteinizing hormone (LH), estradiol, progesterone, and free thyroxin. **Conclusions:** Endometriosis is highly prevalent in the Brazilian population and, dysmenorrhea is the only clinical symptom associated with the diagnosis of endometriosis. Infertile patients with endometriosis have higher levels of FSH, PRL and TSH than infertile women without endometriosis.

1. Introduction

The abnormal growth of endometrial tissue, including stroma and epithelial cells, outside the uterine cavity, named endometriosis, affects an estimated 6% – 10% of North American women in reproduction age[1] and about 2% to 8% of other populations of the same age[2,3]. Despite differences in population characteristics, the definitive diagnosis of endometriosis requires laparoscopy along with surgeon expertise and interest, making it difficult to determine the exact prevalence. Because several medical societies do not recommend laparoscopy during an infertility workup, the epidemiology of endometriosis is further complicated[4]. The two primary clinical features of endometriosis are pelvic pain/dysmenorrhea (4.5%–82.0% of patients) and infertility (2.1% – 78.0% of patients)[5,6]. The pain associated with endometriosis may be caused by extensive angiogenesis, neuroangiogenesis, inflammatory mediator activities, and anatomical distortion within and between the pelvic structures[7]. The relationship between endometriosis and infertility is strong[8], as the monthly fecundity rate for a normal couple 15% – 20% decreases to 2%– 5% when the woman has endometriosis[9]. The mechanism(s) by which endometriosis causes infertility has yet to be determined. Possible mechanisms include altered

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folliculogenesis, impaired oocyte release or oocyte oviduct pickup, defects in the luteal phase function, alterations in the eutopic endometrium, poor oocyte quality, poor embryo quality, decreased fertilization and implantation rates, and anatomic pelvic[10]. Immunological and endocrinological factors may also be envolved. Endocrinological characteristics of infertile women with endometriosis are not frequently demonstrated. Abnormalities in gonadotropin dynamics in the later follicular phase or midcycle have been reported[11,12], but studies reporting on baseline gonadotropin levels in the early follicular phase are scarce. Abnormal long or biphasic LH surges were reported; regarding FSH, both, normal or increased concentrations were reported[11,13]. Granulosa cell steroidogenesis seems to be abnormal and the association between endometriosis and luteal phase defect ranges from 9% to 67% of patients[12]; however, both normal [14,15] or abnormal[13,16] progesterone levels, have been reported. Although PRL concentrations have been found to be higher in women with endometriosis in older studies[17,18], several controlled studies have shown no significant difference between women with or without endometriosis[19,20].

Considering the prevalence and impact of endometriosis on infertile women, a complete diagnostic workup for infertility should include a diagnosis of endometriosis [6,21]. The current clinical opinion is that laparoscopy is not required for patients whose major complain is pain, although there seems a consensus regarding laparoscopy use before any treatment for infertility[4,6]. A detailed history, physical examination, serum marker assessment, ultrasound and magnetic resonance imaging can help to establish a presumptive diagnosis of endometriosis, although, laparoscopy is more reliable method and is required to reach a definitive diagnosis[4,6,21]. In addition to a precise diagnosis, laparoscopy permits staging of the endometriosis which can influence the choice of treatment and its success rate in infertile women [6,22-24]. The present study aimed to re-examine the prevalence of endometriosis in the Brazilian population and compare the clinical and endocrinological characteristics of infertile women with or without endometriosis.

2. Material and methods

2.1. Materials

This study enrolled 387 infertile women who had attended the tertiary infertility center at the Tropical Institute of Reproductive Medicine and Menopause, Cuiabá, MT, Brazil, from August 2008 to April 2013. After study approval was obtained from the local Committe for Ethics in Research, informed consent was obtained from each patient. Several patients with endometriosis had previously participated in a study that had examined the role of laparoscopy in the workup of infertile women and its impact on treatment choice[6]. Power calculations were performed with the assumption of an averaged prevalence of endometriosis of 25% in infertile women [3], precision of 80%, and confidence intervals of 95%. Only patients with infertility duration ≥ 1 year were examined. Patients with ultrasound diagnosis of endometrioma, regardless of size, were also included. Women with previous tubal ligation or women who have husbands with azoospermia or severe oligozoospermia (less than 10×10^6 mobile spermatozoa per ml) were excluded.

Standardized data collection included a full infertility workup, after the initial visit. Male factors were evaluated using medical history, tests for infectious diseases, and semen analysis. In case of normal semen, or mild-to-moderate oligozoospermia, the female evaluation comprised patient history, physical examination, screening for infectious diseases, endovaginal ultrasound, hormonal measurement, serum carcinogen antigen 125 (CA125) measurement, hysterosalpingography, and videolaparoscopy. Blood samples were obtained after 10-12h after fasting, using vacutainer tubes without EDTA (BD, Vacutainer®, São Paulo, Brazil). All samples were initially held at room temperature for 60 min, then centrifuged at 1 500 × g for 15 min, and stored at −20 ℃ until analysis.

Hormones were measured using previously validated methods and their accuracy has been described elsewhere[25]. In short, serum P4 was measured using a electrochemiluminescence, assay (Advia Centaur, Siemens Healthcare Diagnosis, UK) with a sensitivity of 0.67 nmol/L (0.21 ng/mL) and coefficients of intra and inter-assay variation of 3.7%-12.4% and 2.6%-3.9%, respectively. Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), estradiol (E2), prolactin (PRL), and free thyroxyn (FT4) were measured with an electrochemiluminescence assay (Elecsys 1010, Roche Diagnostics GmbH, Mannhein, German). The sensitivity and intra/ inter-assay coefficients of variation, were as follows: 0.1 mUI/L and 1.8/3.4% for LH; 0.1 mUI/mL and 1.8/3.5% for FSH; 18.4 pmol/L and 3.3/6.2% for estradiol; 0.0002 nmol/L and 2.8/5.0% for PRL; 0.27 μUI/mL and 2.1/8.6% for TSH; and 0.3 pmol/L and 3.6/6.2% for FT4. CA125 was measured using chemiluminescence assay (Abbott Laboratories, IL, USA) with a sensitivity of 1.0 U/mL, inter and intra assay coefficients of variation of 1.5/< 10% at different concentrations.

Diagnostic/therapeutic laparoscopy was performed by

three of the authors (SFM, MMWY, MASM) using general anesthesia. Every procedure was video recorded, and the surgeons completed a standardized operative report to record pelvic findings and endometriosis staging which was determined using the revised American Society for Reproductive Medicine classification[26]. The primary outcome of interest for laparoscopy was to accurately determine the prevalence of endometriosis, both visually and histologically. Other outcomes of interest were as follows: tubal patency, tubal sacculation, tubal obstruction, tubal fibrosis or constriction, peritubal adhesions, other pelvic adhesions, peritoneal or ovarian endometriosis, and other concurrent abnormal pelvic conditions. There were complications associated with surgical videolaparoscopy in three patients with advanced stages of endometriosis: two cases of bladder wall deep cauterization and one case with bowel lesion; all required surgical interventions. Tubal patency was tested using 10 mL of methylene blue dye. When necessary, adhesiolysis, excision or electroablation of visualized endometriotic implants, and endometrioma cystectomy were performed. Biopsy tissues were immediately immersed and fixed in 10% formaldehyde solution, embedded in paraffin on the second day, and stained using the hematoxylin–eosin technique.

2.2. Statistical analysis

Data distributions were examined using the Kolmogorov–Smirnov–Lilliefors test. Data with non-Gaussian distribution were log or square transformed before analysis and transformed back to the original units after analysis. Data with Gaussian distribution are presented as mean and standard deviation (SD). Associations were performed using the χ^2 test or test for proportions. Comparisons between variables with parametric distribution were performed using Student's t-test. P values < 0.05 were considered statistically significant. All analysis were performed using the Statistical Package for the Social Science (SPSS) software, version 20 (SPSS Inc., Chicago, IL,USA).

3. Results

A total of 387 infertile patients were recruited for this study, of which 300 (90.18%) were Caucasians, 24(6.2%) were African descent, 12 (31%) did not declare their ethnicity and 2 (0.51%) were of other races. Average patients age was (31.6±4.6) years. Patients presented with dysmenorrhea (289, 69.3%), abdominal distention or bowel alterations related to menstrual bleeding (146, 37.72%), diarrhea (28, 7.23%), deep dyspareunia (84, 21.2%), bleeding during intercourse (12, 3.1%), spotting for several days before starting the menstrual bleeding (31, 7.98%). For the entire group of infertile patients, the mean menarcheal age was (12.63±1.52) years, the entire duration of sexual relationship was (6.65±0.57) years, the mean period of intercourse without contraception was (2.93±2.52) years and intercourse occurred at an averange (2.65±1.57) times per week. Primary infertility was present in 352 (90.96%) patients and secondary infertility in 35 (9.04%). At laparoscopy only 36 (9.3%) women had their pelvic cavity completely normal. Endometriosis was found in 77.5% of patients; 56.4% had endometriosis in stages I–II and 21.1% in stages III–IV. On the 300 patients with a visual diagnosis of endometriosis, 229(76.4%) had their diagnosis confirmed histologically. The comparison of clinical features between infertile patients with and without endometriosis is presented in Table 1. The association of dysmenorrhea with other clinical symptoms is shown in Table 2. Reproductive characteristics of the two groups are shown in table 3. The mean concentration of gonadotropins, gonadal steroids, prolactin, thyroid stimulating hormone, free thyroxin, and carcinogenic antigen 125 in patients with or without endometriosis are compared in Table 4.

Table 1
Comparison of clinical features between infertile women with and without endometriosis (*n*,%).

Variable	With endometriosis	Without endometriosis	*p**
Dysmenorrhea	218(72.66)	51(58.62)	0.012
Abdominal distension	17(5.66)	1(1.14)	0.078
Increased peristalsis	101(33.66)	27(31.03)	0.645
Diarrhea	22(7.33)	6(6.89)	0.888
Deep dyspaurenia	69(23.00)	15(17.24)	0.250
Bleeding during intercourse	10(3.33)	2(0.66)	0.624
Premenstrual spotting	26(8.66)	5(5.74)	0.378

* Z proportion test

Table 2
Association between dysmenorrhea and other clinical features in infertile Brazilian patients with endometriosis.

Variable	Dysmenorrhea Yes	Dysmenorrhea No	χ^2	*P*
Menstrual cycle interval				
Abnormal	45	12		
Normal	163	46	0.024	0.877
Bowel disturbed				
Yes	86	15		
No	132	64	10.819	0.001
Deep dyspaurenia				
Yes	57	12		
No	161	67	3.903	0.048
Premenstrual spotting				
Yes	20	06		
No	198	73	0.181	0.670

Table 3
Comparison of reproductive features between infertile woman with and without endometriosis(±SD).

Variable	With endometriosis	Without endometriosis	*P*
Menarche (year)*	12.61±1.51	12.79±1.65	0.338
Marriage time (year)*	6.60±0.56	6.76±0.60	0.021
Number of intercourse (weekly)*	2.63±1.47	2.63±1.58	1.000
Average of fertility (year)*	2.34±0.43	2.82±0.51	0.078
Primary infertility (%)#	282(94.00%)	70(80.45%)	0.0001
Secondary infertility (%)#	18(6.00%)	17(19.54%)	0.0001

* Student *t* test , # Data given as proportions, Z test.

Table 4
Biochemical and endocrine characteristics of infertile women with and without endometriosis (±SD).

Parameters	With endometriosis	Without endometriosis	*P*#
FSH (mUI/mL)†	6.50±0.37	5.90±0.32	0.0001
LH (mUI/mL)*	5.88±1.90	6.45±1.90	0.0142
Estradiol (pmol/L) †	198.24±25.40	214.91±26.41	0.0001
Progesterone (pmol/L) †	1.53±0.51	1.84±0.54	0.0001
Prolactin (pmol/L) †	661.00±54.31	636.04±53.29	0.0002
TSH (mUI/mL) †	1.90±0.12	1.69±0.10	0.0015
Free Thyroxin(pmol/L) †	14.82±0.68	15.60±1.34	0.0001
CA 125 (UI/mL)*	23.98±2.34	14.45±1.86	0.0001

† data square transformed, * data log transformed, # student *t* test

4. Discussion

The current study's results confirm that endometriosis is highly prevalent among infertile Brazilian women from an Amazonian state (Mato Grosso) where the use of chemical products to control agriculture pests is widespread, as previously reported[6]. The authors argue this infertile population experienced above average exposure to these chemicals, which may increase the prevalence of endometriosis. Since ESHRE Guidelines suggest that negative histology results do not exclude endometriosis[4], the present study considered all patients with visible classic lesions in the diagnosis of endometriosis. Some investigators have reported inconsistencies between visual and histologic diagnoses, and therefore, many researchers believe the final diagnosis must be confirmed with histological specimens collected during laparoscopy[27]. Prevalence of pelvic endometriosis among infertile women ranges from 20% to 76%[6,28], although diagnosis is not histologically confirmed in 6%–36% of cases[6,27,29]. In the present study, biopsy failed to confirm the visual diagnosis of endometriosis in 33% of patients, in whom the most prevalent histological findings were fibrosis and white blood cell invasion.

In the present study, endometriosis was more frequent in Brazilian women with primary infertility than in those with secondary infertility. The prevalence of secondary infertility in the present study (10%) is lower than that reported by others. The prevalence of primary and secondary infertility has been reported at 37%–74% and 26%–44%, respectively, in other populations with similar ages[5,21,30–33]. Differences in population characteristics and environment factors may explain these wide ranges. The mean duration of infertility of 2–3 years found in the present study is in agreement with the majority of studies, which have reported infertility duration as between 2 and 4.8 years[21,28,34].

Dysmenorrhea and bowel disturbances (increased bowel movement or diarrhea) were the most prevalent clinical symptoms, and dysmenorrhea was associated with deep dyspareunia and intestinal dysfunction symptoms. Dysmenorrhea has been reported in 37%–58% of infertile women with endometriosis who were diagnosed using laparoscopy[32]. In the current study, a higher prevalence of dysmenorrhea was detected in the entire population of infertile patients, as well as the patients with endometriosis. In contrast, the worldwide prevalence of dysmenorrhea among infertile women has been reported as equal in those with or without endometriosis. Interestingly, dysmenorrhea was the only clinical symptom, using which we could differentiate between infertile women with and without endometriosis. Regarding the other clinical symptoms, a few studies have reported abnormal bleeding in women with endometriosis compared to those without[35,36]. Nevertheless, the current findings that most clinical symptoms (e.g., abdominal distention, bowel alteration, dyspareunia, premenstrual spotting, or bleeding during intercourse) were similar between women with and without endometriosis are in agreement with a previous report[37]. Unfortunately, it is generally accepted that clinical symptoms alone are unreliable for the diagnosis of endometriosis[37,38].

Studies regarding endocrinological characteristics of women with endometriosis are scarce and limited to evaluating gonadal steroids in later follicular, midcycle, and luteal phases. The coexistence of anovulation and endometriosis is not frequent and has been reported in about 16%–19% of cases[39–41]. Evidence of pituitary–ovarian dysfunction has been found in all stages of endometriosis. Ovulatory dysfunction, luteinized unruptured follicles, abnormal luteal phase, as well, increased prolactin levels and thyroid dysfunction, seem to be frequent among infertile women with endometriosis[12].

In addition to our results, lower baseline LH levels among infertile patients with endometriosis have already been reported[11], although these findings are not consistent with those of previous reports of normal[42], elevated or equal concentrations of LH[43,44] in women with or without endometriosis. On the other hand, in the late follicular phase and midcycle, a lower amplitude serum LH surge has

been reported in two studies[11,13], while normal or biphasic LH surges have been observed in other studies[16,45]. In summary, the association between LH changes and endometriosis remains uncertain, and any theory regarding LH modification as a cause of infertility in endometriosis remains speculative.

Although prolonged follicular phase has been reported in women with endometriosis[46], equal concentrations of FSH in the early follicular phase, of infertile women with or without endometriosis have also been reported in several studies [43,47,48]. However, higher levels of FSH in early follicular phase, found in the current study, have also been reported in other studies, typically in advanced endometriosis stages, indicating progressive loss of ovarian function as the disease advances[34,49]. Even possible, the association between baseline FSH levels and length of follicular phase was not examined; it is intriguing that most patients included in the current study had minimal or mild endometriosis, but still exhibited higher baseline levels of FSH.

The lower early follicular phase P4 concentrations observed in the current study might be attributed to diminished granulosa cell secretion in patients with endometriosis[50]. However, other studies have also reported similar early follicular phase P4 levels in women with or without endometriosis[37]. Usually, P4 concentrations are typically measured from the late follicular phase onward, and so P4 levels have been reported to diminish during the luteal phase[13,16]. In fact, luteal phase defect has been extensively associated with infertility in patients with endometriosis.

Estradiol measurement in women with endometriosis is often performed by sampling patients from the midfollicular phase onward, and the results are conflicting. Although abnormal changes in concentration of estradiol in late follicular phase[11,46] or decreased late follicular phase levels[11] have been reported, the majority of studies report normal estradiol levels in women with endometriosis [13,34,45,51]. At least one study has reported higher baseline concentrations of estradiol in the early follicular phase[49]. To our knowledge, the lower estradiol levels in the early follicular phase of women with endometriosis observed in the current study are novel. However, these results are in agreement with abnormal folliculogenesis and lower estradiol serum concentrations at the time of LH surge, which has been previously documented in patients with endometriosis [45,52].

Prolactin (PRL) levels among infertile patients with endometriosis are reported to be higher than in those without endometriosis[45,53–55]. Moreover, higher concentrations of PRL seem to be more prevalent in stages III–IV[45–56]. Therefore, the higher levels of PRL we observed in women with endometriosis are consistent with most studies. Equal concentrations of PRL in infertile women with or without endometriosis have also been observed[37,56]. The mechanism by which endometriosis and PRL levels determine infertility are poorly understood, although hyperprolactinemia and the presence of PRL receptors in ectopic endometriotic tissue may contribute[57].

Endometriosis has been associated with several autoimmune diseases[58], and women with endometriosis have higher rate of hypothyroidism than the general population[58,59]. Equal frequencies of thyroid disorders in women with or without endometriosis has also been reported[60], and equal TSH blood concentrations between these groups have also been reported[15,61,62]. Several studies have demonstrated that the thyroid response to TRH is equal in women with and without endometriosis[61], and that the annual risk for hypothyroidism may be higher in women with higher TSH levels[63]. In the current study, infertile women with endometriosis, who were diagnosed using laparoscopy, exhibited higher levels of TSH than in infertile women without endometriosis. Heterogeneity in patients' age, ethnicity, and diagnosis of endometriosis without laparoscopy may explain these differences.

Althout the current study has adequate sample size, power, and used the gold standard tool to diagnosis endometriosis, it has a few limitations. Dioxin was not measured in the women's blood, so the relationship between agriculture pets and the higher prevalence of endometriosis remains as a hypothesis to be tested. Gonadotropins and gonadal steroids were measured only in the early follicular phase and, because no association between hormone baseline levels and menstrual cycle features, the results do not permit any conclusion regarding ovulation timing and luteal phase function. Even autoimmune diseases had been associated with endometriosis, antithyroid antibodies were not measured. Despite these weaknesses, this study has some clinical implications. First, it confirms the high prevalence of endometriosis in infertile Brazilian women from an Amazonian state. Second, it creates an opportunity for investigating the possible influence of agriculture pets on endometriosis incidence in this population. Third, it makes clear that dysmenorrhea is the only clinical symptom associated with the diagnosis of endometriosis in infertile women and it would help the clinician to decide regarding the use of laparoscopy in infertility investigation or not. Fourth, the higher baseline concentrations of FSH, PRL, and TSH, and how these results could impact the treatment of infertile patients with endometriosis, needs further investigation.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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