Clinical Presentation and Management of Endometriosis-Related Hemorrhagic Ascites: A Case Report and Systematic Review of the Literature

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Abstract

This study aims to analyze the patient profile and presentation of endometriosis-related hemorrhagic ascites and review its management to raise awareness among gynecologists and improve treatment strategies. We present a case report and engage in a systematic review involving human cases of histologically proven endometriosis with hemorrhagic ascites. Keywords were searched in PubMed/MEDLINE, Cochrane Library, EMBASE, and Ovid Discovery databases from inception until December 2018. Studies that did not include a description of ascites or histopathologic results confirming endometriosis or those that involved patients with other conditions that may contribute to ascites were excluded.

The review yielded 73 articles describing 84 premenopausal women with histologically proven endometriosis-related hemorrhagic ascites. Of note, 83% (65/78) of the patients were nulliparous and 69.35% (45/62) were of African descent. The most common chief complaint was abdominal enlargement (58.33%, 49/84) but a host of other symptoms were also reported. Pleural effusion was reported in 32.14% (27/84), and elevated CA-125 was seen in 74.42% (32/43). The majority (64.29%, 54/84) of the patients underwent laparotomy, and an increasing trend of minimally invasive surgical approaches (p<0.001) and fertility-sparing techniques (p<0.001) was observed.

Introduction

Hemorrhagic ascites is a rare complication of endometriosis. The first description of endometriosis-related ascites has been attributed to Brews in 1954 [1]; however, it was not until 1957 that Charles first chronicled a case of blood-stained ascites in association with endometriosis [2]. Since then, fewer than 100 reports of hemorrhagic ascites related to endometriosis have been published in the literature.

Endometriosis-related hemorrhagic ascites may manifest with varying symptoms. Recognizing it may be difficult as it may present with similar disease processes such as malignancy, infection, cirrhosis, or trauma [3-6]. In light of this, we conducted this study to examine and elucidate the patient profiles and presentation of the disease to raise clinical awareness among gynecologists regarding the diagnosis of hemorrhagic ascites associated with endometriosis.

Case Presentation

A 34-year-old Taiwanese nulligravida woman presented to the outpatient department with a one-year history of irregular dysmenorrhea that was 5/10 in severity. She had no other associated complaints such as...
weight loss, anorexia, dyspareunia, urinary changes, or heavy menstrual bleeding. On further probing, the patient revealed having mild bloating that did not cause discomfort. Her menstruation occurred at regular monthly intervals. On physical examination, she had clear breath sounds and mildly distended flanks. Pelvic examination showed a corpus enlarged to 8-10 weeks’ size without adnexal masses or tenderness. Fullness at the cul-de-sac was palpated. Pelvic ultrasound revealed multiple small leiomyomas with massive ascites and a heterogeneous right ovarian tumor. A CT scan showed a multicystic right ovary with soft tissue seeding to bilateral paracolic gutters, omentum, and recto-uterine pouch, with massive ascites (Figures 1, 2). CA-125 was elevated (819.1 U/mL). With the working diagnosis of a possible malignant ovarian tumor, laparotomy was performed with staging surgery in mind.

Intraoperatively, 2 liters of dark-red ascitic fluid was drained (Figure 3a). Both adnexa were plastered to the posterior uterine wall. An ovarian tumor could not be identified. Friable soft tissue lesions were found on the uterine surface (Figure 3b). The cul-de-sac was obliterated. Multiple gray soft tissue nodules were scattered about the contracted omentum, mesentery, and the appendix (Figures 3c, 3d). Minimal manipulation of the pelvic organs provoked bleeding. The frozen section and final histopathological report of the implants were

FIGURE 1: Abdominal CT scan – sagittal view showing massive ascites (asterisk)

CT: computed tomography

FIGURE 2: Abdominal CT scan – axial view showing massive ascites (asterisk), right adnexal mass (arrow), and soft tissue seeding

CT: computed tomography
consistent with endometriosis. A diagnosis of stage IV endometriosis was made.

The patient had an uncomplicated postoperative course and was started on leuprolelin injections once a month for six months. After two months, a repeat ultrasound showed mild ascites (~100 mL). The patient remained otherwise asymptomatic on her monthly follow-up visits.

**FIGURE 3: Operative findings**

a. Hemorrhagic fluid. b. Friable soft tissue lesions on the uterine surface. c. Granular lesions on intestines, soft tissue nodules at the base of the appendix. d. Contracted omentum with numerous gray soft tissue nodules

**Discussion**

**Methods**

**Literature Search Strategy**

An extensive literature search of all case reports, case series, and letters to the editor was performed. PubMed/MEDLINE, Cochrane Library, EMBASE, and Ovid Discovery were searched with the keywords, "endometriosis" OR "endometriotic "OR "endometrioma" AND "ascites" OR "bloody ascites" OR "hemorrhagic ascites" OR "serosanguinous" OR "chocolate" OR "brown fluid" OR "chocolate ascites" OR "brown ascites" OR "serosanguinous ascites". Human studies involving women with biopsy-proven endometriosis published in any language were included, from inception until December 2018.
Eligibility Criteria

Studies with no available full-texts, non-histologically proven cases of endometriosis, non-hemorrhagic ascites, or those without a description of ascites were excluded. Patients with conditions that may cause ascites or hemorrhage (current tuberculosis, malignancy, other infections, ovulation induction, end-stage renal disease, HIV), history of trauma, pregnancy, were likewise excluded.

Screening and Data Extraction

Two independent reviewers (MCT and WTC) reviewed all titles and abstracts of articles obtained through the online database search. The full-text articles of abstracts that were deemed relevant were retrieved online or by manual searching. Reviewed articles were entered into a standardized data collection matrix. Information on authors, country/continent of origin, year of publication, patient characteristics such as age, parity, and ethnicity were entered into the data matrix. Chief complaint, character and volume of the ascites, interventions, intraoperative findings, severity of endometriosis, and outcomes were likewise recorded. In cases where the exact volume of ascites was not stated in a study, ascites was quantified based on the definitions from the existing literature and consensus reports [7-9]. The severity of endometriosis was recorded in each case or assessed based on intraoperative descriptions vis-a-vis the revised American Society for Reproductive Medicine (ASRM) classification of endometriosis [10].

Quality Assessment of Case Reports

MCT and WTC independently assessed the quality of individual studies based on the checklist for case reports and case series from the Joanna Briggs Institute Critical Appraisal tools for systematic reviews [11].

PRISMA Flow Diagram

The literature search strategy was summarized in a flow diagram based on the protocol laid out by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [12] (Figure 4).

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**FIGURE 4: PRISMA flow diagram**

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
Descriptive statistics were used to report study and patient characteristics, including symptoms and peritoneal involvement. Spearman rank correlation was used. Analyses were done using the Stata software version 16.0 (StataCorp, College Station, TX).

### Results

The literature search initially yielded 1,341 citations for review. After a screening based on the inclusion and exclusion criteria, 73 case reports involving 84 women of endometriosis-related hemorrhagic ascites were included in the final analysis. These were published from 1957 to 2018. The patient demographics, clinical presentation, and management as described in these reports are summarized in Table 1.

| Study | Patient age (years) | Race | Parity | Chief complaint | CA-125 (U/mL) | Ascites volume (mL) | Ascites color | Pleural effusion | Surgery | Main procedure | Medical management | Recurrence |
|-------|--------------------|------|--------|----------------|--------------|-------------------|-------------|----------------|---------|----------------|-------------------|------------|
| 1     | 31                 | B    | 0      | Pain           | <35          | 3500              | H           | No             | Laparotomy | Biopsy         | GnRH              | No         |
| 2     | 31                 | AFR  | 0      | Diaphragm      | 190          | 8500              | H           | No             | Laparoscopy | Biopsy, excision of peritoneum | GnRH, then COC | Yes        |
| 3     | 25                 | C    | 0      | Diaphragm      | ≥1000        | H                 | Yes         | Laparoscopy   | Biopsy   | GnRH, then desogestrel | No         |
| 4     | 37                 | AFR  | 0      | Diaphragm      | 5700         | H                 | No           | Laparoscopy   | Biopsy   | GnRH, for 3 months, then desogestrel | No         |
| 5     | 33                 | A    | 0      | Distension     | 250          | 6000              | SS          | Yes           | Laparoscopy | Biopsy         | GnRH, then denogestrel | Yes        |
| 6     | 31                 | AFR  | 0      | Distension     | 5300         | H                 | Yes         | Laparoscopy   | Cystectomy | Biopsy         | GnRH              | No         |
| 7     | 28                 | AFR  | 0      | Weight loss    | 300-6        | 8000              | H           | No             | Laparoscopy | Biopsy         | GnRH for 6 months | Yes        |
| 8     | 44                 | AFR  | 0      | Meas           | 95.8         | 2900              | B           | No             | Laparoscopy | Partial cystectomy | None      | No         |
| 9     | 21                 | A    | 0      | Distension     | 4900         | H                 | No           | Laparoscopy   | Biopsy   | Monophasic COC | Yes       |
| 10    | 21                 | AFR  | 0      | Distension     | 600          | 6000              | H           | No             | Laparoscopy | Biopsy         | GnRH, then COC | No         |
| 11    | 21                 | A    | 0      | Distension     | 36.3         | 3500              | H           | No             | Laparoscopy | Cystectomy      | GnRH              | No         |
| 12    | 26                 | AFR  | 0      | Distension     | 7800         | H                 | No           | Laparoscopy   | Biopsy, peritoneal stripping | None | Yes         |
| 13    | 24                 | 1    | 0      | Distension     | <35          | 4500              | SS          | No             | Laparoscopy | TAHBSO         | GnRH 250mg/day for 6 weeks | Yes        |
| 14    | 26                 | C    | 0      | Dysemen        | 106          | 3500              | H           | No             | Laparoscopy | Biopsy         | COC                | Yes        |
| 15    | 36                 | AFR  | 0      | Pain           | 1123         | 3500              | H           | No             | Laparoscopy | Biopsy         | GnRH + ibalona    | Yes        |
| 16    | 36                 | A    | 0      | Dysemen        | 184          | 4300              | B           | No             | Laparoscopy | Biopsy, excision of all lesions | None | Yes         |
| 17    | 32                 | 0    | 0      | Distension     | ≥58          | 5500              | H           | Yes           | Laparoscopy | Biopsy         | GnRH for 6 months, then denogestrel | Yes        |
| 18    | 44                 | 0    | 0      | Pain           | >10000       | ≥2000             | B           | No             | Laparoscopy | Biopsy         | USG, cystectomy | NR         | No         |
| 19    | 35                 | A    | 0      | Dysemen        | 22           | 5300              | H           | No             | Laparoscopy | Biopsy         | GnRH, then denogestrel 2 mg PO OD | Yes        |
| 20    | 34                 | AFR  | 0      | Distension     | 4900         | H                 | No           | Laparoscopy   | Biopsy   | GnRH for 6 months | No         |
| 21    | 36                 | A    | 0      | Distension     | 2066         | 3500              | H           | No             | Laparoscopy | Bilateral cystectomy | GnRH              | No         |
| 22    | 22                 | AFR  | 0      | Dysemen        | 61           | 2700              | B           | Yes           | Pancaresectomy | Biopsy         | GnRH, then DMFA | No         |

Ovarian mass
| 22 | Akhila et al., 2012 [32] | 26 | AFR | 0 | Cough | 72.5 | <1500 | H | Yes | Laparotomy excision | GnRH 3.6 mg | No |
| 24 | Akramradeh et al., 2012 [24] | 22 | AFR | 0 | Distension | 5900 | H | No | Laparotomy Biopsy | Danazol | Yes |
| 25 | Queiroz et al., 2011 [35] | 36 | C | 0 | Infertility | 73 | 1500 | H | No | Laparoscopy Cystectomy | COC |
| 26 | Queiroz et al., 2011 [35] | 30 | AFR | 0 | Infertility | 192 | 13000 | B | Yes | Laparoscopy Biopsy | GnRH, then GnRH + COC |
| 27 | Shabani et al., 2012 [26] | 40 | 4 | Distension | <35 | 3000 | B | No | Laparoscopy Biopsy | GnRH for 6 months | Yes |
| 28 | Shabani et al., 2012 [26] | 30 | 2 | Distension | 96 | <1500 | B | No | Laparotomy SubTAH + BSO | None | No |
| 29 | Shabani et al., 2012 [26] | 28 | 0 | Distension | <80 | H | No | Laparotomy TAHBISO | None | Yes |
| 30 | Ferreira and Remorgida, 2011 [37] | 36 | Distension | 88.4 | 4800 | H | No | Laparoscopy Biopsy, excision of nodules | Norethindrone acetate 3.5 mg PO OD | No |
| 31 | Cordeiro-Freitas et al., 2011 [26] | 28 | AFR | 0 | Distension | <35 | 9400 | H | No | Laparoscopy Biopsy | GnRH for 3 months, then COC | No |
| 32 | Souchella et al., 2010 [38] | 36 | 1 | Ascites | <5000 | 8300 | COC | No | Laparoscopy TAHBISO | None | No |
| 33 | Ignacio et al., 2010 [41] | 36 | AFR | 0 | Distension | 30 | 7500 | B | Yes | Laparoscopy Cystectomy | GnRH + add-back therapy | No |
| 34 | Day et al., 2008 [41] | 24 | 0 | Pain | 2500 | H | No | Laparoscopy Biopsy | GnRH | Yes |
| 35 | Park et al., 2009 [42] | 34 | 0 | Pain | 548.1 | 2900 | B | No | Laparoscopy USD | GnRH + tibolone add-back therapy for 6 months | No |
| 36 | Lohda et al., 2009 [43] | 30 | AFR | 0 | Distension | 4900 | H | No | Laparoscopy Biopsy | COC | No |
| 37 | Uzula et al., 2008 [44] | 23 | C | 0 | Dysm | 1500 | H | Yes | Laparoscopy Biopsy | GnRH + intermittent steroids | Yes |
| 38 | Uzula et al., 2008 [44] | 26 | C | 0 | Pain | 2900 | H | No | Laparoscopy USD | GnRH | Yes |
| 39 | Sait, 2006 [45] | 26 | AFR | 0 | Distension | 2140 | 5900 | H | No | Laparoscopy Bilateral cystectomy | GnRH for 6 months, then COC | No |
| 40 | Santos et al., 2007 [46] | 40 | C | 0 | Pain | ≤2500 | SS | No | Laparotomy Biopsy | None, mortality | No |
| 41 | Palayekar et al., 2007 [47] | 46 | AFR | 1 | Distension | 35.6 | 4900-6000 | H | No | Laparoscopy TAHBISO | None | No |
| 42 | Goumenou et al., 2004 [2] | 46 | C | 0 | Dysm | 1504 | 4800 | H | Yes | Laparoscopy TAHBISO | None | No |
| 43 | Rayal et al., 2005 [40] | 30 | 0 | Distension | 2540 | <1000 | B | No | Laparoscopy USO | NR | No |
| 44 | Elouali et al., 2005 [41] | 28 | AFR | 0 | Infertility | 19000 | H | No | Laparoscopy Biopsy | GnRH | Yes |
| 45 | Furtar et al., 2005 [33] | 33 | AFR | 0 | Infertility | 207 | 4900 | SS | Yes | Laparoscopy Cystectomy | GnRH | Yes |
| 46 | Zeppa et al., 2004 [51] | 34 | 0 | Pain | 530 | H | No | Paracentesis | Paracentesis | NR | No |
| 47 | Francis et al., 2002 [52] | 2 | Dysm | <35 | ≤2000 | B | Yes | Laparotomy TAHBISO | None | No |
| 48 | Cheong and Lim, 2003 [53] | 40 | A | 1 | Distension | <35 | 5800 | H | Yes | Laparotomy Biopsy | NR | No |
| 49 | Murthi and Mitchell, 2002 [34] | 37 | AFR | 0 | Dysm | <35 | ≤2000 | B | Yes | Laparoscopy TAHBISO | GnRH | Yes |
| 50 | Dias et al., 2000 [55] | 41 | AFR | 0 | Distension | 19000 | B | No | Laparoscopy USO | GnRH for 6 months | Yes |
| 51 | Bhopawala et al., 2000 [32] | 34 | AFR | 0 | Distension | 8900 | B | Yes | Laparoscopy TAHBISO | None | No |
| 52 | El Khalf et al., 1999 [37] | 36 | Distension | 8900 | H | No | Laparoscopy Biopsy | COC | Yes |
| 53 | Samore-Meta and Feste, 1998 [36] | 43 | C | 3 | Pain | 2900 | B | No | Laparoscopy TAHBISO | None | No |
| 54 | Fletcher et al., 1998 [36] | 27 | AFR | 1 | Distension | 8900 | B | No | Laparoscopy Biopsy | GnRH monthly for 6 months | No |

Danazol 600 mg PO daily for 6
| Page | Author(s) | Study Type | Follow-up | Treatment | Primary Outcome | Comments |
|------|-----------|------------|-----------|------------|-----------------|----------|
| 53   | Muneyyirci-Delale et al., 1986 [42] | 25 | AFR     | Pain      | 6-12 | Laparotomy | Bilateral cystectomy | 3 months, then norethindrone acetate | Yes |
| 54   | Muneyyirci-Delale et al., 1986 [42] | 31 | AFR     | Shortness of breath | 10000 | B | Yes | Laparotomy | TAHBSO | None | Yes |
| 55   | Muneyyirci-Delale et al., 1986 [42] | 32 | AFR | Distension | 4900 | H | No | Laparotomy | Ovarian wedge resection | Gr-RH | No |
| 56   | Muneyyirci-Delale et al., 1986 [42] | 35 | AFR | Dyse  | 366 | 3000 | H | No | Laparotomy | Adrenal mass reaction | Gr-RH for 6 months, then norethindrone acetate | No |
| 57   | Mejia et al., 1987 [41] | 44 | AFR | Distension | 25 | 10000 | H | No | Laparotomy | TAHBSO | None | Yes |
| 58   | Flanagan and Barnes, 1986 [42] | 30 | AFR | Distension | 49 | 2000 | B | Yes | Laparotomy | USO, ovarian wedge resection | Gr-RH | Yes |
| 59   | el-Hawsh, 1985 [52] | 32 | AFR | Distension | 118 | 4500 | B | Yes | Laparotomy | TAHBSO | Gr-RH 4 monthly for 6 months | No |
| 60   | Schlueter and McClennan, 1994 [54] | 20 | AFR | Distension | 5900 | H | No | Laparotomy | Biopsy | Gr-RH monthly | No |
| 61   | Jose et al., 1984 [52] | 20 | A | Distension | 5900 | B | Yes | Laparotomy | USO | Descemet 300 mg TID | No |
| 62   | London and Parham, 1986 [42] | 29 | AFR | Distension | 3000 | B | No | Laparotomy | TAHBSO | None | No |
| 63   | Chen et al., 1990 [57] | 20 | A | Distension | 46 | 5800 | B | Yes | Laparotomy | USO | Danazol 400 mg PO daily + Duphaston 10 mg PO OD for 6 months | No |
| 64   | Toviere et al., 1990 [64] | 31 | Pain | 8000 | B | No | Laparotomy | USO | NR | No |
| 65   | Yu and Grimes, 1981 [54] | 26 | A | Pain | 3000 | H | Yes | Laparotomy | USO | Gr-RH for 6 months | No |
| 66   | Hattori et al., 1993 [70] | 50 | A | Distension | 36 | 3800 | B | No | Laparotomy | TAHBSO | MPA | Yes |
| 67   | Taub et al., 1989 [3] | 32 | AFR | Distension | 2400 | H | Yes | Laparotomy | BSO | DMPA | No |
| 68   | Olubuyide et al., 1988 [71] | 19 | AFR | Distension | 4900 | H | No | Laparotomy | Biopsy | Norethisterone acetate 5 mg PO TID for 1 week, then 10 mg BID | No |
| 69   | Chicharzon and Wettaveakklasert, 1989 [72] | 31 | E | Distension | 1800 | H | No | Laparotomy | TAHBSO | DMPA | Yes |
| 70   | Iwaseka et al., 1988 [72] | 35 | A | Distension | 17 | 2500 | B | No | Laparotomy | TAHBSO | None | No |
| 71   | Iwaseka et al., 1988 [72] | 25 | A | Pain | 150 | H | No | Laparotomy | USO, Ovarian wedge resection | Descemet 400 mg PO daily for 3 months | No |
| 72   | Mehnemboo et al., 1985 [74] | 24 | AFR | Distension | 6800 | H | No | Laparotomy | Biopsy | DMPA IM q2 weeks for 5 months | No |
| 73   | Halme et al., 1985 [73] | 23 | AFR | Distension | 7300 | SS | No | Laparotomy | Biopsy | Descemet 400 mg PO BID | No |
| 74   | Jenks et al., 1984 [74] | 23 | AFR | Distension | 5200 | H | No | Laparotomy | TAHBSO | None | No |
| 75   | Gauker et al., 1983 [77] | 22 | AFR | Pain | ≥2050 | B | Yes | Laparotomy | Ovarian resection | Descemet | No |
| 76   | Chehrevar et al., 1981 [74] | 20 | E | Distension | 1500 | B | No | Laparotomy | BSO | None | No |
| 77   | Chehrevar et al., 1981 [74] | 26 | AFR | Distension | 4900 | B | No | Laparotomy | BSO | Descemet 400 mg daily for 10 months | No |
| 78   | Iwanit et al., 1974 [74] | 32 | AFR | Distension | 2500 | H | Yes | Laparotomy | TAHBSO | None | No |
| 79   | Collier et al., 1983 [83] | 34 | EFR | Distension | 4900 | B | No | Laparotomy | TAHBSO | None | Yes |
| 80   | Bennetson et al., 1986 [81] | 29 | AFR | Distension | 3900 | B | No | Laparotomy | TAHBSO | None | No |
TABLE 1: Case reports of endometriosis-related hemorrhagic ascites

A: Asian; AFR: of African descent; B: brown/dark brown/brownish/chocolate-colored; BS: bilateral salpingo-oophorectomy; BSO: bilateral salpingo-oophorectomy; C: Caucasian; COC: combined oral contraceptive pills; coffee: coffee-colored; distension: abdominal distension; DMPA: depot medroxyprogesterone acetate; Dysm: dysmenorrhea; GnRH: gonadotropin-releasing hormone agonists; H: hemorrhagic/bloody; mass: abdominal mass; MPA: medroxyprogesterone acetate; pain: abdominal pain; SS: serosanguinous/blood-stained/haemoserous; TAHBSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy; USO: unilateral salpingo-oophorectomy; RSO: right salpingo-oophorectomy

Patient characteristics are shown in Table 2. The mean age of the patients at diagnosis was 31.16 years (SD: 6.57; range: 19-50). There was no relationship between the year of publication/presentation and age (p=0.193) or age distribution (p=0.600).

TABLE 2: Endometriosis-related hemorrhagic ascites – patient characteristics

SD: standard deviation

| Characteristics                          | Values                      |
|------------------------------------------|-----------------------------|
| Age, years, mean (SD)                    | 31.16 (6.57)                |
| Age range, years                         | 19-50                       |
| Age distribution, number (%), N=82       |                             |
| <20 years                                | 1 (1.22)                    |
| 20-29 years                              | 31 (37.80)                  |
| 30-39 years                              | 40 (48.78)                  |
| 40-49 years                              | 9 (10.98)                   |
| ≥50 years                                | 1 (1.22)                    |
| Parity, number (%), N=78                 |                             |
| Nulliparous                              | 65 (83.33)                  |
| Parous                                   | 13 (16.67)                  |
| Race distribution, number (%), n=62      |                             |
| African                                  | 43 (69.35)                  |
| Asian                                    | 10 (16.13)                  |
| Caucasian                                | 9 (14.52)                   |
| Ascitic fluid volume, mL, mean (SD)      | 4228.27 (2625.66)           |

The most common presenting symptom was abdominal distension (Table 1). Other initial complaints reported by patients are presented in Table 3. The majority (91.67%, 77/84) of the symptoms were gradual in onset. Pleural effusion was reported in 32.14% (27/84) of cases. The ascitic fluid was predominantly massive with a mean volume of 4228.27 mL (SD: 2625.66; range: 100-10000). CA-125 was elevated in 52 out of 45 patients, with a median value of 86 U/mL (range: 17-10000 U/mL).
| Symptom                       | Number (%) |
|-------------------------------|------------|
| Abdominal distension         | 66 (78.57) |
| Dysmenorrhea                  | 47 (55.95) |
| Abdominal pain                | 28 (33.33) |
| Weight loss                   | 18 (21.43) |
| Primary infertility           | 17 (20.24) |
| Nausea and/or vomiting        | 13 (15.48) |
| Anorexia                      | 11 (13.10) |
| Dyspnea                       | 9 (10.71)  |
| Deep dyspareunia              | 6 (7.14)   |
| Fatigue/malaise               | 6 (7.14)   |
| Chronic pelvic pain           | 5 (5.95)   |
| Constipation                  | 5 (5.95)   |
| Shortness of breath           | 4 (4.76)   |
| Early satiety                 | 4 (4.76)   |
| Cough                         | 3 (4.57)   |
| Dyschezia                     | 3 (3.57)   |
| Menorrhagia                   | 3 (3.57)   |
| Right-sided chest discomfort  | 3 (3.57)   |
| Weight gain                   | 2 (2.38)   |
| Loose stools                  | 2 (2.38)   |
| Dysuria                       | 2 (2.38)   |
| Orthopnea                     | 1 (1.19)   |
| Abdominal mass                | 1 (1.19)   |
| Thoracic pain                 | 1 (1.19)   |

**TABLE 3: Symptoms of hemorrhagic ascites associated with endometriosis (N=84)**

Moderate to severe endometriosis (ASRM stage III to IV) was seen in 97.44% (76/78) of the cases, and adhesions were described in 78.05% (64/82). In 43.90% (36/82) of the cases, an ovarian cyst was identified; 11.11% (4/36) of the cases were ruptured. Peritoneal implants scattered about the abdominopelvic cavity in 42.68% (35/82), while peritoneal nodules were seen in 20/82 (24.39%). Other abdominopelvic areas involved are shown in Table 4.
At the time of presentation, 64.29% (54/84) underwent laparotomy, and laparoscopy was performed in 33.33% (28/84). Two cases (2/84) had paracentesis. Almost half (44.05%, 37/84) of the cases had repeat abdominal surgeries, while 76.19% (64/84) required multiple procedures that included repeat abdominal surgeries (laparoscopy and/or laparotomy), paracentesis, thoracostomy, or thoracotomy. On the other hand, less invasive surgical approaches (p<0.001) and fertility-sparing procedures (p<0.001) are observed to be increasingly favored in recent years.

A cure was reported in 95.45% (21/22) who went through definitive surgery via hysterectomy with bilateral salpingo-oophorectomy. Medical treatment was not given to 68.18% (15/22) after surgery. Four patients tolerated stripping or excision of the peritoneum of all endometriotic implants with no recurrence. Two of these received no additional medical therapy.

Patients who were offered medical therapy post-surgery received gonadotropin-releasing hormone (GnRH) agonists (63.79%, 37/58), either alone, with add-back therapy, or as a preliminary treatment that was eventually transitioned to either a progestogen or a combined oral contraceptive (COC) pill. In 86.49% (32/37) who received GnRH agonists, no recurrences were observed. Other therapies included danazol (13.79%, 8/58), progestogens alone (10.34%, 6/58), or COC alone (10.34%, 6/58). The cure rate with danazol was 100% (eight out of eight), while COC and progestogens were equally effective, each with an 83.33% (five out of six) cure rate.

The recurrence rate observed at the time of presentation or after initial management was 36.90% (31/84), while that after definitive surgery and/or ovarian function suppression was 8.33% (7/84). Five of these cases reported significant ascites upon the cessation of GnRH therapy [35,49,50,62] or upon shifting from GnRH to progestogen therapy [15]. The other two had reaccumulating minimal ascites while on oral COC [35] or oral progestogen [70]. Of note, 71.42% (five out of seven) of recurrences had undergone ovary-preserving procedures (oophorocystectomy or biopsy) prior to medical therapy. Mortality was reported in one case. The Median follow-up period was eight months.

**Analysis**

Very little is known about the pathogenesis of endometriosis-related hemorrhagic ascites. One putative mechanism is peritoneal irritation from the rupture of ovarian cysts. The endometrial cells from this spillage propagate the spread of implants in the pelvic cavity and cause inflammation, which in turn leads to adhesions and ascites [81]. This theory assumes the presence of ovarian cysts. However, in this review, less than half of the study population were found to have ovarian endometriotic cysts, and only four out of 36 of these cysts were ruptured. Alternative hypotheses such as alterations in vascular permeability, lymphatic channel obstruction, as well as individual variations in susceptibility to the disease may be explored [44,49,83,84].

The rubor of ascites may be due to increased angiogenesis seen in endometriosis. Erosions from affected friable soft tissue, serosal, peritoneal surfaces, and implants cause micro-bleeding or frank bleeding, leading to the hemorrhagic character of ascites [49,84]. Pleural effusions associated with the hemorrhagic ascites may be due to several mechanisms. However, based on the presentation of massive ascites in the majority of cases, the most plausible cause is anatomic defects in the diaphragm that allow for the passage of hemorrhagic fluid into the pleural space [85,86].
Endometriosis-related hemorrhagic ascites may affect any woman of reproductive age but is more common in women in their twenties and thirties, without any significant increase or decrease with respect to the age of onset. This finding differs from what was previously described [44]. Many patients may seek a consult for abdominal distension or symptoms secondary to abdominal distension such as pain or pulmonary discomfort in the background of dysmenorrhea or worsening dysmenorrhea. Dysmenorrhea accounted for only 5.9% (5/84) of the chief complaints in this review but is most commonly elicited on history as an accompanying symptom. Massive ascites usually predominate in clinical evaluation.

The utility of CA-125 in the diagnosis of this condition is arguable due to its non-specificity. While the majority presented with CA-125 >35 U/mL, similarly increased levels have been described in various benign gynecologic diseases [87]. Mesothelial cells that line the peritoneum secrete CA-125. Since mesothelial hyperplasia and hypertrophy are associated with endometriosis, CA-125 release is greater, and hence elevated in this condition. However, the same holds true for other diseases of the peritoneum such as malignancy and tuberculosis [84,88,89]. Its clinical use, therefore, is limited to determining whether a patient has peritoneal disease in general.

Management of the condition relies critically on establishing a histologic diagnosis. Surgery is thus warranted, although several studies have achieved cytological confirmation through paracentesis [52,51]. With the case presented, a clinically presumptive diagnosis of ovarian cancer was made, which led to the decision to perform a laparotomy. This is supported by studies on ovarian cancer [90]. However, with the availability of minimally invasive techniques and increasing technical confidence among surgeons, there is a growing trend favoring their use in the management of potentially malignant ovarian tumors [90,91]. The current recommendation for laparoscopy in suspected ovarian tumors is to establish a histologic diagnosis through a frozen section and, if tumors are found malignant, to assess their resectability [91-93]. Since it is difficult to differentiate it from a malignant etiology, surgical management of endometriosis-related hemorrhagic ascites may follow this approach.

Moderate to severe (ASRM stage III to IV) endometriosis almost always presents intraoperatively and with adhesions and implants in the abdominopelvic cavity. Peritoneal involvement can be related to small implants, nodules, or varying degrees of adhesions. Thus, the presence of hemorrhagic ascites, as seen in 97.44% of cases and in the index case, may correlate with the severity of endometriosis.

Since the ascites in this review was found mostly in moderate to severe endometriosis, it seems logical to follow the principles of endometriosis treatment. Termination or suppression of ovarian function is the cornerstone of management. The importance of this cannot be overemphasized as many women undergo multiple surgeries for recurrence or for the treatment of an existing endometriosis. Surgical sterility via hysterectomy with removal of bilateral ovaries is the definitive form of management [19,36,59,61,63,68]. However, fertility-sparing surgeries are currently performed in patients who wish to realize their reproductive potential.

Medical therapy consists of GnRH agonists, which have been used with success in achieving ovarian suppression. Danazol, progestogens, and COC pills are likewise given as primary treatment or upon completion of GnRH agonist therapy for long-term control of the disease. Danazol, an antigonadotropic, anti-estrogenic synthetic steroid, is effective in suppressing ovarian function. However, its various androgenic effects preclude its use [94,95]. In the majority of cases and especially in more recent studies, GnRH agonists have been used more frequently. These are effective in achieving ovarian suppression and increasing fertility rates but their side effect profile limits their long-term use [94,95]. Progestogens and COC pills were effective as medical treatments in this review, but current evidence has failed to demonstrate any benefit of COC in managing pelvic pain in endometriosis [96]. On the other hand, oral medroxyprogesterone acetate has been shown to be effective in decreasing chronic pelvic pain [97]. Other medications of interest are the levonorgestrel-releasing intrauterine system and mifepristone, which were not used in the studies included in this review. Nonetheless, their clinical utility may be explored as these have been shown to be effective in suppressing the menstrual cycles and relieving pain associated with endometriosis [98,99].

Conclusions

Hemorrhagic ascites is a rare manifestation of endometriosis that can present in any premenopausal woman. The most common initial complaint is abdominal distension, but a host of other symptoms may also be associated with the condition. Diagnosis can be challenging because it mimics several disease entities that cause ascites, thus warranting a heightened clinical suspicion. Minimally invasive techniques may be employed to establish a histologic diagnosis. Recognition of hemorrhagic ascites as a manifestation of severe endometriosis is essential for recurrence prevention, which should prompt therapies directed at suppressing ovarian function. Ovary-preserving surgeries are preferred because affected women are of childbearing age. Recurrence is low after appropriate surgical and medical interventions.

Additional Information

Disclosures
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