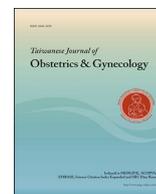




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Review Article

Update on the differential diagnosis of gynecologic organ-related diseases in women presenting with ascites

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ABSTRACT

In 2008, we published a review article entitled “Differential diagnosis of gynecologic organ-related diseases in women presenting with ascites” in the *Taiwanese Journal of Obstetrics and Gynecology*. Ascites might be the results of the physiological or pathological status, and the underlying mechanisms varied greatly in the different genders. The diagnostic challenge is frequently found in clinical practice. This review summarizes the recent knowledge and clinical practice for women presenting with ascites. Approach includes history, physical examination, laboratory examination, ultrasound, paracentesis and possible laparoscopy. Accurate and prompt diagnosis not only provides the better care and management but also diminishes the unnecessary psychological stress in women presenting with ascites.

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Introduction

Although ascites often describes the condition of pathologic fluid collection within the abdominal cavity [1,2], sometimes, women may normally have 20 ml or more intra-abdominal fluid, depending on the phase of their menstrual cycle [3]. Ascites can develop as a result of hepato-renal disease, congestive heart failure, or some malignant diseases, especially tumor with widespread intra-peritoneal involvement, but it is most common accompanying with various kinds of gynecologic organ-related disease [4–8]. Ovary-related diseases, such as epithelial ovarian cancer (EOC), metastatic ovarian cancer, benign ovarian fibroma, stromal hyperplasia, ovarian hyperstimulation syndrome (OHSS), primary

peritoneal serous carcinoma (PPSC), endometriosis, peritoneal tuberculosis (TB) and ruptured ovarian functional cyst, should kept in mind when women are found to have ascites [2,3,6–10].

It is always a challenge while facing women at reproductive age with ovarian mass and ascites, since the malignancy should be considered and subsequent destructive treatment, such as debulking surgery or chemotherapy may significantly impair the future fertility. In clinical practice, the life-threatening condition, such as internal bleeding or cancer should be promptly diagnosed. By contrast, benign diseases, such as Meig's syndrome or TB peritonitis, should be suspected in women during reproductive period, because medical or conservative treatment either by conventional exploratory laparotomy or minimally invasive surgery could cure the diseases without further harmful deteriorations to the fertility. In 2008, we published a review article entitled “Differential diagnosis of gynecologic organ-related diseases in women presenting with ascites” in the *Taiwanese Journal of Obstetrics and Gynecology* [3]. In the review, we update the information of the gynecologic organ-related ascites.

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Formation of ascites

The abdominal space normally contains small volume of fluid providing lubrication between the parietal and visceral membranes and the organs within the abdominal cavity [5]. The Starling hypothesis proposes that net flow into the space is controlled by the hydrostatic and plasma colloidal osmotic pressure gradients and permeability of the membranes and lymphatic drainage was a key pathway to remove excess of fluid within the abdominal cavity. To maintain the low and constant volume of intraperitoneal fluid is based on the balance of the above-mentioned processes, and any change in one or more of these processes may result in ascites formation [4,5].

Hepato-renal problems are the most common cause of ascites formation, regardless of age or genders. Obstruction and following activation of the renin-angiotensin-aldosterone and sympathetic nervous system is the major cause contributing to fluid accumulation [5]. Intraperitoneal infection or malignancy cause fulminant inflammatory processes leading to the extravasation of protein-rich fluid into the peritoneal space [10].

Classification of ascites

Three grades are often used to classify the ascites [4]. Grade 1 is only detectable with ultrasound image; grade 2 is symmetrical distension of the abdomen; and grade 3 presents large volume of ascites with gross abdominal distension [4]. It is hard to distinguish transudate and exudate of ascites based on the traditional classification, such as Light's criteria, including (1) fluid/plasma protein ratio > 0.5; (2) fluid/plasma LDH (lactate dehydrogenase) ratio > 0.6, or (3) fluid LDH > 2/3 upper reference limit for plasma LDH [5]. By contrast, the serum-ascites albumin gradient (SAAG) may be a better tool to distinguish transudate and exudate of ascites, because SAAG values > 11 g/L can be indicated as a transudate, suggesting that underlying cause is secondary to portal hypertension [4,5]. Table 1 shows the common causes of ascites occurred in the women.

Initial investigation for women presenting with ascites

Since hepato-renal diseases might be the most common situation associated with ascites, the initial investigation for women with ascites is often guided by medical association of gastroenterology or liver diseases, such as British Society of Gastroenterology [11], European Association for the Study of the Liver [12], and American Association for the Study of Liver Diseases [13]. The followings are recommended to investigate women with ascites, including careful history taking, ultrasound, diagnostic paracentesis (tap), ascitic fluid culture for bacteria or mycobacteria, Gram's stain, ascites biochemistry evaluation, and cytology examination.

Table 1
Differential diagnosis of female ascites.

Non-malignant	Characteristics	Malignant	Characteristics
Portal hypertension (cirrhosis, congestion, thrombosis, congestive heart failure, constrictive pericarditis)	Transudate	Ovarian cancer	Exudate
Ovarian fibroma (Meig's syndrome), ovarian stromal hyperplasia, corpus luteum rupture, ectopic pregnancy	Most transudate, but if exudate indicated hemorrhage	Endometrial cancer	Exudate
Ovarian hyperstimulation syndrome	Transudate	Primary Peritoneal Serous Carcinoma	Exudate
Endometriosis	Exudate	Carcinomatosis	Exudate
Infection (TB)	Exudate	Mesothelioma	Exudate
Miscellaneous	Transudate/Exudate	Metastatic or primary hepatoma	Exudate

History taking

One of most common emergent complications in women is OHSS [14,15]. When the physician does not know that the woman has underwent assisted reproductive technique (ART), such as in-vitro fertilization and embryo transfer (IVF-ET), it is nearly difficult to make a diagnosis. The clinical features of OHSS are mimic to those of advanced ovarian cancer, including enlarged ovarian cystic lesions accompanied with massive ascites and sometimes, pleural effusion.

Ultrasound (US)

Ultrasound may be the first-line and gold standard for diagnosing ascites in women. Ultrasound can identify as little as 100 mL of fluid, while physical examination is estimated to be only 45%–84% sensitive and 59%–90% specific, with overall accuracy under 60% [16,17]. Pelvic view (transvaginal ultrasound) offers imaging of the most dependent areas of fluid accumulation and may be the region of fist fluid localization, which generally falls posteriorly-inferiorly or lateral to the urinary bladder [17]. In addition, ultrasound also provides additional information to make a diagnosis straightforward [17,18]. Adnexal solid mass lesion accompanied with ascites might be a diagnosis of ovarian fibroma/fibrothecoma. Adnexal cystic complex mass lesions accompanied with ascites might hint the possibility of malignant ovarian tumor. One study used the ascites-to-rectus abdominis muscle echogenicity ratio (ARAER) to evaluate the ascites adjacent to the rectus abdominis muscle and found that ARAERs for exudative ascites were significantly higher than those for transudative ascites ($p < 0.001$) and used 0.002 as the cutoff value for ARAER histogram to give the sensitivity and specificity rate of 87.5% and 79.2% (AUC = 0.843), respectively [18]. Recently, point-of-care ultrasonography (POCUS), defined as ultrasound used by a clinician at the bedside to aid in diagnosis and procedure guidance, which is aware by physicians, continues to spread throughout medical or surgical specialists and medical education, because POCUS has been shown to significantly improve diagnostic accuracy, increase procedure safety and success, and subsequently decrease hospital lengths of stay and reduce health care costs [17,19]. However, ultrasound not always allows to determine the nature of ascites based solely on its characteristics [20]. Therefore, paracentesis is a common procedure and also recommended in women presenting with new-onset ascites [11–13], if the diagnosis by ultrasound alone is inconclusive. Fig. 1 shows the ultrasound findings of various kinds of ascites in women; however, it is sometimes hard to distinguish malignant from nonmalignant ascites.

Blood test and tumor markers

General laboratory examinations, including complete blood counts, biochemical evaluation and tumor marker examinations

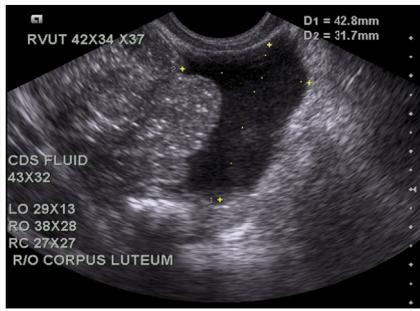
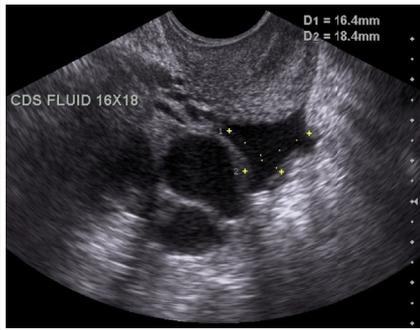
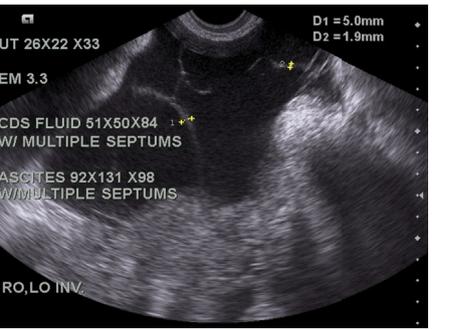
	<p>(a) Metastatic ovarian cancer from the colon: Ultrasound shows hypoechoic to anechoic, heterogeneity fluid; Operative finding was clear yellowish fluid and pathologic report confirmed malignant ascites (BL: urinary bladder)</p>		<p>(d) Endometriosis with reactive ascites: Ultrasound shows hypoechoic content, and operation shows yellowish and clear fluid without malignant cells.</p>
	<p>(b) Ectopic pregnancy with internal bleeding: Ultrasound showed hypoechoic, heterogeneity and laparoscopic surgery confirmed bloody ascites.</p>		<p>(e) Ovarian stromal hyperplasia with reactive ascites: Ultrasound shows hypoechoic and operation shows clear fluid without malignant cells.</p>
	<p>(c) Borderline ovarian tumor with reactive ascites: Ultrasound shows anechoic fluid at cul-de-sac; and operation shows yellowish and clear fluid without malignant cells.</p>		<p>(f) Primary peritoneal serous cancer with malignant ascites: Ultrasound shows a lot amount of fluid but hypoechoic characteristics and operation shows clear yellowish fluid with malignant cells.</p>
	<p>(g) TB peritonitis with ascites: Ultrasound shows little echoic content and hypo to heteroechoic characteristics and operation shows chylous like fluid with positive TB culture.</p>		

Fig. 1. Ultrasound features of various kinds of ascites in women. (a) Metastatic ovarian tumor from the colon cancer, (b) Ectopic pregnancy with internal bleeding, (c) Borderline ovarian tumor with reactive ascites, (d) endometriosis with reactive ascites, (e) ovarian stromal hyperplasia with reactive ascites, (f) primary peritoneal serous carcinoma with malignant ascites, and (g) Tuberculous peritonitis with reactive ascites.

can be done in the aids of the differential diagnosis of the women presenting with ascites. Some laboratory data are reported to help the diagnosis of certain diseases. For example, serum levels of creatinine, urea, electrolytes, coagulation factor, liver function test and complete blood counts with differential counts of white blood cells could make a diagnosis straightforward [21]. Some tumor markers are specific to special clinical condition. Beta-human chorionic gonadotropin (beta-hCG) can be used to exclude the possibility of pregnancy and specific to

beta-hCG secreting clinical condition, such as OHSS, ectopic pregnancy, and trophoblastic diseases [22–24]. Alpha-fetoprotein (AFP) is important for the help of the diagnosis of hepatoma or yolk-sac tumor of the ovary [25–27]. However, other tumor markers, such as carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA 19-9), carbohydrate antigen 125 (CA 125), et al., although they may be useful in monitoring the response after treatment, are not specific to certain type tumors [7,28–31].

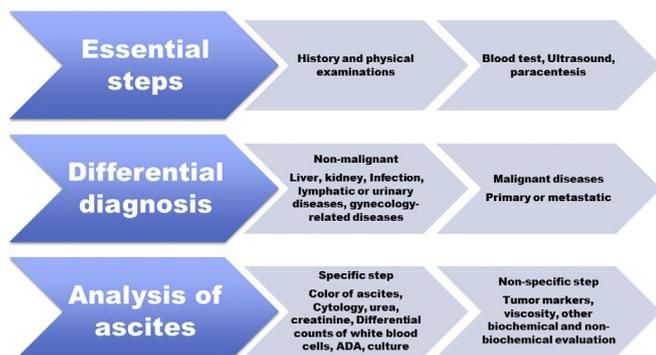


Fig. 2. A systemic and structural approach for women presenting with ascites.

Paracentesis

As shown above, paracentesis with the appropriate ascetic fluid analysis is probably the most rapid and cost-effective method of diagnosing the cause of ascites; however, it may be complicated by infection, bowel perforation, bleeding, leak of fluid through abdominal wall, injury to solid organs, such as kidney and resultant electrolyte imbalance [21]. Combination of ultrasound and paracentesis helps avoid solid organ or vascular injury and increases success of procedures by identifying the largest areas of fluid closest to the skin surface or vaginal-Douglas pouch, and especially overcoming the difficult attempts due to complicated loculated effusion, septations and paucity of fluid [17,32].

Ascites analysis

Visual inspection of the ascites is important, because ascites can show a milky (the presence of chylomicrons rich with triglycerides suspecting malignancy, trauma, liver cirrhosis, infection, pancreatitis, or other uncommon diseases, including congenital diseases), cloudy (pseudochylous ascites, suspecting peritonitis, pancreatitis, or a perforated bowel), bloody (suspecting malignancy or internal bleeding), straw colored or clear appearance (suspecting hepatorenal disease) [33]. Oey et al. established an excellent flow chart for patients with ascites [33]. Before arranging ascites analysis, the suspected diagnosis should be made. The differential diagnosis of ascites includes (1) portal hypertension (cirrhosis, congestion, thrombosis, congestive heart failure, constrictive pericarditis et al.), (2) malignancy (gynecological organ, carcinomatosis, mesothelioma, metastatic or primary hepatoma or ovarian cancer, et al.), (3) benign ovarian tumor (fibroma, stroma hyperplasia, luteoma, fibrothecoma, et al.), (4) infection (spontaneous or secondary bacterial infection, TB, actinomycosis, et al.), (5) miscellaneous (pancreatitis, hypoalbuminemia, nephrotic syndrome, lymphatic leakage, urinary leakage, hollow organ perforation, endometriosis, et al.) [33–57]. Cytology is important for suspicious malignancy, although some did not favor the paracentesis with patients with highly suspicious EOC [1,3,38–40]. TB peritonitis should include adenosine deaminase (ADA) activity, *Mycobacterium* culture, and polymerase chain reaction (PCR) *Mycobacterium* [2,33,35–37]. The cut-off value between 36 and 40 IU/L of the activity of ADA has a high sensitivity (100%) and specificity (97%) for diagnosing TB [33]. Urea and creatinine are needed for the diagnosis of urinary leakage [33,38–40]. Other evaluations, such as biochemical testing (SSAG, total protein, amylase, triglycerides, glucose, LDH etc.) and non-biochemical testing (polymorphonuclear leukocyte count, lymphocyte count, bacterial culture, PCR bacterial DNA etc.) should be made based on clinical suspicions.

Minimally invasive procedures

One of the most powerful tools to face inconclusive diagnosis of women during reproductive age presenting with ascites is laparoscopy, although controversy is always present. There are many examples in the literature to reveal the needs of this procedure [58–63]. The potential risk and complications, such as tumor implantation, hernia, and injury of this procedure have been extensively reviewed before [64–70].

Conclusion

It is always a challenge while facing women during reproductive age presenting with ascites, and the differential diagnosis of ascites is broad and includes a large number of diseases, regardless benign or malignant causes. A systemic and structure approach is very important in the routine clinical practice (Fig. 2).

Competing interests

The authors declare that they have no competing interests.

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