Decidualized ovarian endometriosis in pregnancy: a challenging diagnostic entity

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BACKGROUND: The hormonal milieu that characterizes pregnancy may determine profound modifications of ovarian endometriomas leading to lesions mimicking malignancy. In this study, we report on our experience and perform a review of the literature on this issue.

METHODS: Data from women evaluated at our referral center for prenatal diagnosis were reviewed in order to identify those who were detected with an ovarian endometrioma in pregnancy mimicking malignancy. A review of the literature on this issue (1990–2008) was also performed, using the PubMed database.

RESULTS: Three cases were identified at our center. The literature reports on a further 19 cases (11 studies). Sonographic and color Doppler examination consistently documented rapidly growing and abundantly vascularized intracystic excrescences. Conversely, the presence of septations or significant free fluid was never reported. The vast majority of cases underwent surgical removal. Interestingly, in our experience, in a woman who declined surgery and had spontaneous miscarriage at 10 weeks’ gestation, the sonographic examination performed 6 weeks after dilatation and curettage revealed an unremarkable typical endometrioma, thus suggesting that it is a transitory transformation.

CONCLUSIONS: Pregnancy-related modifications of an ovarian endometrioma leading to the rapid development of vascularized intracystic excrescences are an uncommon but possible event. An expectant management and serial monitoring should first be envisaged in these cases provided that other features of malignancy, such as septations or free fluid, are absent.

Key words: endometriosis / endometrioma / pregnancy / malignancy

Introduction

Endometriosis affects ~10% of the female population in their fertile years (Eskenazi and Warner, 1997). Ovarian endometriomas are a common form of the disease and may be present in up to 30–40% of women with endometriosis (Redwine, 1999; Vercellini et al., 2006). In contrast to peritoneal lesions, endometriomas can be detected with a high level of accuracy with transvaginal ultrasonography (Moore et al., 2002).

In this field, an emerging area of controversy is represented by ovarian endometriomas detected during pregnancy (Asch and Levine, 2007). On the one hand, an expectant management strategy appears reasonable considering that pain symptoms are generally improved during pregnancy and that surgery is more demanding and risky due to the presence of the enlarged and pregnant uterus. On the other hand, concerns have been recently raised regarding the accuracy of sonography in pregnancy. The hormonal milieu that characterizes pregnancy may determine profound modifications of the sonographic appearance of the endometrioma so that diagnosis may be more challenging (Asch and Levine, 2007). Of relevance here is the recent report of some cases of endometriomas detected during pregnancy mimicking malignancy (Miyakoshi et al., 1998; Tanaka et al., 2002; Fruscella et al., 2004; Guerriero et al., 2005; Sammour et al., 2005; Iwamoto et al., 2006; Asch and Levine, 2007; Machida et al., 2008; Poder et al., 2008; Takeuchi et al., 2008; Yoshida et al., 2008). In the present study, we will document three further cases of this condition and will review and discuss current evidence on this issue.

Materials and Methods

Patients evaluated at our tertiary care referral center for prenatal diagnosis between January 2006 and June 2008 were reviewed to identify...
Endometriomas in pregnancy

A review of the literature regarding ovarian endometriomas in pregnancy mimicking malignancy was also performed. To this aim, we identified all English language medical papers published in the period 1990–2008 by means of the PubMed electronic database using the following search terms: endometriosis, endometrioma, endometriotic, decidualized, deciduosis, cancer, malignancy, tumor and pregnancy. Cross references picked up during the research review were included. Data were collected using patients’ chart and by directly contacting the patient if necessary. Ecographic evaluations were performed by a single operator (M.B.) using an ESAOTE-HITACHI Logos (Genoa, Italy) sonographic instrument equipped with both 4–8 MHz (transvaginal) and 3–6 MHz (transabdominal) curvilinear color Doppler probes. All women were extensively informed about the possibility that the lesion may represent decidualized ovarian endometriomas but also that malignancy could not be definitely ruled out. On this basis, surgery was offered. However, given that a benign nature of the lesion was likely, a conservative surgical approach was initially decided and, if possible, the intervention had to be performed by laparoscopy. During surgery, frozen section was requested to reliably rule out malignancy, considering that the macroscopic appearance of the lesions (the presence of intracystic excrescences, in particular) did not allow us to reach firm conclusions. All patients in our unit routinely give an informed consent for the use of their data for research purposes. The possibility to receive subsequent phone calls to ascertain follow-up was also stated in this informed consent. The study was approved by the Local Institution Review Board.

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Results

Three pregnant patients who were diagnosed with an endometriotic ovarian cyst mimicking malignancy were identified at our center. The main clinical characteristics and sonographic findings of these cases are summarized in Tables I and II, respectively.

The cyst was bilateral in one case and monolateral in the other two. Ultrasound examination identified an intracystic solid part in all the cases. Color Doppler examinations consistently revealed abundant vascularization with resistance index between 0.37 and 0.55. The examination failed to identify septations or significant free fluid in all the cases. The first woman (Fig. 1) underwent laparoscopy at 14 weeks gestation. At surgery, the right ovary was fixed to the pelvic peritoneum by firm adhesions. The presence of intracystic solid excrescences was macroscopically confirmed. The cyst was removed using the classical stripping technique. Frozen section evaluation and subsequent definite histological examination showed ovarian endometriosis with extensive decidualization (Fig. 2). The subsequent course of pregnancy was uneventful, and the woman delivered vaginally a healthy infant at term. The second case who was referred later in pregnancy (24 weeks gestation) declined surgery and underwent close monitoring until delivery. She underwent cesarean section at 36 weeks gestation in order to allow for the concomitant treatment of the ovarian lesion. She delivered a healthy infant and had concomitant cyst excision. Both ovaries were involved, with endometriosis-related thick adhesions, and a conservative surgery was decided based on the benign appearance of the lesions. Again, frozen section evaluation and definite analyses showed ovarian endometriosis with extensive decidualization. The third case is probably the most intriguing (Fig. 3). Due to severe dysmenorrhea occurring during the last 2 months, she underwent an echographic evaluation revealing a normal ovarian endometrioma. One month later, she became pregnant and underwent serial echographies showing the rapid growth of richly vascularized intracystic excrescences. At 10 weeks gestation, she had a spontaneous miscarriage and underwent dilatation and curettage, but declined pelvic surgery. She was then scanned 6 weeks later and the cysts resumed the typical appearance of an ovarian endometrioma (Fig. 3). The sonographic appearance was unmodified at 6 months follow-up. Three months later, she became pregnant again and pregnancy is now on-going. At the most recent follow-up assessment, performed at 15 weeks gestation, the diameter of the cyst was lower (diameter 18 × 15 mm) and no intracystic excrescences could be visualized.

The literature review led us to identify 11 studies reporting on 19 cases of ovarian endometriomas in pregnancy mimicking malignancy (Miyakoshi et al., 1998; Tanaka et al., 2002; Fruscella et al., 2004; Guerriero et al., 2005; Sammour et al., 2005; Iwamoto et al., 2006; Asch and Levine, 2007; Machida et al., 2008; Poder et al., 2008; Takeuchi et al., 2008; Yoshida et al., 2008). The first case was reported in 1998, whereas the remainder was reported since 2002. The median (range) age of the women was 28 (24–41) years. A history of endometriosis was reported in four cases. A diagnosis before pregnancy was never reported. In two cases, an unremarkable endometrioma was detected at the beginning of pregnancy (12 and 6 weeks gestation), which subsequently developed sonographic malignant characteristics (Poder et al., 2008; Yoshida et al., 2008). The median (range) gestational age at the time of detection of the lesion mimicking malignancy was 14 (7–28) weeks gestation. The lesion was bilateral in only one case. A contralateral endometrioma with typical sonographic appearance was concomitantly identified in two cases. The main sonographic findings of these cysts are summarized in Table II. A rapid growth of the lesions was documented in nine

| Table I Main characteristics of the three identified cases with an ovarian endometrioma in pregnancy, mimicking malignancy |
|---|---|---|
| Characteristics | Patient 1 | Patient 2 | Patient 3 |
| Age (years) | 32 | 36 | 39 |
| Previous deliveries | No | No | 1 |
| Previous surgery for endometriosis | No | No | No |
| Detection of the endometrioma prior to pregnancy | No | No | Yes |
| Gestational age at referral (weeks gestation) | 14 | 24 | 8 |
| Pain symptoms at referral | Absent | Present | Absent |
| CA-125 (IU/ml) | 30 | 159 | 85 |
| Surgical intervention during pregnancy | Yes | No | No |

CA: cancer antigen.
Table II  Summary of the sonographic findings of the reported cases

<table>
<thead>
<tr>
<th>Reference [number of cases]</th>
<th>Laterality</th>
<th>Dimension (mm)</th>
<th>Intracystic excrescences</th>
<th>Solid part (mm)</th>
<th>Abundance of blood flow</th>
<th>Resistance index</th>
<th>Septations</th>
<th>Free fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruscella et al. (2004) [1]</td>
<td>Monolateral</td>
<td>55 (max diam)</td>
<td>Present</td>
<td>8 × 10 and 5 × 5</td>
<td>Present</td>
<td>n.r.</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Sammour et al. (2005) [2]</td>
<td>Monolateral</td>
<td>40 × 50 × 63</td>
<td>Present</td>
<td>23 × 18 × 14</td>
<td>Present</td>
<td>0.51</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Guerriero et al. (2005) [1]</td>
<td>Monolateral</td>
<td>40 × 48</td>
<td>Present</td>
<td>15 × 20 × 25</td>
<td>Present</td>
<td>0.46</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Iwamoto et al. (2006) [1]</td>
<td>Monolateral</td>
<td>75 (max diam)</td>
<td>Present</td>
<td>n.r.</td>
<td>Present</td>
<td>0.50</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Monolateral</td>
<td>160</td>
<td>Present</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>50/60</td>
<td>Present</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>Bilocular</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Monolateral</td>
<td>74 × 48</td>
<td>Present</td>
<td>n.r.</td>
<td>Absent</td>
<td>n.r.</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Present study [3]</td>
<td>Monolateral</td>
<td>66 × 44</td>
<td>Present</td>
<td>20 × 14</td>
<td>Present</td>
<td>0.37</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>85 × 63/50 × 30</td>
<td>Present</td>
<td>27 × 14/7 × 7</td>
<td>Present</td>
<td>0.41</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Monolateral</td>
<td>38 × 14</td>
<td>Present</td>
<td>19 × 12</td>
<td>Present</td>
<td>0.51</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Data refer to the first detection of the lesion. n.r., not reported. The study of Takesuchi et al. (2008) was not included in the table since the authors provided only data from magnetic resonance (MR) imaging.
cases. Ten women additionally underwent magnetic resonance (MR) imaging, which confirmed the presence of solid-tissue nodules inside the tumor. In addition, Takeuchi et al. (2008) reported five cases of MR imaging without including sonographic findings. Serum level of cancer antigen (CA)-125 was reported in nine cases, and it was above 35 IU/ml in seven of them (median 76, range 28–220 IU/ml). Fifteen women (79%) underwent surgery: in two cases, the time of surgery was not specified; in 10 cases, the intervention took place in the second trimester; in one case, it was performed at 28 weeks gestation; and in two cases, surgery was delayed to the time of Caesarean section. Surgery was reported to be uneventful on pregnancy outcome in 14 women (93%). In one case, premature rupture of the membranes occurred at the day of the intervention, and pregnancy was interrupted 2 weeks later (Machida et al., 2008). In the four cases managed expectantly, women were followed-up for 1 year or more, and the lesions gradually shrank and/or disappeared after delivery (Takeuchi et al., 2008).

Figure 1 Case 1: sonographic findings of ovarian endometrioma in pregnancy mimicking malignancy. The upper panel shows the irregular solid part of the endometrioma protruding within the lumen of the cyst. Above this excrescence, an echogenic debris which was mobile under probe manipulation can also be noted. As illustrated in the lower panel, color Doppler analysis detected multiple vascularization signals index within the solid part. The resistance index was 0.37.

Figure 2 Case 1: histological findings of the intracystic solid part. The low-power histological slide (hematoxylin and eosin stain) clearly shows decidualized endometriotic tissue.

Figure 3 Case 3: reversibility of pregnancy-related modifications. The upper panel illustrates the sonographic appearance of the endometrioma at 10 weeks gestation when miscarriage was diagnosed. Intracystic excrescences can easily be recognized. In the lower panel, the appearance of the lesion 6 weeks after dilatation and curettage is shown. The endometrioma has resumed its typical sonographic appearance.
Discussion

Sonography is the imaging method of choice for the diagnosis of ovarian endometriomas. These cysts typically present as a round-shaped cystic mass with a minimum diameter of 10 mm with thick walls, regular margins, homogeneous low echogenic fluid content with scattered internal echoes and without papillary proliferations (Eskenazi et al., 2001). This sonographic pattern has been documented in up to 95% of cases (Patel et al., 1999). However, many other uncommon appearances have also been described, including anechoic cyst, a solid-appearing mass, solid element in a cyst with low-level internal echoes and punctuate echogenic foci in the wall of the cyst. The most common misdiagnoses are hemorrhagic cysts and dermoidos (Moore et al., 2002; Asch and Levine, 2007). However, the accuracy of transvaginal sonography in the non-pregnant state is high. Sensitivity and specificity have been reported to be 84–100 and 90–100%, respectively (Mais et al., 1993; Kurjak and Kupesic, 1994; Alcázar et al., 1997; Eskenazi and Warner, 1997).

In the present study, we confirmed that pregnancy may cause radical modifications of the endometrioma, which may determine relevant diagnostic difficulties. The presence of rapidly growing and abundantly vascularized intraluminal vegetations poses a challenging diagnostic dilemma because this is a classical feature of malignancy (Alcázar et al., 2003). Previous reports pointed out that color Doppler sonography is not effective in distinguishing a benign endometrioma from malignancy during pregnancy since low resistance flow may be present in both conditions (Miyakoshi et al., 1998; Tanaka et al., 2002; Fruscella et al., 2004; Guerriero et al., 2005; Sammour et al., 2005; Iwamoto et al., 2006; Asch and Levine, 2007; Machida et al., 2008; Poder et al., 2008; Yoshida et al., 2008). Our data are totally in line with these findings. The available literature also showed that MR does not add significant information in this context (Miyakoshi et al., 1998; Tanaka et al., 2002; Fruscella et al., 2004; Iwamoto et al., 2006). Moreover, CA-125 levels are not diagnostically useful during pregnancy, since they are physiologically elevated (Aslam et al., 2000). On the other hand, it is noteworthy that other sonographic findings suggesting malignancy, such as septations or free fluid, are consistently missing (Table II).

The rapid development of intracystic vegetations within an endometrioma is intriguing. It is believed to be consequent to decidual modification of the endometriotic implants, also named deciduosis. In this regard, it is noteworthy that endometrial decidualization is a well-known phenomenon of pregnancy. It is the process of conversion of the normal endometrium during pregnancy into a specialized uterine lining adequate for optimal accommodation of the gestation (Sammour et al., 2005). Decidualized tissue in ectopic sites can grow during pregnancy to acquire a gross appearance that macroscopically mimics a malignant tumor. Even if deciduosis is usually an asymptomatic phenomenon and goes undetected throughout pregnancy, some upsetting complications have been repeatedly reported (Aziz et al., 2004; O’Leary et al., 2006; Chiodo et al., 2008). They were all related to the clinical appearance of a massive intraperitoneal hemorrhage due to the rupture of pelvic vessels by enlarging deep peritoneal implants. Data regarding ovarian deciduosis are more reassuring. We failed to identify studies reporting on frightening clinical complications associated with its presence. Erosion into the pelvic sidewall vessels originating from ovarian deciduosis has not been described. Most likely, this is due to the specific localization and growth within the ovary. Finally, it is wise to note that in the woman of our series who declined surgery and had spontaneous miscarriage at 10 weeks gestation, the subsequent sonographic examination revealed an unremarkable typical endometrioma, thus suggesting that ovarian deciduosis is a transitory transformation. Intriguingly, in this case, the dimension of the cyst had subsequently shrunk; this phenomenon was also observed in all four of the previously reported cases managed expectantly (Takeuchi et al., 2008).

It is of relevance that the radical and rapid modifications documented in ovarian endometriomas during pregnancy in the present study and in the 19 cases previously described is a condition developing only in certain women and not in others. Interestingly, in their case reports, both Fruscella et al. (2004) and Guerriero et al. (2005) concomitantly documented an endometrioma in the contralateral ovary whose sonographic appearance was typical and unremarkable and did not change over time. In a case series of 15 pregnant women with endometriomas, Bromley and Benacerraf (1997) did not report any case with atypical sonographic appearance. The precise frequency of ovarian endometrioma modifications leading to a lesion mimicking malignancy is unknown. Based on the available literature, it seems to be a rare event. Prior to the present study, only 19 cases were reported, thus indirectly suggesting that the phenomenon is rare. However, it is noteworthy that ovarian scanning is not a main focus of attention during the first trimester of pregnancy, and the gonads are seldom visualized in the subsequent two trimesters. Moreover, it cannot be excluded that in most cases modifications are more subtle than those reported in the present and previous studies on this topic, thus explaining a low rate of detection. Overall, we believe that the magnitude of this problem may be more significant than indirectly suggested by the availability of just a few case reports.

Factors determining the rapid growth of intracystic excrescences in certain cases but not in others are also unknown. The observation that none of the women were aware of carrying an endometrioma, despite in some cases being diagnosed with endometriosis in the past, suggests that this transformation may occur only in endometriomas that have formed recently. A further possible explanation is related to the peculiar histological characteristics of the endometriomas. It is well known that most of these cysts lack an epithelial lining and that some endometrium is usually observed in correspondence of the stigma of inversion (Brosens et al., 1994). Accordingly, it may well be that modifications are observed at ultrasonography only in those cysts in which a discrete amount of endometrium is present, whereas nothing happens if there is no, or very little, mucosa.

Difficulty in estimating the frequency of this phenomenon has direct clinical consequences. If rare, the indication to surgery would remain mandatory since misdiagnosis of an early ovarian cancer may have remarkable clinical consequences. Conversely, the demonstration that these modifications occur commonly would support the possibility of an expectant management. Unfortunately, we are currently unable to definitely disentangle this issue. In balancing pros and cons of the intervention, it is noteworthy that pregnancy outcome in women who were operated on for benign ovarian neoplasms during pregnancy has been generally reported to be uneventful (Bromley...
and Benacerraf, 1997; Whitecar et al., 1999; Usui et al., 2000). However, surgery should not be postponed in the second part of pregnancy since the risk of adverse events has been reported to increase after 23 weeks gestation and the greatly enlarged uterus may pose significant technical problems to surgeons (Whitecar et al., 1999; Usui et al., 2000). Of note, in our review, we documented surgery-related adverse pregnancy outcome in 1 out of 16 operated cases, suggesting that the intervention may not be systematically uneventful for the course of pregnancy. A final concern is the prognostic impact of a delayed diagnosis and treatment of ovarian cancer. Early diagnosis and appropriate treatment are indeed considered to offer the best prognosis (Ghaemmaghami and Hasanzadeh, 2006).

In conclusion, pregnancy-related modifications of an ovarian endometrioma leading to the rapid development of vascularized intracytic excrescences are an uncommon but possible event. However, drawing definite guidelines for the management of these cases is currently challenging. Further evidence is warranted. Nevertheless, we believe that some suggestions can be stated. First of all, physicians should be aware of this possibility and a reassuring attitude has to be assumed with the patient. Based on the findings emerging from the present study, we also believe that an expectant management and serial monitoring should now first be envisaged in these women provided that other features of malignancy, such as septations or free fluid, are absent. Furthermore, if surgery is decided, a conservative intervention and, possibly, a minimally invasive approach should be adopted considering that the nature of the lesion is most likely benign. In these cases, a frozen section may, however, be of value since the diagnostic value of direct visualization of intracytic excrescences does not add significantly more information than their sonographic identification. Finally, given the difficulties in the management of these cases, referral to tertiary care centers with vast experience in gynecological ultrasonography, gynecological oncology and, possibly, endometriosis seems to us mandatory.

References


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