Adenoma malignum of the uterine cervix: ultrasonographic findings in 11 patients

S. B. PARK*,†, M. H. MOON*, S. R. HONG†, M. S. LEE*, H. C. CHO*, B. H. HAN* and K. T. LIM‡

*Department of Radiology, Cheil General Hospital and Women’s Healthcare Center, Kwandong University College of Medicine, Jung-gu, Seoul, Korea; †Departments of Radiology, Ulsan University Hospital, University of Ulsan, Dong-gu, Ulsan, Korea; ‡Department of Pathology, Cheil General Hospital and Women’s Healthcare Center, Kwandong University College of Medicine, Jung-gu, Seoul, Korea; §Department of Obstetrics and Gynecology, Cheil General Hospital and Women’s Healthcare Center, Kwandong University College of Medicine, Jung-gu, Seoul, Korea

ABSTRACT

Objective To evaluate the ultrasonographic features of adenoma malignum, a minimal deviation adenocarcinoma of the uterine cervix.

Methods Eighteen consecutive patients with pathologically confirmed adenoma malignum were enrolled in this study at two institutions. Preoperative ultrason examination was performed and the results were available in 11 patients. We analyzed retrospectively the gray-scale ultrasound findings for the following morphologic characteristics: cervical enlargement, as well as size, location and ultrasonographic characteristics of lesions. In five patients we also evaluated Doppler features with regard to intrallesional vascularity.

Results The cervix was enlarged in 73% (8/11) of cases. The mean greatest tumor diameter was 4.2 (range, 2.5–6.8) cm. In five (45%) cases, the cervix was completely infiltrated by the tumor. At grayscale ultrasound examination, three (27%) tumors were multilocular lesions, four (36%) were multilocular lesions with solid components and four (36%) were solid lesions. In the multilocular lesions with or without a solid component, locules tended to be 1 cm or less in size. At color or power Doppler, most (75%, 3/4) solid lesions manifested heterogeneous echogenicity. The five (100%) tumors examined with Doppler manifested moderate or abundant color content on color or power Doppler.

Conclusions Adenoma malignum can appear sonographically as solid, multilocular and multilocular solid cervical lesions. Awareness of its clinical and ultrasonographic features might improve diagnosis before surgery.

KEYWORDS: adenoma malignum; minimal deviation adenocarcinoma; ultrasound

INTRODUCTION

Adenoma malignum, also known as minimal deviation adenocarcinoma, is a subtype of mucinous adenocarcinoma of the cervix. Its prevalence is very low: about 1.3% of cervical adenocarcinomas. Adenoma malignum is often associated with Peutz–Jeghers syndrome and mucinous tumors of the ovary. The most common initial symptom is watery vaginal discharge. Several studies have reported a poor prognosis, whereas some found a relatively favorable prognosis similar to that of other well-differentiated cervical adenocarcinomas.

At magnetic resonance imaging (MRI), adenoma malignum appears as multilocular lesions with solid components that extend from the endocervical glands to the deep cervical stroma. The characteristic MRI findings of adenoma malignum may be useful in early diagnosis. However, in recent years, there have been reports describing benign glandular lesions being confused histologically and radiologically with adenoma malignum.

To the best of our knowledge, reports of ultrasound examination of adenoma malignum are very few. Here we report the ultrasonographic findings of adenoma malignum of the cervix in 11 patients.

PATIENTS AND METHODS

Our study was approved by the institutional review board of Cheil General Hospital. As this study was a clinical, retrospective study, informed consent was not required by the board.

Correspondence to: Dr S. B. Park, Department of Radiology, Cheil General Hospital and Women’s Healthcare Center, Kwandong University College of Medicine, 1-19, Mookjeong-dong, Jung-gu, Seoul, 100-380, Korea (e-mail: pk sungbin@paran.com)

Accepted: 3 May 2011

Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.
Patient population

A computerized search was conducted to identify cases of adenoma malignum surgically confirmed between January 1996 and August 2009 at two institutions. This revealed 18 such cases: 15 patients from Cheil General Hospital and three from Ulsan University Hospital. Each patient’s medical records, including clinical and pathologic data, were reviewed retrospectively. Of the 18 adenoma malignum patients, seven were excluded from the study because results of preoperative ultrasound examinations were not available. Thus, 11 adenoma malignum patients (nine from Cheil General Hospital and two from Ulsan University Hospital) with available results of preoperative ultrasound examinations were included in this study. The mean patient age was 40.7 (range, 30–58) years.

Ultrasonographic examination

All ultrasound examinations were performed within 2 weeks before surgery, using an HDI 3000, HDI 5000 or IU22 (Philips Medical Systems, Bothell, WA, USA) machine. Transvaginal ultrasound was performed with an end-viewing endovaginal 5–9-MHz transducer and transabdominal ultrasound with a convex or sector 5–7-MHz transducer. Six patients underwent transvaginal ultrasound only, two patients transabdominal ultrasound only and three patients underwent both transvaginal and transabdominal ultrasound examination. Color or power Doppler was used in five patients. Machine settings were adjusted as follows: spatial peak temporal average intensity < 90 mW/cm²; wall filter, 100 Hz; pulse repetition frequency, 2–10 kHz.

Analysis

We reviewed the original 11 ultrasonographic reports and defined detection of adenoma malignum as any suspicion of cervical pathology (benign or malignant) by the original ultrasound examiner. Using the pathological reports as a reference, the sensitivity (detection rate) was determined.

Two radiologists (S.B.P. and M.H.M.), who were aware of the final diagnosis of adenoma malignum, evaluated the sono- graphic features of the 11 patients in a consensus fashion. Gray scale images were evaluated regarding: cervical enlargement; lesion location; size (largest diameter) and appearance of lesion, including presence or absence of solid components; tumor invasion of the vagina, parametrium/parametria and adjacent organs; metastases; ascites; and associated ovarian lesions.

Cervical enlargement was assessed semiquantitatively, being defined as a decreased fundus-to-cervix ratio (normal ratio, 2:3 in premenopausal women). We classified the location of the lesion as: intracervical without disruption of the exocervix (a rim of normal stroma around the lesion and absence of a normal symmetric endocervical canal); exocervical protrusion into the vagina; or completely infiltrated cervix (exocervix and stroma). We classified the appearance of the lesion as: multilocular (no solid tissue seen in the mass); multilocular with solid component (solid tissue including wall thickening within the cervical mass < 80%); or solid lesion (solid tissue within the cervical mass ≥ 80%). We evaluated the following lesion characteristics: margin of the whole lesion (smooth or irregular); average maximum diameter of locules ≤ 1 cm, > 1 cm); mean number of locules <= 10, 11–20); locule fluid homogeneity (homogeneously hyperechoic, isoechoic, hypoechoic or anechoic, or heterogeneous); and echogenicity of the solid components (homogeneously hyperechoic, isoechoic or hypoechoic, or heterogeneous).

We evaluated Doppler features in five patients with regard to intrallesional vascularity (subjective assessment of presence or absence of intralvesional vessels and semiquantitative assessment of the amount of vascularization: none; minimal; moderate; or high).

Accuracy of the original ultrasound examiner regarding whether the tumor was local or had spread was analyzed on the basis of retrospective analysis by S.B.P. and M.H.M. of the ultrasound images.

We analyzed retrospectively the clinical features in the 11 patients, focusing on typical symptoms and signs, such as watery discharge and signs of Peutz–Jeghers syndrome.

Seven of the patients underwent radical hysterectomy and specimens evaluated using the TNM staging system, and four patients underwent simple hysterectomy, specimens being evaluated using the FIGO staging system. We compared the ultrasonographic features with the surgical and pathologic findings as described in the medical records with regard to tumor morphology, invasion and metastases.

RESULTS

Ultrasonographic findings

In nine of the 11 patients, the original ultrasound examiner suggested or suspected cervical pathology (benign or malignant). Thus, the detection rate of cervical pathology on ultrasound was 82%. In the remaining two patients, cervical abnormalities were suspected only on the retrospective analysis of the ultrasound images.

Ultrasonographic features are summarized in Table 1. The cervix was enlarged in 73% (8/11) of cases. The mean of the largest tumor diameter was 4.2 (range, 2.5–6.8) cm. The largest tumor diameter was > 4 cm in six (55%) patients. Five (45%) of the 11 tumors grew intracervically without disruption of the exocervix, one grew exocervically and protruded into the vagina, and five (45%) infiltrated the cervix completely.

Three (27%) of the 11 tumors were multilocular lesions (Figure 1), four (36%) were multilocal lesions with solid components (Figure 2) and four were solid lesions (Figure 3). Eight (73%) of the 11 tumors had smooth margins and three had irregular margins. In the multilocal lesions with or without solid parts, locules tended to be 1 cm or less in average diameter (86%,
Table 1 Ultrasonographic features in 11 confirmed cases of adenoma malignum

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Lesion detected</th>
<th>Cervix enlarged</th>
<th>Lesion size (cm)</th>
<th>Lesion location</th>
<th>Lesion appearance</th>
<th>Invasion/ Metastasis</th>
<th>Ovarian lesion</th>
<th>Intraliteral vascularization on Doppler</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>+</td>
<td>+</td>
<td>5.4 cm</td>
<td>Infiltrative</td>
<td>Multi (≤ 1 cm, 11–20); S, Hetero</td>
<td>Invasion</td>
<td>Metastasis</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>+</td>
<td>+</td>
<td>5.0 cm</td>
<td>Infiltrative</td>
<td>Solid, I, Hetero</td>
<td>Invasion</td>
<td>Metastasis</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>+</td>
<td>+</td>
<td>3.3 cm</td>
<td>Infiltrative</td>
<td>Solid, I, Hetero</td>
<td>Invasion</td>
<td>Metastasis</td>
<td>NE</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>5.0 cm</td>
<td>Infiltrative</td>
<td>Multi-solid (≤ 1 cm, 11–20); I, Hetero</td>
<td>Invasion</td>
<td>Metastasis</td>
<td>NE</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>3.7 cm</td>
<td>Infiltrative</td>
<td>Solid, S, Hetero</td>
<td>Invasion</td>
<td>Metastasis</td>
<td>High</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>–</td>
<td>–</td>
<td>2.5 cm</td>
<td>Intracervical</td>
<td>Solid, S, Iso</td>
<td>Benign tumor</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>–</td>
<td>–</td>
<td>2.5 cm</td>
<td>Intracervical</td>
<td>Multi (≤ 1 cm, 11–20); S, Hypo</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>+</td>
<td>–</td>
<td>2.7 cm</td>
<td>Intracervical</td>
<td>Multi-solid (≤ 1 cm, ≤ 10); S, Hypo</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>+</td>
<td>+</td>
<td>4.7 cm</td>
<td>Intracervical</td>
<td>Multi-solid (≤ 1 cm, 11–20); S, Hypo</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>+</td>
<td>+</td>
<td>6.8 cm</td>
<td>Exocervical</td>
<td>Multi (&gt; 1 cm, ≤ 10); S, Hetero</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>+</td>
<td>+</td>
<td>4.6 cm</td>
<td>Intracervical</td>
<td>Multi-solid (≤ 1 cm, ≤ 10); S, Hypo</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Lesion detection defined as detection of any cervical pathology on ultrasound according to original ultrasonographic report. †Cervical enlargement assessed semiquantitatively, defined as decreased fundus-to-cervix ratio (normal ratio, 2 : 3 in premenopausal women). ‡Largest diameter. §Lesion location defined as infiltrative when cervix was completely infiltrated (exocervix and stroma), intracervical when there was no exocervical disruption and exocervical when there was exocervical protrusion into the vagina. ¶Appearance classified as multilocular (Multi), multilocular-solid (Multi-solid) or solid (in case of locules, average locule diameter ≤ 1 cm or > 1 cm; mean number of locules ≤ 10 or 11–20); margin smooth (S) or irregular (I); echogenicity of fluid or solid components heterogenous (Hetero), homogenous hypoechoic (Hypo) or homogenous Isoechoic (Iso). +, Yes; –, No; NE, not evaluated.

Figure 1 Gray-scale transvaginal ultrasound image showing a multilocular lesion (arrows) within an enlarged uterine cervix with post-acoustic enhancement, in a 48-year-old woman with adenoma malignum in the uterine cervix (Case 1). The dominant locule is also evident.

Figure 2 Gray-scale transvaginal ultrasound image showing a multilocular lesion with solid component (arrows) within an enlarged uterine cervix with post-acoustic enhancement, in a 30-year-old woman with adenoma malignum (Case 9).

Considering pathology as the reference, ultrasound examination detected three (75%) of the four cases with vaginal invasion and both cases with ovarian or peritoneal metastases, but it did not detect the single case with parametrial infiltration. The single case of mucinous ovarian cystadenoma was diagnosed with ultrasound.
extended from the surface to the deeper portion of the cervix. Pathological analysis demonstrated conjugation of small cystic spaces lined predominantly by mucin-containing columnar epithelial cells, with cystic spaces filled with mucin. The interstitial space was composed of normal cervical stroma, which was often edematous. Lesions judged to be non-cystic on ultrasound appeared grossly as solid lesions. Histologically, very few dilated glands were recognized in the cases with non-cystic appearance.

**DISCUSSION**

The presence on imaging studies of a multilocular lesion that invades the deep cervical stroma and contains solid components may suggest malignancy. There appears to be a continuous spectrum from hyperplasia to high-grade malignancy, based on the percentage of solid components within a lesion^{18,19}. In contrast, benign lesions do not generally invade the cervical stroma deeply, are of small size with well-defined margins and do not contain solid components^{1,2,19}.

However, in recent years, there have been many reports describing benign glandular lesions, including uterine cervixes, tunnel cluster, deep endocervical glands, deep nabothian cysts, endocervical hyperplasia, metaplasias, endometriosis and infectious and reactive atypias, that were confused histologically and radiologically with malignant adenoma malignum. Even on MRI, it can be extremely difficult to differentiate between malignant adenoma malignum and benign glandular lesions^{11–13}. Ultrasound imaging with Doppler may be a more efficient and accurate method for evaluation of a multilocular lesion in the cervix. In our study, ultrasound suggested that the cervix was completely infiltrated by tumor in five (45%) cases, a feature that can help to discriminate benign from malignant lesions in the cervix. Doppler imaging detected moderate or abundant vascularization in all five (100%) of the tumors examined, including one multilocular lesion without solid components. Such lesions may be difficult to discriminate from benign glandular lesions on Doppler examination. In general, benign multilocular lesions, such as multiple nabothian cysts, show no intraluminal vascularity on Doppler examination^{19}. Ultrasound imaging may be used to evaluate local (such as adjacent organ invasion) or distant spread as well as the primary tumors.

In our study, ultrasound detected three of four (75%) cases with vaginal invasion and both (100%) cases with ovarian or peritoneal metastases. We observed that adenoma malignum appeared as solid or multilocular lesions. In cases where cystic lesions are microscopic or few in number, lesions may appear solid and should be differentiated from leiomyoma. In our study, the echogenicity of the solid lesions tended to be heterogeneous (75%, 3/4). This is in contrast to leiomyomas, which are usually homogeneously hypoechoic. On Doppler examination, adenoma malignum showed intraluminal vascularity (Figure 3). However, the

---

**Clinical and pathologic features**

Clinical and pathologic features are summarized in Table 2. Seven of the 11 patients had classical symptoms or signs: five (45%) had watery discharge, three (27%) had Peutz–Jeghers syndrome and one had both. The remaining four patients had non-specific symptoms.

On pathologic examination, the mean of the largest tumor diameter was 4.5 (range, 2.5–6.5) cm. There were seven patients with Stage I disease, one was Stage II, one Stage III and two Stage IV. Four patients had vaginal tumor invasion, and one of whom also had bilateral parametrial tumor invasion. Two patients had both ovarian and peritoneal metastases. Tumors judged to be multilocular tumors on ultrasound appeared grossly as multicystic lesions (multilocular and multicystic with solid component). Microscopic evaluation revealed that these lesions were composed mainly of well-differentiated endocervical glands that

---

Figure 3 Gray-scale transabdominal ultrasound (a) and power Doppler (b) imaging in a 37-year-old woman with adenoma malignum in the uterine cervix (Case 2). (a) Gray-scale ultrasound shows a solid lesion (arrows) within an enlarged uterine cervix. The mass has infiltrated the whole cervix and invaded the vagina. Both the original ultrasound examiner and the assessors performing the retrospective analysis (not shown) noted ascites and complex cystic lesions, probably metastases. (b) Power Doppler imaging showed intralesional moderate vascularity.

---

Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.
Sonography of adenoma malignum

Table 2 Clinical and pathologic features in 11 confirmed cases of adenoma malignum

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Indication</th>
<th>Surgery (hysterectomy)</th>
<th>Lesion size* (cm)</th>
<th>FIGO stage17</th>
<th>TMN stage18</th>
<th>Invasion</th>
<th>Metastases</th>
<th>Ovarian lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48</td>
<td>Watery discharge</td>
<td>Radical</td>
<td>5.5 cm</td>
<td>I</td>
<td>IB2</td>
<td>T1b2N0M0</td>
<td>Both ovaries, omentum</td>
<td>Metastases</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>Watery discharge, P–J syndrome</td>
<td>Radical</td>
<td>5.0 cm</td>
<td>IV</td>
<td>IVB</td>
<td>T2a2N0M1</td>
<td>Vagina</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>Watery discharge</td>
<td>Radical</td>
<td>3.0 cm</td>
<td>II</td>
<td>IIA1</td>
<td>T2a1N0M0</td>
<td>Vagina</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>Watery discharge</td>
<td>Radical</td>
<td>5.0 cm</td>
<td>III</td>
<td>IIIA</td>
<td>T3aN0M0</td>
<td>Vagina</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>P–J syndrome</td>
<td>Radical</td>
<td>3.0 cm</td>
<td>IV</td>
<td>IVB</td>
<td>T2bN1M1</td>
<td>Vagina, parametria</td>
<td>Both ovaries, peritoneum</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>Abnormal Pap smear</td>
<td>Simple</td>
<td>2.5 cm</td>
<td>I</td>
<td>IB1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>Vaginal bleeding</td>
<td>Simple</td>
<td>2.5 cm</td>
<td>I</td>
<td>IB1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>48</td>
<td>Abdominal pain</td>
<td>Radical</td>
<td>2.5 cm</td>
<td>I</td>
<td>IB1</td>
<td>T1b1N0M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>30</td>
<td>P–J syndrome</td>
<td>Simple</td>
<td>4.5 cm</td>
<td>I</td>
<td>IB2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>Abdominal pain</td>
<td>Simple</td>
<td>6.5 cm</td>
<td>I</td>
<td>IB2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>Watery discharge</td>
<td>Radical</td>
<td>4.5 cm</td>
<td>I</td>
<td>IB2</td>
<td>T1b2N0M0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Largest diameter. •Staging (I, II, III or IV) came from FIGO and TMN stages. P–J syndrome, Peutz–Jeghers syndrome.

ACKNOWLEDGMENTS

We would like to thank eWorldEditing.com, for their editorial assistance in preparing the manuscript.

REFERENCES


QUERIES TO BE ANSWERED BY AUTHOR & EDITOR

IMPORTANT NOTE: Please list all query corrections in an e-mail and send to the production contact as detailed in the covering e-mail, or mark all corrections directly on the proofs and send the scanned copy via e-mail. Please do not send corrections by annotated PDF file and do NOT mark your corrections on this query sheet.

Queries to Author:

AQ1 Is the new short title (top of page 3) ok: “Sonography of adenoma malignum”?

AQ2 Please check that all affiliations are correct and complete

AQ3 As a result of your reply later, I’ve changed ‘cyst’ to ‘locule’ throughout – is this correct in all places, for example here – “locular fluid”?

AQ4 Table 1 footnote – note definition for cervical enlargement may need rewording to match text.

AQ5 Table 2 footnote – the following has been added: “†Staging (I, II, III or IV) came from FIGO and TMN stages.” – can this be clarified further – how exactly?

AQ6 Sorry – your reply was slightly ambiguous. I’ve changed the last two commas to semi-colons – is this appropriate?

AQ7 ‘Cervical enlargement was assessed semiquantitatively, being defined as a decreased fundus-to-cervix ratio (normal ratio, 2 : 3 in premenopausal women).’ Note my slight rewording to your added sentence. However, please could you clarify – what exactly is meant by ‘decreased’ relative to the normal – by how much for it to be classified as ‘decreased’? Also, presumably this is a ratio of their diameters? Note your response here needs to be applied to Table 1 footnote also.

AQ8 “average maximum diameter of locules” - How was the average calculated – was this an average of a certain number of repeated measurements? Also, how was mean number of cysts in each case evaluated? In both cases, is ‘average/mean’ correct?

AQ9 ‘11–20’ - what if there were 21 or more?

AQ10 The table has FIGO staging for all 11 cases – please clarify. Also, please can we mention here how your final stage (I, II, III or IV) was assigned?

AQ11 Is ‘cystic’ ok here or change to ‘locular’?

AQ12 I left ‘multicystic’ here rather than saying “Tumors judged to be multilocular tumors on ultrasound appeared grossly as multicystic lesions (multilocular and multilocular with solid component).” – is this ok? Or is it somewhat repetitive?

AQ13 ‘cystic’ appears twice in this sentence – should these also be changed to ‘locular’?

AQ14 ‘non-cystic’ appears twice here, in this and in the next sentence – should these also be changed to ‘non-locular’?

AQ15 Can I just check I understood your reply – I’ve added here ‘on Doppler examination’ – is this OK?

AQ16 As above, should ‘cysts’ here be ‘locules’?

AQ17 Should ‘cyst’ here be ‘locule’?
After receipt of your corrections your article will be published initially within the online version of the journal.

**PLEASE AIM TO RETURN YOUR CORRECTIONS WITHIN 48 HOURS OF RECEIPT OF YOUR PROOF, THIS WILL ENSURE THAT THERE ARE NO UNNECESSARY DELAYS IN THE PUBLICATION OF YOUR ARTICLE**

- **READ PROOFS CAREFULLY**
  - Once published online or in print it is not possible to make any further corrections to your article
    - This will be your only chance to correct your proof
    - Please note that the volume and page numbers shown on the proofs are for position only

- **ANSWER ALL QUERIES ON PROOFS** (Queries are attached as the last page of your proof.)
  - List all corrections and send back via e-mail to the production contact as detailed in the covering e-mail, or mark all corrections directly on the proofs and send the scanned copy via e-mail. Please do not send corrections by fax or post

- **CHECK FIGURES AND TABLES CAREFULLY**
  - Check size, numbering, and orientation of figures
  - All images in the PDF are downsampled (reduced to lower resolution and file size) to facilitate Internet delivery. These images will appear at higher resolution and sharpness in the printed article
  - Review figure legends to ensure that they are complete
  - Check all tables. Review layout, title, and footnotes

- **COMPLETE COPYRIGHT TRANSFER AGREEMENT (CTA)** if you have not already signed one
  - Please send a scanned signed copy with your proofs by e-mail. **Your article cannot be published unless we have received the signed CTA**

- **OFFPRINTS**
  - Free access to the final PDF offprint or your article will be available via Author Services only. Please therefore sign up for Author Services if you would like to access your article PDF offprint and enjoy the many other benefits the service offers.

### Additional reprint and journal issue purchases

- Should you wish to purchase additional copies of your article, please click on the link and follow the instructions provided: [http://offprint.cosprinters.com/cos/bw/](http://offprint.cosprinters.com/cos/bw/)
- Corresponding authors are invited to inform their co-authors of the reprint options available.
- Please note that regardless of the form in which they are acquired, reprints should not be resold, nor further disseminated in electronic form, nor deployed in part or in whole in any marketing, promotional or educational contexts without authorization from Wiley. Permissions requests should be directed to mailto: permissionsuk@wiley.com
- For information about ‘Pay-Per-View and Article Select’ click on the following link: [http://www3.interscience.wiley.com/aboutus/ppv-articleselect.html](http://www3.interscience.wiley.com/aboutus/ppv-articleselect.html)
COPYRIGHT TRANSFER AGREEMENT

WILEY

ISUOG

Wiley Production No. __________

Date: ____________________________

To: _____________________________

Re: Manuscript entitled ____________________________

(the "Contribution") for publication in Ultrasound in Obstetrics & Gynecology (the "Journal") published by John Wiley & Sons Ltd ("Wiley").

Thank you for submitting your contribution for publication. In order to expedite the publishing process and enable Wiley to disseminate your work to the fullest extent, we need to have this Copyright Transfer Agreement signed and returned to us as soon as possible. If the Contribution is not accepted for publication this Agreement shall be null and void.

A. COPYRIGHT

1. The Contributor assigns to the International Society of Ultrasound in Obstetrics and Gynecology ("ISUOG"), during the full term of copyright and any extensions or renewals of that term, all copyright in and to the Contribution, including but not limited to the right to publish, republish, transmit, sell, distribute, and otherwise use the Contribution and the material contained therein in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so.

2. Reproduction, posting, transmission or other distribution or use of the Contribution or any material contained therein, in any medium as permitted hereunder, requires a citation to the Journal and an appropriate credit to the ISUOG as copyright owner and to Wiley as Publisher, suitable in form and context as follows: (Title of Article, Author, Ultrasound in Obstetrics & Gynecology, Volume/Issue Copyright © [year] International Society of Ultrasound in Obstetrics and Gynecology, first published by John Wiley & Sons Ltd.)

B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor’s Employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure, or article of manufacture described in the Contribution, and the right to make oral presentations of material from the Contribution.

C. OTHER RIGHTS OF CONTRIBUTOR

The International Society of Ultrasound in Obstetrics and Gynecology grants back to the Contributor the following:

1. The right to share with colleagues print or electronic "preprints" of the unpublished Contribution, in form and content as accepted by Wiley for publication in the Journal. Such preprints may be posted as electronic files on the Contributor’s own website for personal or professional use, or on the Contributor’s internal university or corporate networks/intranet, or secure external website at the Contributor’s institution, but not for commercial sale or for any systematic external distribution by a third party (eg: a listserv or database connected to a public access server). Prior to publication, the Contributor must include the following notice on the preprint: "This is a preprint of an article accepted for publication in Ultrasound in Obstetrics & Gynecology Copyright © (year) International Society of Ultrasound in Obstetrics and Gynecology." After publication of the Contribution by Wiley, the preprint notice should be amended to read as follows: "This is a preprint of an article published in [include the complete citation information for the final version of the Contribution as published in the print edition of the Journal] and should provide an electronic link to the Journal’s WWW site, located at the following Wiley URL: http://www.interscience.wiley.com. The Contributor agrees not to update the preprint or replace it with the published version of the Contribution.

2. The right, without charge, to photocopy or to transmit on-line or to download, print out and distribute to a colleague a copy of the published Contribution in whole or in part, for the Contributor’s personal or professional use, for the advancement of scholarly or scientific research or study, or for corporate informational purposes in accordance with paragraph D3 below.

3. The right to republish, without charge, in print format, all or part of the material from the published Contribution in a book written or edited by the Contributor.

4. The right to use selected figures and tables, and selected text (up to 250 words) from the Contribution, for the Contributor’s teaching purposes, or for incorporation within another work by the Contributor that is made part of an edited work published (in print or electronic format) by a third party, or for presentation in electronic format on an internal computer network or external website of the Contributor or the Contributor’s employer. The abstract shall not be included as part of such selected text.

5. The right to include the Contribution in a compilation for classroom use (course packs) to be distributed to students at the Contributor’s institution free of charge or to be stored in electronic format in datarooms for access by students at the Contributor’s institution as part of their coursework (sometimes called "electronic reserve rooms") and for in-house training programmes at the Contributor’s employer.

D. CONTRIBUTIONS OWNED BY EMPLOYER

1. If the Contribution was written by the Contributor in the course of the Contributor’s employment (as a "work-made-for-hire" in the course of employment), the Contribution is owned by the company/employer which must sign this Agreement (in addition to the Contributor’s signature), in the space provided below. In such case, the company/employer hereby assigns to the ISUOG, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in paragraph A above.
2. In addition to the rights specified as retained in paragraph B above and the rights granted back to the Contributor pursuant to paragraph C above, the ISU/OG hereby grants back, without charge, to such company/employer, its subsidiaries and divisions, the right to make copies of and distribute the published Contribution internally in print format or electronically on the Company’s internal network. Upon payment of the Publisher’s reprint fee, the institution may distribute (but not re-sell) print copies of the published Contribution externally. Although copies so made shall not be available for individual re-sale, they may be included by the company/employer as part of an information package included with software or other products offered for sale or license. Posting of the published Contribution by the institution on a public access website may only be done with Wiley’s written permission, and payment of any applicable fee(s).

E. GOVERNMENT CONTRACTS

In the case of a Contribution prepared under US Government contract or grant, the US Government may reproduce, without charge, all or portions of the Contribution and may authorize others to do so, for official US Government purposes only, if the US Government contract or grant so requires. (Government Employees: see note at end.)

F. COPYRIGHT NOTICE

The Contributor and the company/employer agree that any and all copies of the Contribution or any part thereof distributed or posted by them in print or electronic format as permitted herein will include the notice of copyright as stipulated in the Journal and a full citation to the Journal as published by Wiley.

G. CONTRIBUTORS REPRESENTATIONS

The Contributor represents that the Contribution is the Contributor’s original work. If the Contribution was prepared jointly, the Contributor agrees to inform the co-Contributors of the terms of this Agreement and to obtain their signature(s) to this Agreement or their written permission to sign on their behalf. The Contribution is submitted only to this Journal and has not been published before, except for “preprint” as permitted above. (If excerpts from copyrighted works owned by third parties are included, the Contributor will obtain written permission from the copyright owners for all uses as set forth in Wiley’s permissions form or in the Journal’s Instructions for Contributors, and show credit to the sources in the Contribution.) The Contributor also warrants that the Contribution contains no libelous or unlawful statements, does not infringe on the right or privacy of others, or contain material or instructions that might cause harm or injury.

Tick one box and fill in the appropriate section before returning the original signed copy to the Publisher

☐ Contributor-owned work

Contributor’s signature ____________________________________________ Date ____________________________

Type or print name and title ____________________________________________

Co-contributor’s signature ____________________________________________ Date ____________________________

Type or print name and title ____________________________________________

Attach additional signature page as necessary

☐ Company/Institution-owned work (made-for-hire in the course of employment)

Contributor’s signature ____________________________________________ Date ____________________________

Type or print name and title ____________________________________________

Company or Institution

(Employer-forged Hire) ____________________________________________

Authorised signature of Employer ______________________________________

Date ____________________________

Type or print name and title ____________________________________________

☐ US Government work

Note to US Government Employees

A Contribution prepared by a US federal government employee as part of the employee’s official duties, or which is an official US Government publication is called a “US Government work”, and is in the public domain in the United States. In such case, the employee may cross out paragraph A1 but must sign and return this Agreement. If the Contribution was not prepared as part of the employee’s duties or is not an official US Government publication, it is not a US Government work.

☐ UK Government work (Crown Copyright)

Note to UK Government Employees

The rights in a Contribution by an employee of a UK Government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown. In such case, the Publisher will forward the relevant form to the Employee for signature.
WILEY AUTHOR DISCOUNT CLUB

We would like to show our appreciation to you, a highly valued contributor to Wiley’s publications, by offering a unique 25% discount off the published price of any of our books*.

All you need to do is apply for the Wiley Author Discount Card by completing the attached form and returning it to us at the following address:

The Database Group (Author Club)
John Wiley & Sons Ltd
The Atrium
Southern Gate
Chichester
PO19 8SQ
UK

Alternatively, you can register online at www.wileyeurope.com/go/authordiscount
Please pass on details of this offer to any co-authors or fellow contributors.

After registering you will receive your Wiley Author Discount Card with a special promotion code, which you will need to quote whenever you order books direct from us.

The quickest way to order your books from us is via our European website at:

http://www.wileyeurope.com

Key benefits to using the site and ordering online include:
Real-time SECURE on-line ordering
Easy catalogue browsing
Dedicated Author resource centre
Opportunity to sign up for subject-orientated e-mail alerts

Alternatively, you can order direct through Customer Services at:
cs-books@wiley.co.uk, or call +44 (0)1243 843294, fax +44 (0)1243 843303

So take advantage of this great offer and return your completed form today.

Yours sincerely,

Verity Leaver
Group Marketing Manager
author@wiley.co.uk

*TERMS AND CONDITIONS
This offer is exclusive to Wiley Authors, Editors, Contributors and Editorial Board Members in acquiring books for their personal use. There must be no resale through any channel. The offer is subject to stock availability and cannot be applied retrospectively. This entitlement cannot be used in conjunction with any other special offer. Wiley reserves the right to amend the terms of the offer at any time.
To enjoy your 25% discount, tell us your areas of interest and you will receive relevant catalogues or leaflets from which to select your books. Please indicate your specific subject areas below.

<table>
<thead>
<tr>
<th>Accounting</th>
<th>Architecture</th>
<th>Business/Management</th>
<th>Computer Science</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td>[]</td>
<td>[]</td>
<td>Database/Data Warehouse</td>
</tr>
<tr>
<td>Corporate</td>
<td>[]</td>
<td>[]</td>
<td>Internet Business</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
<td>Networking</td>
</tr>
<tr>
<td>Analytical</td>
<td>[ ]</td>
<td></td>
<td>Programming/Software</td>
</tr>
<tr>
<td>Industrial/Safety</td>
<td>[ ]</td>
<td></td>
<td>Development</td>
</tr>
<tr>
<td>Organic</td>
<td>[ ]</td>
<td></td>
<td>Object Technology</td>
</tr>
<tr>
<td>Inorganic</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymer</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spectroscopy</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encyclopedia/Reference</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Business/Finance</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life Sciences</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Sciences</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Sciences</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Earth &amp; Environmental Science</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitality</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioinformatics/</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Computational Biology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteomics</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genomics</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gene Mapping</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Genetics</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Science</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrinology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrics/Gynaecology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatry</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Profit</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finance/Investing</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institutional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal Finance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engineering</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Civil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communications Technology</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electronic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industrial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life Science</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Landscape Architecture</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mathematics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Materials Science</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forensic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social &amp; Personality</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health &amp; Sport</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organizational</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental &amp; Special Ed</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child Welfare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-Help</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physics/Physical Science</td>
<td>[ ]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please complete the next page /
I confirm that I am (*delete where not applicable): 

a Wiley Book Author/Editor/Contributor* of the following book(s):  
ISBN:  
ISBN:  

a Wiley Journal Editor/Contributor/Editorial Board Member* of the following journal(s):  

SIGNATURE: ................................................................. Date: ........................................

PLEASE COMPLETE THE FOLLOWING DETAILS IN BLOCK CAPITALS: 

TITLE: (e.g. Mr, Mrs, Dr) ……………………  FULL NAME: ………………………………………………………………………………

JOB TITLE (or Occupation): ………………………………………………………………………………………………………………………

DEPARTMENT: ………………………………………………………………………………………………………………………………………

COMPANY/INSTITUTION: ………………………………………………………………………………………………………………………

ADDRESS: ………………………………………………………………………………………………………………………………………

TOWN/CITY: ………………………………………………………………………………………………………………………………………

COUNTY/STATE: …………………………………………………………………………………………………………………………………

COUNTRY: ………………………………………………………………………………………………………………………………………

POSTCODE/ZIP CODE: ………………………………………………………………………………………………………………………

DAYTIME TEL: …………………………………………………………………………………………………………………………………

FAX: ……………………………………………………………………………………………………………………………………………

E-MAIL: ………………………………………………………………………………………………………………………………………

YOUR PERSONAL DATA  
We, John Wiley & Sons Ltd, will use the information you have provided to fulfil your request. In addition, we would like to:  

1. Use your information to keep you informed by post of titles and offers of interest to you and available from us or other 
   Wiley Group companies worldwide, and may supply your details to members of the Wiley Group for this purpose.  
   [ ] Please tick the box if you do NOT wish to receive this information  
2. Share your information with other carefully selected companies so that they may contact you by post with details of 
   titles and offers that may be of interest to you.  
   [ ] Please tick the box if you do NOT wish to receive this information.

E-MAIL ALERTING SERVICE  
We also offer an alerting service to our author base via e-mail, with regular special offers and competitions. If you DO wish to 
receive these, please opt in by ticking the box [ ].

If, at any time, you wish to stop receiving information, please contact the Database Group (databasegroup@wiley.co.uk) at John Wiley & Sons Ltd, 
The Atrium, Southern Gate, Chichester, PO19 8SQ, UK.

TERMS & CONDITIONS  
This offer is exclusive to Wiley Authors, Editors, Contributors and Editorial Board Members in acquiring books for their personal use. There should 
be no resale through any channel. The offer is subject to stock availability and may not be applied retrospectively. This entitlement cannot be used 
in conjunction with any other special offer. Wiley reserves the right to vary the terms of the offer at any time.

PLEASE RETURN THIS FORM TO:  
Database Group (Author Club), John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, PO19 8SQ, UK author@wiley.co.uk  
Fax: +44 (0)1243 770154