Reproductive BioMedicine Online (2014) **28**, 232–238

www.sciencedirect.com
www.rbmonline.com

ARTICLE

Pathophysiology proposed as the basis for modern management of the ovarian endometrioma

Ivo Brosens [a,*], Stephan Gordts [a], Patrick Puttemans [a], Giuseppe Benagiano [b]

[a] *Leuven Institute for Fertility and Embryology, Leuven, Belgium;* [b] *Department of Gynaecology, Obstetrics and Urology, Sapienza University, Rome, Italy*
[*] Corresponding author. *E-mail address:* ivo.brosens@med.kuleuven.be (I Brosens).

Ivo Brosens is Emeritus Professor at the Catholic University, Leuven, Belgium. After obtaining his PhD at the University of London, he became full professor at the KU Leuven in 1975, where he founded the Centre for Reproductive Medicine. He received Honorary Fellowship of the Royal College of Obstetrics and Gynaecology in UK and is emeritus member of the World Endometriosis Society. He was visiting professor at several universities worldwide and published numerous original research articles, reviews and book chapters and is member of the several editorial boards.

Abstract Present management of the ovarian endometrioma focuses on the size of the cyst and dictates that surgery should not be performed unless this exceeds 3 cm, which neglects the complex pathology of this condition. Studies of ovaries with the endometrioma *in situ* show progressive smooth muscle cell metaplasia and fibrosis of the cortical layer as the main ovarian lesion. There is no correlation between the size of the endometrial cyst and the degree of ovarian pathology: it is the mere presence of an ovarian endometrioma that has a detrimental impact on the cortical layer's follicle reserve. Cystectomy in young patients with an endometrioma may be particularly detrimental to follicle reserve, with the ovarian parenchyma loss at the time of surgery being related to the cyst's diameter. An underutilized diagnostic procedure, transvaginal hydrolaparoscopy with in-situ inspection of the cyst wall by ovarioscopy, allows careful diagnosis of ovarian pathology and selection of appropriate surgery with minimal invasiveness. Thus, available evidence shows that expectant management may not be the best choice when an endometrioma is suspected. On the contrary, early diagnosis through a minimally invasive technique, followed by early ablative surgery whenever indicated, represents the management of choice to preserve normal ovarian function.

KEYWORDS: cystectomy, endometrioma, hydrolaparoscopy, metaplasia, ovary, pathology

Introduction

Current expert opinion dictates that in infertility patients with an ovarian endometrioma, surgery should not be performed unless the size exceeds 3 cm (Gelbaya et al., 2010). Such advice has been justified because of the risk of further decreasing fertility, while at the same time it raises major concerns. What seems both remarkable and questionable is the use, not of the pathology so well described in the old literature, but of the size as key criterion for judging

1472-6483/$ - see front matter
http://dx.doi.org/10.1016/j.rbmo.2013.09.024

both severity of the disease and indication for surgery (Garcia-Velasco and Somigliana, 2009; Kumar and Balasubramanian, 2012). Moreover, it is illogical that the management should vary according to whether the patient is infertile, has never had a prior diagnosis of endometriosis or is symptomatic.

This paper intends in the first place to review the ovarian pathology associated with the endometrioma, secondly to discuss the risk factors associated with delaying diagnosis and surgery and finally to discuss how the appropriate surgery can be selected on the basis of ovarian pathology. Knowledge of the pathology of the ovarian endometrioma requires investigation of the pathology of ovaries with the endometrioma *in situ*. Recently ovarioscopy (i.e. inspection of the cortical cystic structure under hydroflotation) has been proposed to assess the cortical pathology of the endometrioma *in situ* before surgery (Brosens, 1994; Darwish et al., 2000).

Pathology of the ovarian endometrioma

Intraovarian pathology

A search of the world literature for ovarian pathology associated with the endometrioma reveals that only two ancient authors have investigated systematically a series of ovaries with the endometrioma *in situ*, while in recent years pathology has been investigated on cystectomy specimens and biopsies.

Ovaries with endometrioma *in situ*

Two historical papers have documented the pathology of ovaries with endometrioma *in situ*. The first is the seminal paper by Sampson (1921) on 'Perforating hemorrhagic (chocolate) cysts of the ovary', describing in a series of 23 cases the main features of the ovary at the site of 'perforation' (i.e. inversion of the endometrioma). The main features included the following: (i) cysts were usually small, between 2 and 4 cm and even $<$2 cm, but also occasionally $>$4 cm; (ii) the presence of 'adenomyomas' (currently called deep endometriosis) in the adhering uterus, parametrium, rectovaginal wall, sigmoid, etc.; (iii) the endometrial lining manifested similar 'activity' as the uterine mucosa during the menstrual cycle; Sampson observed, in two women operated on at the time of menstruation, endometrial shedding and bleeding in the tissue lining the wall, which were the proof of their endometrial origin; (iv) luteal and endometrial lining was present in 9% of cases; and (v) cysts were bilateral in 35% of cases. Sampson's first hypothesis, that rupture of an ovarian endometrioma caused superficial peritoneal endometriosis, changed after the observation that in the absence of an endometrioma the free, superficial peritoneal implants were bleeding like eutopic endometrium at the time of menstruation (Sampson, 1927).

The second paper, by the pathologist Hughesdon (1957), described a series of 29 ovaries with chocolate cysts; all specimens were obtained at the time of hysterectomy in older, even post-menopausal women. The main features were as follows: (i) in 90% of the cases, the wall is identifiable as cortex, disrupted and disorganized; (ii) in many instances, invagination is not uniform, but remains on one side as a more or less definite local mass covering a good portion of the wall, extending at its margin to surround the cavity with a relatively thin wall; (iii) owing to stretching, recognizable survival of inner cortex is not uniform; (iv) the identity of the inner cortex can be further obscured by its metaplasia into smooth muscle: metaplasia into muscle did occur in any of its layers in 86% of the chocolate cysts and as a result, the inner cortex may become quite unrecognizable by stretching and muscular metaplasia; in addition, there is no cleavage plane; and (v) luteal and endometrial lining occurred together in 3% of the specimens.

Smooth muscle cell metaplasia has been described in deep endometriosis and in the ovarian endometrioma (Khare et al., 1996; Doss et al., 1999; Anaf et al., 2000). The pelvic nodules described by Sampson (1921) as 'adenomyomas' have in recent years been redefined as 'deep' endometriosis (Cornillie et al., 1990). Smooth muscle cell metaplasia in the ovary may be explained in two ways (Fukunaga, 2000). First, smooth muscle may originate from metaplastic endometrial stromal cells in endometriotic foci. Second, it may come from metaplastic ovarian stromal cells in the rim of endometriosis. The identification of oxytocin receptor, vasopressin receptor, smooth muscle myosin heavy chain, oestrogen and progesterone receptors leads to the hypothesis that the endometriosis-associated smooth muscle cells might be functionally active and be possibly involved in the generation of pain (De Arellano et al., 2011).

Recent research on the molecular features confirm that the ovarian endometrioma is a progressive disease associated with chronic inflammation as manifested by an increase in reactive oxygen species (Ngô et al., 2009), expression of vascular endothelium growth factor and thrombospondin-1 (Tan et al., 2002; Gilabert-Estellés et al., 2007), presence of nerve fibres (Zhang et al., 2010) and expression of cyclooxygenase-2 (Cho et al., 2010). These findings may explain the associated cellular fibrosis and smooth muscle metaplasia in the affected ovarian cortex.

Cystectomy specimens

In a recent study of two oophorectomy and 27 cystectomy specimens from women under the age of 35 years, Scurry et al. (2001) distinguished four different types of endometriotic cysts: (i) cortical invagination cysts; (ii) surface inclusion cyst-related endometriotic cysts; (iii) physiological cyst-related endometriotic cysts; and (iv) unclassified type. The authors concluded that ovarian cystectomy specimens were more difficult to categorize as the surgical procedure induces variables such as considerable adherence between the cyst and the underlying ovarian parenchyma, the often artificial planes of cleavage and the fragmentation and tearing of the tissue during the incision. Cortical invagination cysts were the only common diagnosable sort of the three classifiable types. The presence of oocytes in the inner wall of the cyst is proof of an inner cortex and allows diagnosis of the cortical invagination type. However, in addition to age, the presence of oocytes is influenced by other factors such as the fibrosis of the wall, smooth muscle metaplasia and stretching of the cortex, which make the origin of the cyst frequently unrecognizable.

Several studies have demonstrated that healthy ovarian tissue is found adjacent to the wall of the cystectomy specimen in women with ovarian endometrioma (Alborzi et al., 2009; Biacchiardi et al., 2011). Muzii et al. (2011) concluded from a prospective trial that the level of expertise in endometriosis surgery is inversely correlated with inadvertent removal of healthy ovarian tissue along with the endometrioma capsule.

Ovarian biopsies from cortex and endometrioma bed

In a study of cortical biopsies obtained at the most bulging part of benign ovarian cysts, Maneschi et al. (1993) showed that ovarian cortex which is stretched and thinned by the growth of a benign tumour is, in contrast with teratomas or benign cystadenomas, morphologically altered in the presence of endometriomata and shows fibrosis, haemosiderin-laden macrophages, thickened-wall blood vessels and reduced follicle complexes. On the other hand, Kitajima et al. (2011) demonstrated on biopsies obtained from the ovarian bed after resection of cysts <4 cm in size that the follicular density is statistically significantly lower than in cortex from contralateral normal ovaries. In addition, histological alterations in cortical tissue, such as formation of fibrosis and concomitant loss of cortex-specific stroma, were found in cortex from ovaries with endometriomata. The authors suggest that early diagnosis and intervention in women with endometriomata may be beneficial to protect their reproductive function.

Kuroda et al. (2012) obtained a small amount of ovarian tissue during cystectomy in 61 patients with an endometrioma ≥ 4 cm and 42 patients with non-endometriotic cysts to evaluate histologically the density of follicles. The density of follicles correlated with the age of the patients in both groups. In women aged <35 years, the relative density of follicles in healthy ovarian tissues was consistently lower in the endometriotic cyst group compared with the non-endometriotic cyst group, with the relative ratio at age 20, 30 and 35 years calculated to be 35.4%, 46.8% and 62.7%, respectively. There was no significant difference between the groups in patients over the age of 35. The study strongly suggests that ovarian endometriomata have a detrimental impact of follicle reserve in younger women and that cystectomy in young patients with an endometrioma may be particularly detrimental on the follicle reserve. This is in agreement with the observations of one study demonstrating that ovarian surgery for endometriomata prior to IVF results in longer stimulation, higher FSH requirement and lower oocyte number (Demirol et al., 2006).

Extraovarian pathology

Although the ovarian endometrioma is described as an ovarian cyst, the pathology represents in most cases a pseudocyst with a partial or complete endometrial-like lining of the cyst and, in addition to the intraovarian metaplasia, also extraovarian adhesions and endometriosis. These extraovarian implants are likely to occur at the site of ovarian adhesion and invagination and at the ceiling of the ovarian fossa. In a recent study of 99 consecutive patients with unilateral or bilateral endometrioma, Mereu et al. (2012) found that ovarian endometriosis is very often (98%) associated with posterior broad ligament endometriosis and adhesions; this was superficial in 29.5% and adenomyotic or deep in 70.5% of the histological preparations; adenomyotic endometriosis correlated with preoperative pain. These data are in agreement with Sampson's observations in 1921.

Risks and late complications

Sampson (1921) clearly showed that there is no correlation between the size of the endometrial cyst and the degree of ovarian pathology as manifested by cortical sclerosis and smooth muscle cell metaplasia. His patients were older women and although they had severe cortical metaplasia, the diameter of the cyst varied in the majority between 2 and 4 cm. It is questionable on which basis the ESHRE guidelines (Gelbaya et al., 2010) recommend that endometriomas >3 cm should be removed before IVF. As far as the endometrioma size is concerned, there is no consensus on a cut-off value above which surgical treatment is warranted. It is acceptable that large endometriomas of 6 cm or more in diameter may carry additional risks, including increased likelihood of rupture, infection or presence of malignancy and therefore the management may differ; nevertheless, they may be polycystic or partially dysfunctional and represent an endometrioma with a communicating or non-communicating luteal cyst, as observed by Sampson (1921) in 9% of his cases.

Presence of ovarian endometrioma in spontaneously conceived pregnancies is a rare event, but a 4-fold increase has been reported in recent years, making it today the most common adnexal mass detected during pregnancy (Ueda et al., 2010). The endometrioma may not be large but, although benign, may cause significant complications at any stage during gestation (Gregora and Higgs, 1998). Recently, Reif et al. (2011) presented a case of acute haemoperitoneum caused by a ruptured endometrioma in a late twin pregnancy. The increased use of assisted reproduction technology has led to higher fertility rates in patients with endometriosis and to a higher incidence of multiple gestations. The number of pregnant women with endometriosis and associated complications may rise, particularly when they are no longer operated on before pregnancy occurs. Therefore, further monitoring is required to predict risk factors such as abscess formation or rupture of the endometrioma during pregnancy (Brosens et al., 2012).

Pregnancy-related modifications leading to the rapid development of vascularized intracystic excrescences are an uncommon but possible event and may suggest malignancy. 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 (Barbieri et al., 2009).

Testa et al. (2011) recently described in a retrospective study the sonographic characteristics of malignant transformation in ovarian endometriomata and found that borderline tumours and carcinomas arising in endometrioid cysts show a vascularized solid component at ultrasound examination. A prospective study by Kawaguchi et al. (2008) demonstrated that 46 (0.72%) of 6398 women with ovarian

endometrioma developed histologically proven ovarian cancer, in the majority clear cell (39%) and endometrioid adenocarcinomas (35%). The risk increased with increasing age at endometrioma diagnosis. By multivariate analysis, tumour size $\geq$9 cm in diameter and post-menopausal women were independent predictive factors for development of ovarian cancer.

How to assess the ovarian endometrioma in the clinic

The complex ovarian pathology associated with ovarian endometrioma requires careful investigation to select the most appropriate surgical procedure. While the pathologist claims that ovarian cystectomy specimens are often difficult to categorize because of the unknown variables, the endoscopic surgeon can perform careful evaluation of the macroscopic pathology using transvaginal ultrasound and transvaginal ovarioscopy or endoscopy of the endometriotic cyst *in situ* under hydroflotation.

Transvaginal ultrasound

Transvaginal ultrasound is generally considered as a useful method for early detection of the ovarian endometrioma and proposed as a reliable method to exclude significant ovarian endometriosis in patients with infertility (Chamié et al., 2011). However, a recent critical review on the accuracy of ultrasound in the diagnosis of endometriosis found that all published prospective studies included endometriomata with a diameter of at least 14 mm (Moore et al., 2002). The technique failed in the detection of smaller ovarian lesions and peritoneal defects. Even a highly attentive sonographer using high-resolution transvaginal sonography will systematically miss endometriomata $<$7—9 mm in diameter.

Ovarioscopy and guided biopsies

Ovarioscopy has been proposed as a useful tool to differentiate in doubtful cases between a haemorrhagic functional and an endometriotic cyst and to select the sites for biopsies (Brosens, 1994). In contrast with other ovarian cysts, the walls of the endometrioma show no collapse after flushing, and the lining of the cyst, in this case the ovarian cortex, can be clearly inspected under hydroflotation. In young infertile patients, a thin layer of vascularized endometrium is seen partially or fully covering the invaginated cortex. Fifty-one women with one or two ovarian chocolate cysts of 3 cm or more were investigated. The study described the typical characteristics of the inner wall of the endometrioma and location of the active red cobblestone-like implants for biopsy (Figure 1). The colour of the wall makes it possible to distinguish between pearl-white, normal-looking ovarian cortex and yellow-pigmented and dark fibrotic depending on the age of the endometrioma (Figure 2). Small ovarioscopy-guided biopsies revealed endometrial tissue in 82% of the cases versus 42% in large random biopsies. In a study of 68 women with unilateral or bilateral ovarian cysts, Darwish et al. (2000) found that ovarioscopy had the highest specificity for detecting benign ovarian cysts (98%) compared with 72.6% and 72% for tumour markers and transvaginal sonography, respectively. Its positive predictive value was 50% compared with 5% and 6% for tumour markers and transvaginal sonography, respectively. Its findings agreed with the histopathological diagnosis in 39 patients (57%, $P = 0.000$, $k = 0.85$).

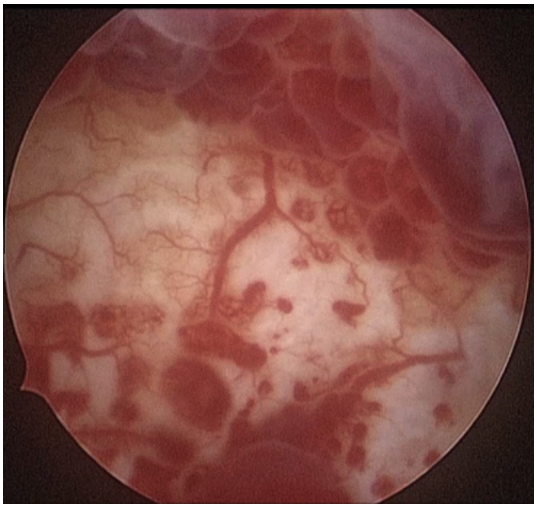

Figure 1 Ovarioscopy showing typical superficial cobble-stone endometrial implants lining normal ovarian cortex. Under hydrofloatation, the extensive angiogenesis is visualized.

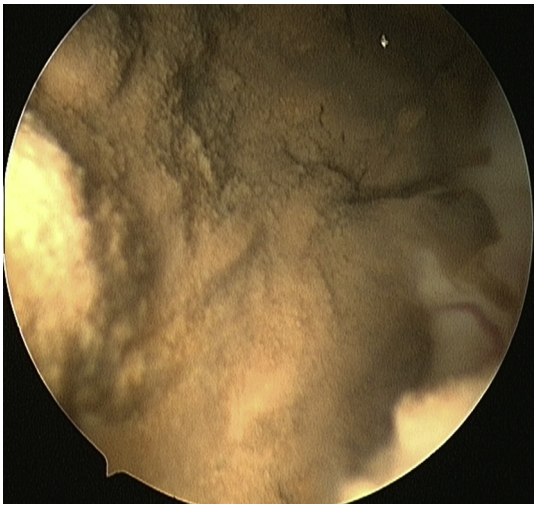

Figure 2 Ovarioscopy showing the dark fibrotic and pigmented ovarian wall reflecting severe metaplasia of the ovarian cortex.

Transvaginal hydrolaparoscopy

Transvaginal laparoscopy is performed as a one-step, single-access, needle-puncture technique via the pouch of Douglas using a solution of prewarmed Ringer lactate as distension medium (Gordts et al., 1998, 2000). The use of hydroflotation and the absence of the high intra-abdominal pressure of CO_2-pneumoperitoneum of standard laparoscopy,

allows an accurate 3-dimensional visualization of small lesions and free-floating vascularized adhesions (Brosens et al., 2001; Campo et al., 1999), with a contrast and resolution that is far superior than in an environment of CO_2 gas. With the transvaginal entrance, the endoscope is in the same longitudinal axis of the tubo-ovarian organs, there is easy access to the fossa ovarica, the preferred initiation site of endometriotic lesions that can be inspected easily without any additional manipulation. Although there is a potential risk of rectal needle perforation, these lesions are considered as minimal complications and can be treated conservatively with antibiotics (Gordts et al., 2001).

Transvaginal hydrolaparoscopy has been shown as superior to standard laparoscopy for detection of subtle endometriotic adhesions of the ovary (Brosens et al., 2001). Videotapes of standard laparoscopy and transvaginal hydrolaparoscopy were viewed by an independent observer in random order and in a blinded manner. The subtle adhesions seen on transvaginal hydrolaparoscopy but not on standard laparoscopy were filmy, microvascularized and nonconnecting.

Transvaginal surgery of ovarian endometrioma

The transvaginal approach offers the possibility of early exploration and the choice of surgical treatment of ovarian endometriotic lesions. Ovarian endometrioma up to a maximum diameter of 3 cm can be treated (Gordts et al., 2003). In the absence of a panoramic view, major surgery is excluded. At inspection, the site of inversion can clearly been seen without disruption of the different structures and opening of the cyst. As the different planes of cleavage are easily detected under water, a meticulous dissection is performed using 5Fr. microscissors and a 5Fr. bipolar coagulation needle and probe. After adhesiolysis, the cyst can be opened at the site of invagination. Access at the site of invagination minimizes the ovarian trauma. As the cystic walls are formed by the ovarian cortex, no collapsing of the walls occurs. Inside the cyst, careful inspection under water reveals the presence of endometrial like tissue surrounded by a marked neo-angiogenesis. The bipolar coagulation probe allows accurate under water coagulation for complete ablation of the inside of the endometriotic cyst and adjacent endometriotic lesions of the broad ligament and in the ovarian fossa. Because the procedure is performed under water, there is an absence of carbonization and diminished risk of post-operative adhesion formation.

Even in endometriotic cysts as small as 1—2 cm, adhesions are frequently present. After dissection between the place of invagination and the broad ligament, invasion of endometriotic tissue in the posterior leaf of the broad ligament with fibrosis can be treated. Besides the possibility of an early diagnosis, the transvaginal laparoscopy offers the possibility of treatment at an early stage in a minimally invasive way, limiting the damage to normal ovarian tissue (i.e. without impairment of the patient's fertility potential and the functional prognosis of her ovaries).

This articles has already stressed that ovarian pathology has been somewhat neglected in randomized studies, and this is specifically true for the employment of transvaginal endoscopy followed by ovarioscopy as a tool to select the type of surgery to be performed in the presence of an 'early endometrioma'. At the same time, it should be borne in mind that there are ethical issues involved in an randomized controlled trial of this type; indeed, 'early' cysts are usually not 'intraovarian' and have no cleavage plane. Under the circumstances, if the structure of the endometrioma can be recognized as an inverted pseudocyst with normal cortex, it would not be possible to propose at random an excision that would harm the ovary.

Conclusions

Surgery of the ovarian endometrioma should in the first place address preservation of ovarian function by removal of the endometriotic pathology, which in most cases may affect the outside of the ovary, but progressively directly or indirectly affects the cortical layer.

Recent studies have provided evidence that surgical removal of the endometrioma >3 cm is deleterious to ovarian reserve and function in women with infertility. There are now convincing data that surgery for removal of the endometrioma not only is no cure of infertility, but may even harm follicle reserve and increase the risk of premature ovarian failure and earlier age at menopause. The surgical technique of cystectomy for ovarian endometrioma has undoubtedly improved in recent years to reduce damage to the cortical follicular system (Jadoul et al., 2012; Kondo et al., 2011). Unfortunately, cystectomy specimens provide no information on the degree of smooth muscle metaplasia and fibrosis in the ovarian wall. In addition, after healing, the cortex is replaced by scar tissue that may interfere with the cortical function in follicle maturation and ovulation.

At present, some authors propose expectant management rather than cystectomy (Ruiz-Flores and Garcia-Velasco, 2012). The question then arises whether management of ovarian endometrioma is swinging from overtreatment to undertreatment. Unfortunately, ovarian endometrioma is not a simple chocolate cyst that can disappear spontaneously when it is not more that 3 cm in diameter; on the contrary, the pathology of small endometriomas depends not on the size but largely on the inflammatory disease resulting in smooth muscle cell metaplasia, fibrosis of the ovarian cortex and loss of follicles. For this reason the ectopic endometrial tissue should be eliminated, the sooner the better and irrespective of the size of the cyst.

References

Alborzi, S., Foroughinia, L., Kumar, P.V., Asadi, N., Alborzi, S., 2009. A comparison of histopathologic findings of ovarian tissue inadvertently excised with endometrioma and other kinds of benign ovarian cyst in patients undergoing laparoscopy versus laparotomy. Fertil. Steril. 92, 2004—2007.

Anaf, V., Simon, P., Fayt, I., Noel, J., 2000. Smooth muscles are frequent components of endometriotic lesions. Hum. Reprod. 15, 767—771.

Barbieri, M., Somigliana, E., Oneda, S., Ossola, M.W., Acaia, B., Fedele, L., 2009. Decidualized ovarian endometriosis in pregnancy: a challenging diagnostic entity. Hum. Reprod. 24, 1818—1824.

Biacchiardi, C.P., Piane, L.D., Camanni, M., Deltetto, F., Delpiano, E.M., Marchino, G.L., Gennarelli, G., Revelli, A., 2011. Laparoscopic stripping of endometriomas negatively affects ovarian

follicular reserve even if performed by experienced surgeons. Reprod. Biomed. Online 23, 740—746.
Brosens, I.A., 1994. Endoscopic exploration and classification of the chocolate cysts. Hum. Reprod. 9, 2213—2214.
Brosens, I., Gordts, S., Campo, R., 2001. Transvaginal hydrolaparoscopy but not standard laparoscopy reveals subtle endometriotic adhesions of the ovary. Fertil. Steril. 75, 1009—1012.
Brosens, I., Brosens, J.J., Fusi, L., Al-Sabbagh, M., Kuroda, K., Benagiano, G., 2012. Risks of adverse pregnancy outcome in endometriosis. Fertil. Steril. 98, 30—35.
Campo, R., Gordts, S., Rombauts, L., Brosens, I., 1999. Diagnostic accuracy of transvaginal hydrolaparoscopy in infertility. Fertil. Steril. 71, 1157—1160.
Chamié, L.P., Blasbalg, R., Pereira, R.M., Warmbrand, G., Serafini, P.C., 2011. Findings of pelvic endometriosis at transvaginal US, MR imaging, and laparoscopy. Radiographics 31, 77—100.
Cho, S., Park, S.H., Choi, Y.S., Seo, S.K., Kim, H.Y., Park, K.H., Cho, D.J., Lee, B.S., 2010. Expression of cyclooxygenase-2 in eutopic endometrium and ovarian endometriotic tissue in women with severe endometriosis. Gynecol. Obstet. Invest. 69, 93—100.
Cornillie, F.J., Oosterlynck, D., Lauweryns, J.M., Koninckx, P.R., 1990. Deeply infiltrating pelvic endometriosis: histology and clinical significance. Fertil. Steril. 53, 978—983.
Darwish, A.M., Amin, A.F., El-Feky, M.A., 2000. Ovarioscopy, a technique to determine the nature of cystic ovarian tumors. J. Am. Assoc. Gynecol. Laparosc. 7, 539—544.
De Arellano, M.L.B., Gericke, J., Reichelt, U., Okuducu, A.F., Ebert, A.D., Chiantera, V., Schneider, A., Mechsner, S., 2011. Immunohistochemical characterization of endometriosis-associated smooth muscle cells in human peritoneal endometriotic lesions. Hum. Reprod. 26, 2721—2730.
Demirol, A., Guven, S., Baykal, C., Gurgan, T., 2006. Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study. Reprod. Biomed. Online 12, 639—643.
Doss, B.J., Wanek, S.M., Jacques, S.M., Qureshi, F., Ramirez, N.C., Lawrence, W.D., 1999. Ovarian smooth muscle metaplasia: an uncommon and possibly underrecognized entity. Int. J. Gynecol. Pathol. 18, 58—62.
Fukunaga, M., 2000. Smooth muscle metaplasia in ovarian endometriosis. Histopathology 36, 348—352.
Garcia-Velasco, J.A., Somigliana, E., 2009. Management of endometriomas in women requiring IVF: to touch or not to touch? Hum. Reprod. 24, 496—501.
Gelbaya, T.A., Gordts, S., D'Hooghe, T.M., Gergolet, M., Nardo, L.G., 2010. Management of endometrioma prior to IVF: compliance with ESHRE guidelines. Reprod. BioMed. Online 21, 325—330.
Gilabert-Estellés, J., Ramón, L.A., España, F., Gilabert, J., Vila, V., Réganon, E., Castelló, R., Chirivella, M., Estellés, A., 2007. Expression of angiogenic factors in endometriosis: relationship to fibrinolytic and metalloproteinase systems. Hum. Reprod. 22, 2120—2127.
Gordts, S., Campo, R., Rombauts, L., Brosens, I., 1998. Transvaginal hydro-laparoscopy as an outpatient procedure for infertility investigation. Hum. Reprod. 13, 99—103.
Gordts, S., Campo, R., Brosens, I., 2000. Office transvaginal hydrolaparoscopy for early diagnosis of pelvic endometriosis and adhesions. J. Am. Assoc. Gynecol. Laparosc. 7, 45—49.
Gordts, S., Watrelot, A., Campo, R., Brosens, I., 2001. Risk and outcome of bowel injury during transvaginal pelvic endoscopy. Fertil. Steril. 76, 1238—1241.
Gordts, S., Campo, R., Brosens, I., Puttemans, P., 2003. Endometriosis: modern surgical management to improve fertility. Best Pract. Res. Clin. Obstet. Gynaecol. 17, 275—287.
Gregora, M., Higgs, P., 1998. Endometriomas in pregnancy. Aust. N. Z. J. Obstet. Gynaecol. 38, 106—109.
Hughesdon, P.E., 1957. The structure of endometrial cysts of the ovary. J. Obstet. Gynaecol. Br. Emp. 44, 481—487.
Kawaguchi, R., Tsuji, Y., Haruta, S., Kanayama, S., Sakata, M., Yamada, Y., Fujita, H., Hitomi, S., Keiji, T., Kobayashi, H., 2008. Clinicopathologic features of ovarian cancer in patients with ovarian endometrioma. J. Obstet. Gynaecol. Res. 34, 872—877.
Khare, V.K., Martin, D.C., Eltorky, M., 1996. A comparative study of ovarian and pelvic wall-infiltrating endometriosis. J. Am. Assoc. Gynecol. Laparosc. 3, 235—239.
Kitajima, M., Defrre, S., Dolmans, M.-M., Colette, S., Squifflet, J., Van Langendonckt, A., Donnez, J., 2011. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. Fertil. Steril. 96, 685—691.
Kondo, W., Bourdel, N., Zomer, M.T., Slim, K., Rabischong, B., Pouly, J.L., Mage, G., Canis, M., 2011. Laparoscopic cystectomy for ovarian endometrioma — a simple stripping technique should not be used. J. Endometriosis 3, 125—134.
Kumar, P., Balasubramanian, A., 2012. Endometrioma cyst: to remove or not? Int. J. Infertil. Fetal. Med. 3, 26—29.
Kuroda, M., Kuroda, K., Arakawa, A., Fukumura, Y., Kitade, M., Kikuchi, I., Kumakiri, J., Matsuoka, S., Brosens, I.A., Brosens, J.J., Takeda, S., Yao, T., 2012. Histological assessment of impact of ovarian endometrioma and laparoscopic cystectomy on ovarian reserve. J. Obstet. Gynaecol. Res. 38, 1187—1193.
Jadoul, P., Kitajima, M., Donnez, O., Squifflet, J., Donnez, J., 2012. Surgical treatment of ovarian endometriomas: state of the art? Fertil. Steril. 98, 556—563.
Maneschi, F., Marasa, L., Incandela, S., Mazzarese, M., Zupi, E., 1993. Ovarian cortex surrounding benign neoplasms: a histologic study. Am. J. Obstet. Gynecol. 169, 388—393.
Mereu, L., Florio, P., Carri, G., Pontis, A., Petraglia, F., Mencaglia, L., 2012. Clinical outcomes associated with surgical treatment of endometrioma coupled with resection of the posterior broad ligament. Int. J. Gynaecol. Obstet. 116, 57—60.
Moore, J., Copley, S., Morris, J., Lindsell, D., Golding, S., Kennedy, S., 2002. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis Ultrasound. Obstet. Gynecol. 20, 630—634.
Muzii, L., Marana, R., Angioli, R., Bianchi, A., Cucinella, G., Vignali, M., Benedetti Panici, P., Busacca, M., 2011. Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter? Fertil. Steril. 95, 2116—2119.
Ngô, C., Chéreau, C., Nicco, C., Weill, B., Chapron, C., Batteux, F., 2009. Reactive oxygen species controls endometriosis progression. Am. J. Pathol. 175, 225—234.
Reif, P., Schöll, W., Klaritsch, P., Lang, U., 2011. Rupture of endometriotic ovarian cyst causes acute hemoperitoneum in twin pregnancy. Fertil. Steril. 95, 2125e1—2125e3.
Ruiz-Flores, F.J., Garcia-Velasco, J.A., 2012. Is there a benefit for surgery in endometrioma-associated infertility? Curr. Opin. Obstet. Gynecol. 24, 136—140.
Sampson, J.A., 1921. Perforating hemorrhagic (chocolate) cysts of the ovary. Arch. Surg. 3, 245—323.
Sampson, J.A., 1927. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am. J. Obstet. Gynecol. 14, 422—469.
Scurry, J., Whitehead, J., Healey, M., 2001. Classification of ovarian endometriotic cysts. Int. J. Gynecol. Pathol. 20, 147—154.
Tan, X.J., Lang, J.H., Liu, D.Y., Shen, K., Leng, J.H., Zhu, L., 2002. Expression of vascular endothelial growth factor and thrombospondin-1 mRNA in patients with endometriosis. Fertil. Steril. 78, 148—153.

Testa, A.C., Timmerman, D., Van Holsbeke, C., Zannoni, G.F., Fransis, S., Moerman, P., Vellone, V., Mascilini, F., Licameli, A., Ludovisi, M., Di Legge, A., Scambia, G., Ferrandina, G., 2011. Ovarian cancer arising in endometrioid cysts: ultrasound findings. Ultrasound Obstet. Gynecol. 38, 99—106.

Ueda, Y., Enomoto, T., Miyatake, T., Fujita, M., Yamamoto, R., Kanagawa, T., Shimizu, H., Kimura, T., 2010. A retrospective analysis of ovarian endometriosis during pregnancy. Fertil. Steril. 94, 78—84.

Zhang, X., Yao, H., Huang, X., Lu, B., Xu, H., Zhou, C., 2010. Nerve fibres in ovarian endometriotic lesions in women with ovarian endometriosis. Hum. Reprod. 25, 392—397.

Declaration: The authors report no financial or commercial conflicts of interest.

Received 8 April 2013; refereed 5 July 2013; accepted 12 September 2013.