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Case report

Pregnancy-related decidualization of subcutaneous endometriosis occurring in a post-caesarean section scar: Case study and review of the literature

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ABSTRACT

Endometriosis of surgical scars is a rare complication of caesarean sections (incidence: 0.03–0.4%) and other surgical procedures. As endometriosis could be responsive to hormonal stimulation, decidualization and other secondary changes may occur during pregnancy or progestin therapy, sometimes causing a clinically-evident increase in the size of the endometriotic nodules, which could be mistaken for malignant tumors. To our knowledge, we report the 8th subcutaneous case of a pregnancy-related decidualization occurring in a post-caesarean section scar endometriosis. A 33-year-old woman showed a painless, firm, subcutaneous nodule (size: 1 cm) located near the scar of a caesarean section performed 3 years before. Ultrasound examination revealed a well-delimited, hypoechogenic nodule showing perilesional inflammatory reaction without vascular signals. The nodule was considered a post-surgical granuloma: its size did not increase during 4 years of follow-up. Finally, the nodule was totally excised during a second caesarean section performed at 39 weeks of gestation. Histological examination showed nodules of decidualized stromal cells surrounding rare, small, atrophic endometrial glands. Nuclear atypia and mitoses were absent. On immunohistochemical examination, the epithelial cells were pan-CK(AE1/AE3) + /ER + /PR + /S100-/Calretinin-/Vimentin-, while the stromal cells were pan-CK (AE1/AE3)-/Vimentin + /ER + /PR + /CD10 + /S100-/Calretinin-. We reviewed the literature, discussing the main clinic-pathological diagnostic pitfalls and the possible differential diagnoses.

1. Introduction

Endometriosis is the finding of endometrial tissue outside the uterine cavity [1]. Ectopic endometrium is frequently found in the pelvis (ovaries, Fallopian tubes, bladder, sigmoid colon and rectum, peritoneum, etc.), while extrapelvic sites (abdominal walls or viscera, skin, lungs, serous membranes, kidneys, lymph nodes, breasts, brain, etc.) are rarely involved by endometriosis (prevalence: 9–15%) [1,2]. Endometriotic foci are occasionally found in scars due to procedures such as caesarean section (incidence: 0.03–0.4%), episiotomy, amniocentesis, laparotomic or laparoscopic surgery (appendicectomy, hysterectomy, etc.) [1,2]. As endometriosis could be responsive to hormonal stimulation, decidualization and other secondary changes may occur during pregnancy or progestin therapy, sometimes causing a clinically-evident increase in the size of the endometriotic nodules: this atypical presentation could represent a diagnostic pitfall, which could lead to consider this benign condition as a malignant tumor (especially in case of extrapelvic localizations) [3–9]. To our knowledge, we report the 8th subcutaneous case of a pregnancy-related decidualization occurring in a post-caesarean section scar endometriosis [3–9].

2. Case report

A 33-year-old healthy woman presented with a painless, firm, subcutaneous nodule covered by normal skin.

The lesion was located near the left side of a Pfannenstiel incision scar: a caesarean section was performed during her first delivery (3 years before). Ultrasound examination revealed a well-delimited, hypoechogenic subcutaneous nodule (maximum size: 1 cm), showing perilesional inflammatory reaction without evident vascular signals. No uterine or adnexal abnormalities were found. The nodule was considered as a post-surgical granuloma: its size did not increase during 4 years of follow-up. Finally, the nodule was totally excised during a subsequent caesarean section performed at 39 weeks of gestation.

Gross examination of the surgical specimen revealed a well-delimited, white, firm nodule (maximum size: 1 cm) surrounded by

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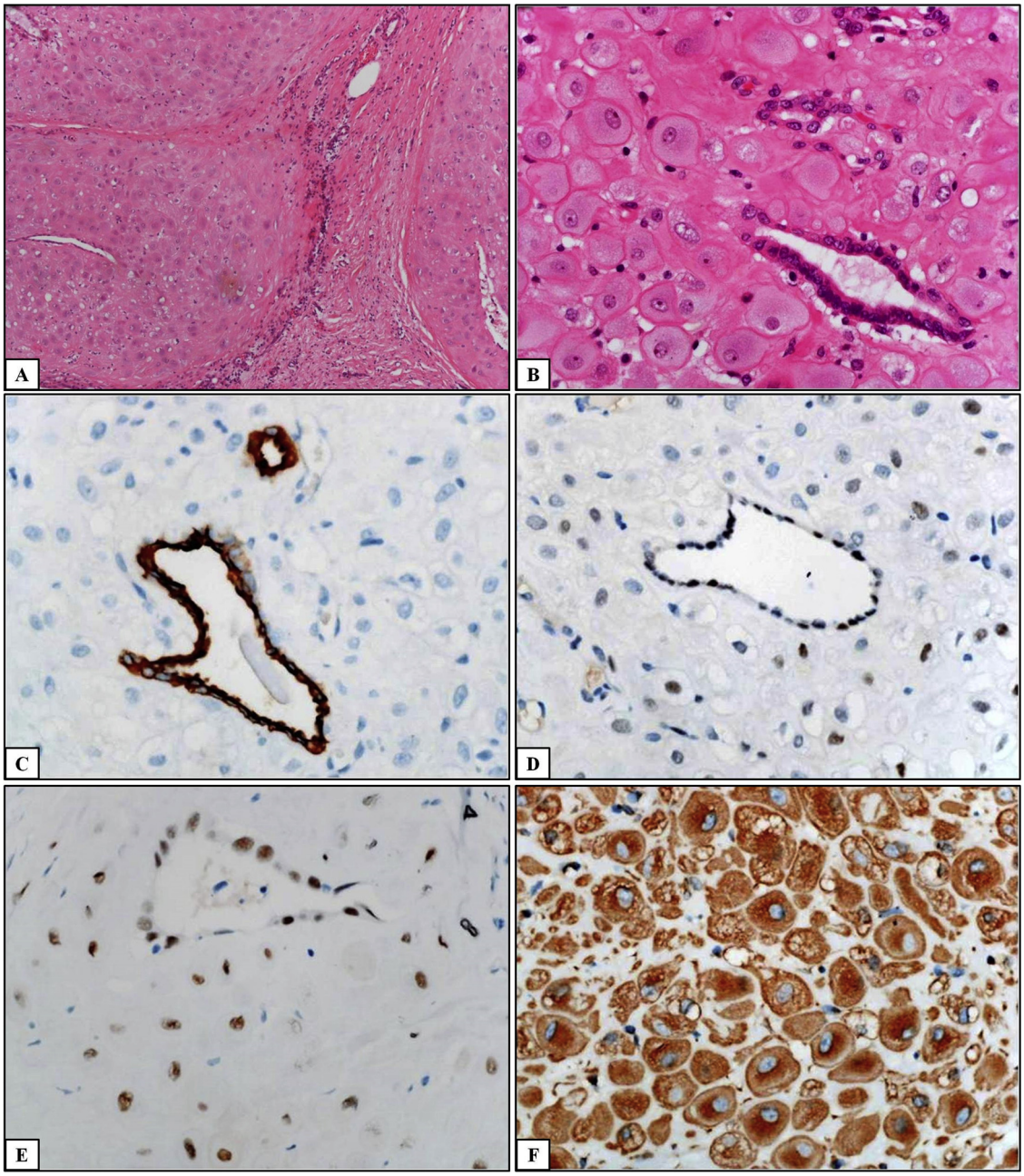

Fig. 1. Histological and immunohistochemical features. 1A) Nodules of small atrophic glands surrounded by large polygonal stromal cells. The nodules were delimited by fibrotic connective tissue focally infiltrated by lymphocytes and pigmented macrophages (Hematoxylin and Eosin, 10x). **1B)** The small atrophic glands were lined by a monolayer of cuboidal epithelium. The large polygonal stromal cells (decidual cells) showed abundant eosinophilic cytoplasm and round nuclei with fine chromatin and an inconspicuous nucleolus. Nuclear atypia and mitoses were absent in both the stromal and the epithelial cells. (Hematoxylin and Eosin, 20x). **1C)** The epithelial cells were immunohistochemically positive for pan-cytokeratins (AE1/AE3) (strong; > 75% of the cells) (20x). **1D, 1E)** The epithelial and stromal cells were positive for ER (Fig. 1D; 20x) and PR (Fig. 1E; 20x). **1F)** Vimentin was strongly and diffusely positive in the stromal cells (20x).

subcutaneous adipose tissue. A peripheral fibrotic area represented part of the caesarean section scar. Histological examination (Fig. 1) revealed large stromal cells with abundant pale eosinophilic cytoplasm and round nuclei showing fine chromatin and an inconspicuous nucleolus. These cells were arranged in a nodular pattern, surrounding rare, small, atrophic glands lined by a monolayer of cuboidal epithelium. Nuclear atypia and mitoses were absent in both the stromal and the epithelial cells. The nodules were surrounded by a fibrotic rim, which was focally infiltrated by lymphocytes and pigmented macrophages. On immunohistochemical examination, the epithelial cells were positive for Cytokeratins (clone AE1/AE3, mouse monoclonal, Dako, Agilent Technologies, Santa Clara, CA, US) (strong; > 75% of the cells) and Estrogen receptor (ER) (clone SP1, rabbit monoclonal, Ventana Medical Systems, Tucson, AR, US) (moderate; 10–75%), less frequently for Progesterone receptor (PR) (clone 1E2, rabbit monoclonal, Ventana) (moderate; 10–50%). The stromal cells were positive for Vimentin (clone V9, mouse monoclonal, Ventana) (strong; > 75%) and PR (moderate; > 75%), less frequently for CD10 (clone SP67, rabbit monoclonal, Ventana) (strong; 10–50%) and ER (weak; 10–50%). The epithelial and stromal cells were negative for S100 protein (clone 4C4.9, mouse monoclonal, Ventana) and Calretinin (clone SP65, rabbit monoclonal, Ventana). A diagnosis of "subcutaneous endometriosis occurring in a caesarean section scar and showing progestational changes related to pregnancy" was made.

We searched for "((scar OR Pfannenstiel OR caesarean OR cesarean) AND (((endometriosis OR endometriotic OR endometrioma) AND (decidualized OR decidualize OR decidualization OR ((progestin OR progesterone OR progestins OR progestational OR progestinic OR hormones OR hormonal) AND (changes OR change OR effect OR effects)))) OR deciduosis OR deciduoma))" in Pubmed (all fields), Worldcat (all fields), Web of Science (Topic/Title) and Scopus (Title/Abstract/Keywords) databases. Relevant articles were obtained in full-text format and screened for additional references. The bibliographic research ended on January 5, 2019.

3. Discussion

According to a recent review, about 300 cases of cutaneous/subcutaneous endometriosis were reported [10].

Endometriotic foci may be sensitive to hormonal fluctuations and they could become clinically evident as nodules rapidly increasing in size [3–15]. This tumor-like presentation is due to intralesional hemorrhages for mucosal cleavage (as in eutopic endometrium), inflammation (lymphocytes, siderophages, etc.), decidualization and/or other secondary changes [3–9,11]. During pregnancy or hormonal therapy, decidualization could be extensive or involve only few endometriotic nodules in patients with multiple endometriotic implants [11,13].

Including our patient, only 8 subcutaneous cases of post-caesarean scar endometriosis showing pregnancy-related decidualization were described in literature (Table 1) [3–9]. Moreover, DeClerk et al. identified areas of decidualized endometriosis in a 3-cm nodule at the right side of a Pfannenstiel incision: the patient was a 31-year-old woman using norgestimate/ethinyl estradiol oral contraceptives [13]. Finally, it was not clear if the decidualization that occurred in 2 additional cases of post-caesarean scar endometriosis was pregnancy-related [14,15]. Gezer et al. removed a 3-cm nodule from a 33-year-old patient: it was not stated when the caesarean section had been performed [14]. Kilinç et al excised a 4-cm nodule associated with pain, pruritus and erythema: the patient was a 34-year-old woman that had undergone a caesarean section 1 year before [15].

According to our review, the age of the patients ranged from 22 to 36 years (mean age: 27.5 years) (Table 1).

Clinical data were sometimes scant, especially in 1 old case [9]. All the patients were multiparous and they had at least one caesarean section reported in their history [3–9]. In each case, the nodules were detected after the first caesarean section [3–9]. The interval from the first caesarean section to the clinical presentation was 6–36 months [4,6,8]: no information was available in 4 cases [3,5,7,9]. The endometriotic nodules became clinically evident during the subsequent pregnancy in 2 cases [5,8]. In our patient and in 4 additional cases, the nodule was discovered when the patient was not pregnant [3,4,6,7].

The size of the nodules ranged from 10 to 42 mm, increasing (3 cases) [6–8] or remaining stable (2 cases) [4,5] during pregnancy. One nodule was associated with cyclic pain, requiring systemic treatment [7]. Another patient reported a history of ovarian endometriosis [3].

In 6 cases, the surgical excision of the nodules was performed during a subsequent caesarean section [3–5,7,9]. The excision was partial in 1 case [3]. Before surgery, 3/6 endometriotic nodules were followed up for 2, 4 and 6 years respectively [3,4].

Fine-needle aspiration cytology (FNAC) favored a diagnosis of decidualized endometriosis in 2 additional cases [6,8]. Sections of the cell block revealed fragments of decidua in one case [8], while immunostains were performed directly on the cytological slides to confirm the diagnosis of decidualized endometriosis in the other case [6]. These 2 patients avoided the surgical excision of the nodules: the histologic confirmation of the FNAC diagnosis was not available [6,8]. Detailed follow-up information was not provided as well: one patient "*continued with her pregnancy*" after the FNAC procedure [8]. The other woman had been followed-up for 2 years before the FNAC diagnosis, but no data of

Table 1
Subcutaneous cases of post-caesarean scar endometriosis showing pregnancy-related decidualization: review of the literature.

Authors	Age (years)	Parity (n°)	Size (mm)	Interval from the 1st CS to the clinical presentation (months)	Clinical information	Treatment
Present case	33	2	10	36	The nodule was found after the 1st CS	Follow-up (4 years) + Excision at the time of the 2nd CS
Natale et al.: case 2 [3]	26	2	42	NR	The nodule was found after the 1st CS	Follow-up (6 years) + Partial excision at the time of the 2nd CS
Val-Bernal et al. [4]	36	2	21	12 (*)	The nodule was found after the 1st CS and it remained stable in size during the 2nd pregnancy	Follow-up (2 years) (*) + Excision at the time of the 2nd CS
Günal et al. [5]	24	2	30	NR	The nodule was found during the 2nd trimester of the 2nd pregnancy, remaing stable in size during the following gestational months	Excision at the time of the 2nd CS (40 weeks of gestation)
El-Gohary et al. [6]	24	2	30	6 (**)	The nodule was found after the 1st CS and it remained stable size for 2 years; then, it increased in size during the 2nd pregnancy (4th gestational month)	Follow-up (2 years) (**) + FNAC
Nogales et al. [7]	25	3	20	NR	The nodule was found after the 2nd CS and it was associated with cyclic pain. It increased in size during the 3rd pregnancy (after the 12th gestational week)	Danazol until the 3rd pregnancy. Biopsy during the 3rd pregnancy. Total excision at the time of the 3rd CS (38 weeks of gestation)
Berardo et al.: case 2 [8]	22	3	20	36 (***)	The nodule was found at the beginning of the 3rd pregnancy with a subsequent slow increase in size	FNAC (19th gestational week)
Pellegrini AE [9]	30	3	NR	NR	NR	Excision at the time of the 3rd CS

CS: Caesarean section; NR: Not reported; FNAC: Fine-needle aspiration cytology. (*): The 1st caesarean section was performed 3 years before the 2nd pregnancy; (**): The 1st caesarean section was performed 2.5 years before the 2nd pregnancy; (***): The previous caesarean sections were performed 3 and 6 years before the 3rd pregnancy, respectively.

the follow-up after that procedure were reported [6].

In patients with a history of endometriosis, a pregnancy-related increase in the size of a previously identified nodule could allow the clinicians to include decidualized endometriosis among the clinical suspects. However, the hormonal and immunological changes of pregnancy sometimes favor the development of benign or malignant tumors [1,3–11,14,15]. So, other non-tumoral lesions (granuloma, haematoma, abscess, fat necrosis, hernia, nodular and proliferative fascitis, etc.), benign neoplasms (lipoma, neuroma, desmoid tumor, etc.) or malignancies (carcinomas, melanoma, deciduoid mesothelioma, trophoblastic tumors, sarcomas, metastases, etc.) should be considered in the clinic-pathological differential diagnosis [1,3–11,14,15].

A misleading presentation of decidualized endometriotic implants can occasionally occur [3–12]. The following features could represent pitfalls for the clinical diagnosis: (1) extrapelvic localizations (as our case); (2) multiple endometriotic nodules; (3) hormone-related, tumor-like increase in the size of the endometriotic nodules (as they could be mistaken for malignant tumors); (4) nodules not increasing in size during the hormonal stimulation of pregnancy (because they could be mistaken for other non-tumoral lesions or benign/low-grade neoplasms not sensitive to hormonal fluctuations, as our case); (5) few of multiple nodules increasing in size during pregnancy; (6) no history of endometriosis (as our case); (7) no awareness of an ongoing pregnancy; (8) unavailable information regarding the presence and the size of the nodules before the beginning of the current pregnancy [3–12].

Diagnostic difficulties for general pathologists may include: (1) extrapelvic localizations (especially if the patient has no history of endometriosis or the anamnestic data are not furnished by clinicians); (2) inadequate material (as regards its quality and quantity) sent to the pathologist for cytological and/or histological examination; (3) histological evidence of endometrial stroma in the absence of glands (stromal endometriosis); (4) one or more concomitant secondary histological changes (tubal, mucinous, oxyphil, papillary syncytial, smooth muscle and other metaplasias, myxoid or signet ring changes, decidualization, calcification); (5) histological evidence of reactive or premalignant nuclear atypia; (6) malignant transformation (endometrioid and clear cell carcinoma, carcinosarcoma, endometrial stromal sarcoma) [11,12]. The absence of mitoses and nuclear atypia, the pushing borders of the lesion, the immunohistochemical profile and the data of the previous caesarean section supported our diagnosis. As regards the immunophenotype, CD10 is usually diffusely and strongly positive in the endometrial stromal cells but it could be focally positive (as in our case) [5]. In our case, PR was mainly expressed by the stromal cells, while ER was more diffusely positive in the epithelial cells: these findings may be due to the hormonal down-regulation of pregnancy [11,12,14,16]. Calretinin was performed to exclude deciduoid mesothelioma, S100 protein to rule out nerve or adipose tumors, as well as melanoma.

In conclusion, post-caesarean section scar endometriosis of the subcutis with pregnancy-associated stromal decidualization is a rare, sometimes misleading entity. Medical doctors (in particular, general practitioners, dermatologists and surgeons) should be aware of this condition, especially in case of an atypical presentation. In difficult cases, clinic-pathological correlation is essential and an immunohistochemical panel can help to avoid misdiagnoses. In pregnant patients, FNAC could represent a less-invasive aid, even if it could be not diagnostic. Surgical excision of superficial nodules provides more useful material for the pathological examination and it could be advised in the absence of contraindications or relevant risks.

Declarations of interest

None.

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References

[1] H. Bektaş, Y. Bilsel, Y.S. Sari, F. Ersöz, O. Koç, M. Deniz, B. Boran, G.E. Huq, Abdominal wall endometrioma; a 10-year experience and brief review of the literature, J. Surg. Res. 164 (2010) e77–81, https://doi.org/10.1016/j.jss.2010.07.043.

[2] I. Catalina-Fernández, D. López-Presa, J. Sáenz-Santamaria, Fine needle aspiration cytology in cutaneous and subcutaneous endometriosis, Acta Cytol. 51 (2007) 380–384, https://doi.org/10.1159/000325751.

[3] K.E. Natale, M.C. Royer, W.L. Rush, G.P. Lupton, Cutaneous deciduosis: a report of two cases of an unusual pseudomalignancy, J. Cutan. Pathol. 39 (2012) 777–780, https://doi.org/10.1111/j.1600-0560.2012.01907.x.

[4] J.F. Val-Bernal, D. Val, F. Gómez-Aguado, M.T. Corcuera, M.F. Garijo, Hypodermal decidualized endometrioma with aberrant cytokeratin expression. A lesion mimicking malignancy, Am. J. Dermatopathol. 33 (2011) e58–e62, https://doi.org/10.1097/DAD.0b013e3181f704f6.

[5] A. Günal, U. Keskin, G. Deveci, M.S. Deveci, M.C. Yenen, M. Dede, Tumor-like myxoid change in decidualized scar endometriosis of pregnancy: a case report and review of literature, Turk. Patoloji Derg. 25 (2009) 49–52.

[6] Y.M. El-Gohary, M.T. Garcia, P. Ganjei-Azar, Decidualized endometrioma diagnosed by fine needle aspiration citology: a case report with immunocytochemical confirmation, Diagn. Cytopathol. 37 (2009) 373–376, https://doi.org/10.1002/dc.21029.

[7] F.F. Nogales, F. Martin, J. Linares, R. Naranjo, A. Concha, Myxoid change in decidualized scar endometriosis mimicking malignancy, J. Cutan. Pathol. 20 (1993) 87–91.

[8] M.D. Berardo, P.T. Valente, C.N. Powers, Cytodiagnosis and comparison of non-decidualized and decidualized endometriosis of the abdominal wall, Acta Cytol. 36 (1992) 957–962.

[9] A.E. Pellegrini, Cutaneous decidualized endometriosis. A pseudomalignancy, Am. J. Dermatopathol. 4 (1982) 171–174.

[10] M. Stojanovic, D. Brasanac, M. Stojicic, Cutaneous inguinal scar endosalpingiosis and endometriosis: case report with review of literature, Am. J. Dermatopathol. 35 (2013) 254–260, https://doi.org/10.1097/DAD.0b013e3182726e09.

[11] D.V. Kazakov, O. Ondic, M. Zamecnik, K.V. Shelekhova, P. Mukensnabl, O. Hes, V. Dvorak, M. Michal, Morphological variations of scar-related and spontaneous endometriosis of the skin and superficial soft tissue: a study of 71 cases with emphasis on atypical features and types of müllerian differentiations, J. Am. Acad. Dermatol. 57 (2007) 134–146, https://doi.org/10.1016/j.jaad.2006.11.036.

[12] J. Wang, D.C. Strauss, C. Messiou, K. Thway, Endometriosis of extra-abdominal soft tissues: a tertiary center experience, Int. J. Surg. Pathol. 24 (2016) 497–503, https://doi.org/10.1177/1066896916644322.

[13] B.K. DeClerck, M.D. Post, J.A. Wisell, Cutaneous decidualized endometriosis in a nonpregnant female: a potential pseudomalignancy, Am. J. Dermatopathol. 34 (2012) 541–543, https://doi.org/10.1097/DAD.0b013e3182473172.

[14] E. Kaymaz Gezer, E. Ayhan Çınar, D. Gürsoy, A lesion mimicking malignancy in the cesarean scar: decidualize endometriosis, Kaohsiung J. Med. Sci. 32 (2016) 50–51, https://doi.org/10.1016/j.kjms.2015.12.003.

[15] N. Kilinç, A. Yalinkaya, M. Özaydin, Nondecidualized and decidualized endometriosis of the abdominal wall (A report of two cases secondary to cesarean section), Turk. J. Med. Sci. 32 (2002) 505–508.

[16] M.E. Coccia, F. Rizzello, A. Palagiano, G. Scarselli, The effect of the hormonal milieu of pregnancy on deep infiltrating endometriosis: serial ultrasound assessment of changes in size and pattern of deep endometriotic lesions, Eur. J. Obstet. Gynecol. Reprod. Biol. 160 (2012) 35–39, https://doi.org/10.1016/j.ejogrb.2011.10.004.