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Fertility preservation in women with ovarian endometriosis

Préservation de la fertilité en cas d'endométriose ovarienne

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Abstract. Endometriosis is one of the most frequently encountered benign diseases in gynecology [1]. It is the cause of pelvic pain (dysmenorrhea, dyspareunia) and infertility in more than 35% of women of reproductive age [1]. Complete resolution of endometriosis is not possible, but therapy has essentially three main objectives: to preserve and improve fertility; to reduce pain; and to delay recurrence for as long as possible [2]. The aim of this manuscript is to focus on fertility preservation in women with severe endometriosis.

Key words: endometriosis, surgery, endometrioma, fertility preservation, ovarian tissue cryopreservation, embryo and oocyte cryopreservation

Résumé. L'endométriose est l'une des maladies bénignes les plus fréquentes en gynécologie. Elle est responsable de douleurs pelviennes (dysménorrhée, dyspareunie), et d'infertilité chez plus de 35% des femmes en âge de reproduction. Une guérison complète de l'endométriose est souvent impossible mais sa thérapie comporte 3 objectifs principaux : préserver et améliorer la fertilité des patientes, réduire la douleur et limiter au maximum les récidives. Dans ce chapitre, nous passons en revue les options de préservation de la fertilité chez les patientes atteintes d'une endométriose sévère.

Mots clés : chirurgie, endométriome, préservation de la fertilité, cryopréservation du tissu ovarien, cryopréservation d'embryon et d'ovocyte

A model described by Wallace *et al.* enables the number of primordial follicles present in the ovary to be estimated at any given age *(figure 1)* [3]. They demonstrated that 95% of variation in the population of primordial follicles is attributable to age alone up to the age of 25 years [3, 4].

In ovarian endometriosis, the ovarian reserve could already be depleted in the lower part of the Y axis *(figure 1)* [5].

The ovarian reserve

Indeed, in a first paper published by our team in 2011 [5], we clearly established that follicular density was significantly lower in cortex from ovaries with endometriomas than in cortex from contralateral ovaries without cysts. Thus, the ovarian reserve may well be reduced in case of endometriomas, even before surgery. In a second paper [6], it was clearly shown by cleaved caspase-3 immunostaining that cortex from ovaries with endometriomas contained significantly more atretic early follicles than contralateral normal ovaries. Diameters of primordial follicles and oocytes were also found to be decreased in cortex from ovaries with endometriomas, whereas early follicles with proliferating cell nuclear antigen (PCNA)-positive granulosa cells were significantly increased in number.

In our opinion *(figure 2)*, the presence of an endometrioma (even if relatively small (≤ 4 cm)) induces local inflammation in ovarian cortex, which causes activation of follicular recruitment and atresia of early follicles. This observed "follicle burnout" is a strong argument for early diagnosis and surgical management [5, 6].

Very recently, Brosens *et al.* [7] corroborated this notion. They demonstrated that smooth muscle cell metaplasia and fibrosis observed in ovarian cortex close to an

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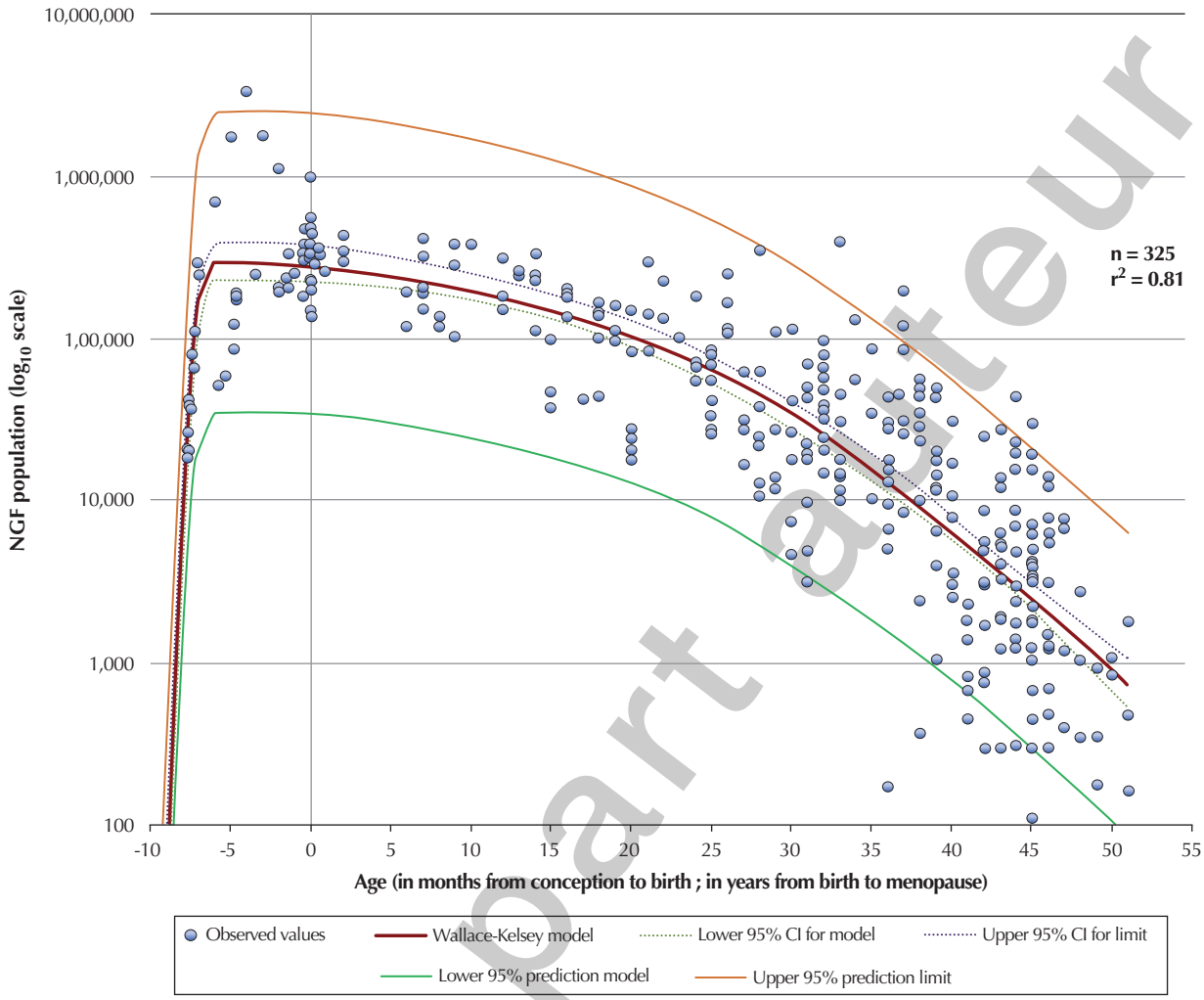

Figure 1. The ovarian reserve: the model that best fits histological data according to Wallace and Kelsey. The ovarian reserve is depicted throughout a woman's life, from conception to the age of 55 years: hypothetical ovarian reserve in women with ovarian endometriosis (according to Donnez *et al.*).
This figure is adapted from Wallace, W.H. and Kelsey, T.W. from *PLoS One* 27, e9772 (2010), published under an open-access license by PLoS.

endometrioma are also present in case of small endometriomas (< 3 cm). However, European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend that ovarian endometriomas < 3 cm in size should not be removed.

From recent studies [5-7], we can conclude that expectant management may not be the best choice, as the delay in treatment could lead to progression of inflammation and fibrosis, inducing early loss of follicles.

On the other hand, many papers [8-10] have clearly demonstrated a decline in anti-Müllerian hormone (AMH) after cystectomy, but we believe the technique itself is responsible for this follicle loss.

Prevention: how to keep the ovarian reserve intact

Laparoscopic management of endometriomas using a combined technique of excisional and ablative surgery

The most widely performed surgery for ovarian endometriosis is cystectomy, but there are some concerns. Indeed, excessive surgery may lead to normal ovarian tissue destruction, whereas incomplete surgery could be associated with a higher risk of recurrence in non-experienced hands [11-13]. Muzii *et al.* [14, 15] were one of the first teams to demonstrate the presence of

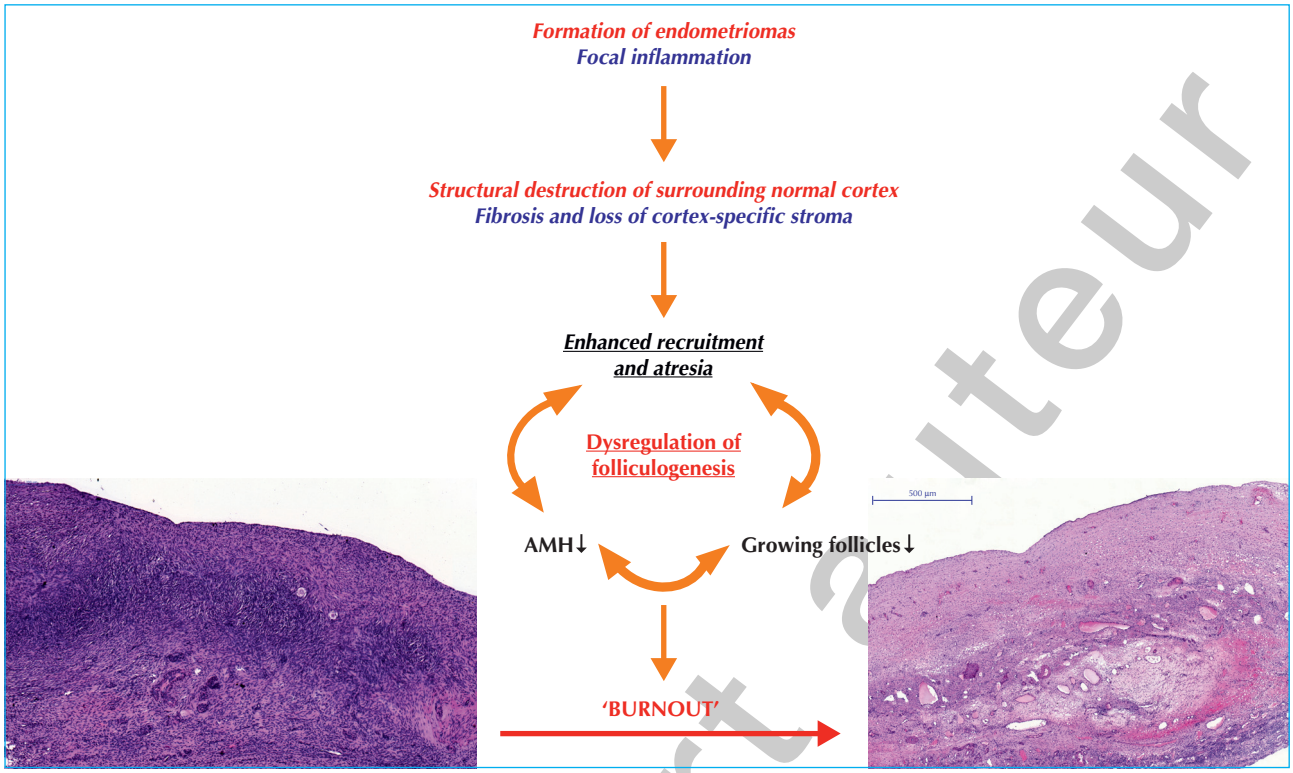

Figure 2. Burnout hypothesis.

primordial, primary and secondary follicles in 69% of cases (especially close to the ovarian hilus), while Donnez *et al.*, as far back as 1996, already stressed that the plane of cleavage of endometriomas was in fact a pseudo-plane as, histologically, the endometrioma capsule was stuck to ovarian tissue where primordial follicles are located [11].

Since 1996, numerous papers have described a low ovarian reserve after laparoscopic cystectomy for endometriomas. Indeed, normal ovarian tissue is very frequently excised together with the endometrioma wall [15-21], and two meta-analyses [8, 10] have also demonstrated that AMH levels decline significantly after cystectomy.

Ovarian surgery for endometriosis should therefore be performed by experienced surgeons in order to both preserve and improve fertility, especially because the ovarian reserve could already be depleted [22].

In case of severe recurrent pelvic endometriomas, normal residual ovarian tissue and/or ovarian vascularization may be compromised by previous surgery. Ovarian tissue preservation should therefore be considered in these patients with seriously impaired fertility, particularly before any treatment carrying a high risk of ovarian endometriosis recurrence [23].

Cystectomy versus ablation

There are two main risks associated with surgical management of endometriomas:

– the risk of excessive surgery (removal or destruction of normal ovarian cortex together with the endometrioma);

– the risk of incomplete surgery (with subsequent early recurrence of endometriomas).

Depending on the risk, two techniques are currently used, with both advantages and disadvantages: either cystectomy involving removal of the endometrioma wall, or ablative surgery that entails opening the endometrioma and destroying the internal cyst wall by laser vaporization or bipolar coagulation.

Ablative surgery may prove difficult because of the thickness and hypervascularization of the cyst wall. A Cochrane Review reported a higher rate of recurrence after ablative surgery than cystectomy [13]. On the other hand, recent data in the literature appear to indicate that excisional surgery of endometriomas may be deleterious for ovarian function, causing ovarian trauma and removal of follicles [8-10, 15-21].

In view of these data, we set out to develop a new approach that combines the techniques of cystectomy and ablative surgery, in order to take the best elements from both, while avoiding the corresponding risks

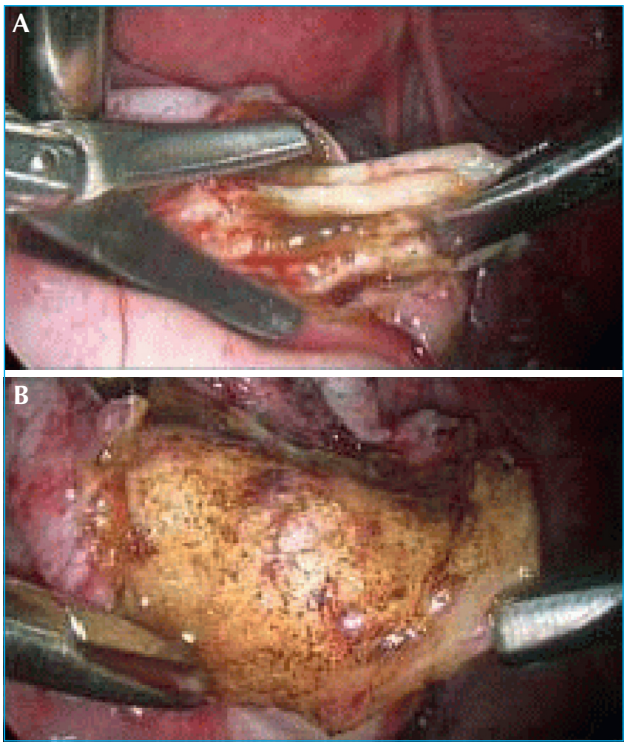

Figure 3. The combined technique. **A)** Stripping and excision allows removal of 80% of the cyst; **B)** The ablative technique (here CO_2 laser) is used to vaporize the remaining 20%.

(excessive surgery or incomplete surgery respectively) [12]. In this approach, illustrated in *figure 3*, a large part of the endometrioma is first excised according to the cystectomy technique. The endometrial cyst is opened and washed out with irrigation fluid. After identifying the correct plane of cleavage between the cyst wall and ovarian tissue by applying opposite bimanual traction and countertraction with two grasping forceps, providing strong but non-traumatic force, the inner lining of the cyst is stripped from the normal ovarian tissue. When approaching the hilus, where the ovarian tissue is more functional, partial cystectomy is performed by resecting the excised tissue with scissors *(figure 3A and B)*. The stripping technique allows removal of 80-90% of the cyst. If the excision provokes bleeding or the plane of cleavage is not clearly visible, the cystectomy is stopped because of the risk of removing normal ovarian tissue containing primordial, primary and secondary follicles along with the endometrioma. After this first step (partial cystectomy), CO_2 laser is used to vaporize the remaining 10-20% of the endometrioma close to the hilus *(figure 3B)*. Care must be taken to vaporize all the residual cyst wall in order to avoid recurrence.

The combined technique was feasible in all cases in a first series [12]. The volume of the ovary after this approach was similar to that of the contralateral normal ovary, as well as that observed in infertile women without endometriosis presenting for male factor infertility. Antral follicle count (AFC) on days 2-5 showed the same number of antral follicles *(table 1)* [12]. Histopathology of the excised part of the endometrioma revealed the presence of follicles in only one case (2%), proving that away from the hilus, follicles are infrequently found [12].

In conclusion, ablative techniques (CO_2 laser [11, 12, 21-23], plasma jet [25, 26], bipolar coagulation [27]) have proved less deleterious for the ovarian reserve, even if a slightly increased risk of recurrence has been observed after ablation (*versus* cystectomy) in some studies.

We nevertheless consider that an ovary with a small recurrent endometrioma is more functional in terms of fertility than an ovary without follicles or a diminished ovarian reserve.

The combined technique appears to incorporate the best results of the stripping technique in terms of recurrence outcomes, since most of the cyst wall is excised, and the ablation technique, since the hilus area of the ovary is spared from surgical damage.

Embryo and oocyte cryopreservation

Only a small fraction of patients at risk of premature ovarian failure (POF) are referred to specialists to discuss fertility preservation options; of this number, only a few women actually undergo fertility preservation due to social, economic or technical hurdles [28, 29]. In addition, women are increasingly postponing childbearing to later

Table 1. Ovarian volume and antral follicle count (AFC) six months after surgery in women treated for endometriomas by the combined technique and women of similar age with normal ovaries and regular ovulatory cycles presenting for IVF because of male factor infertility.

	Ovarian volume (cm^3)	Antral follicle count (AFC)
Combined technique ($n = 31$)	7.64 ± 2.95	6.1 ± 3.2
Women without endometriosis ($n = 20$)	7.99 ± 5.33	6.2 ± 4.8

in life for social or financial reasons, while the incidence of most cancers increases with age *(table 2)*.

Fertility preservation, in the context of treating cancer or benign diseases or for social reasons *(table 2)*, will be a major challenge over the next 5 years [30].

Table 2. Indications for cryopreservation of ovarian tissue in case of malignant and non-malignant disease.

Malignant pathology
- Systemic diseases
  - Hodgkin's disease
  - Non-Hodgkin's lymphoma
  - Leukemia
  - Medulloblastoma
- Extrapelvic diseases
  - Bone cancer (osteosarcoma, Ewing's sarcoma)
  - Breast cancer
  - Melanoma
  - Neuroblastoma
  - Bowel malignancy
- Pelvic diseases
  - Non-gynecological malignancy
    - Pelvic sarcoma
    - Sacroblastoma
    - Rhabdomyosarcoma
    - Rectosigmoid tumor
  - Gynecological malignancy
    - Early cervical carcinoma
    - Early vaginal carcinoma
    - Early vulvar carcinoma
    - Selected cases of ovarian carcinoma (stage IA)
    - Borderline ovarian tumor

Non-malignant pathology
- Unilateral or bilateral oophorectomy
  - Benign ovarian tumor
  - Severe and recurrent endometriosis
  - BRCA1 or BRCA2 mutation carrier
- Risk of premature menopause
  - Turner syndrome
  - Family history
  - Benign diseases requiring chemotherapy: autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Behçet's disease, Wegener's granulomatosis)
- Bone marrow transplantation
  - Benign hematological diseases: sickle cell anemia, thalassemia major, aplastic anemia
  - Autoimmune diseases unresponsive to immunosuppressive therapy

Social reasons
- Age of the patient
- Childbearing postponed to later in life for social or financial reasons

Source: Adapted from *Human Reprod Update* (2006) and from *Nature End Rev* (2013).

Currently, embryo and mature oocyte cryopreservation following *in vitro* fertilization (IVF) are the only methods endorsed by the American Society for Reproductive Medicine (ASRM). However, in the opinion of many pioneers, enough evidence now exists to support the technique of ovarian tissue cryopreservation and stop considering it an experimental and investigational approach [31].

Embryo cryopreservation (for review see Cakmak and Rosen [32])

Embryo cryopreservation is a well established procedure that can be applied to preserve fertility in women of reproductive age with an available partner (or women using donor sperm). This technique has proved safe and effective in patients undergoing IVF treatment and is proposed for different clinical reasons: storage of supernumerary embryos, risk of ovarian hyperstimulation syndrome (OHSS), impaired endometrial development, impractical embryo transfer, etc.

Both slow-freezing and vitrification techniques offer good results in experienced hands and their use is becoming more widespread, especially for blastocyst cryopreservation.

Embryo cryopreservation has reliable success rates and a very recent meta-analysis by Roque *et al.* [33] suggests that frozen embryo transfer is more successful than fresh embryo transfer, probably due to improved embryo-endometrium synchrony. There are no randomized controlled trials evaluating the impact of cryopreservation on the health of children born, but outcome data after frozen embryo transfer are generally reassuring.

Oocyte cryopreservation (for review see Cobo et al. [34])

The introduction of vitrification into assisted reproduction technology has yielded female gamete (oocyte) cryopreservation outcomes similar to those obtained with fresh oocytes. Among the main cryobiology strategies (slow-freezing and vitrification), vitrification was found to be very effective for avoiding crystallization, thus reducing damage to cells caused by ice crystal formation and chilling injury during the freezing process.

Evidence from recent studies demonstrates that the meiotic spindle is able to restore itself, ensure proper chromosome segregation and generate embryos from either slow-frozen or vitrified oocytes.

Two reviews [34, 35] concluded that slow-freezing of mature oocytes yields low survival rates compared to vitrification and that resultant embryo development appears impaired, with outcomes favoring vitrification. Although direct contact with liquid nitrogen is controversial, open systems seem to be more efficient than currently available closed systems, at least for oocytes.

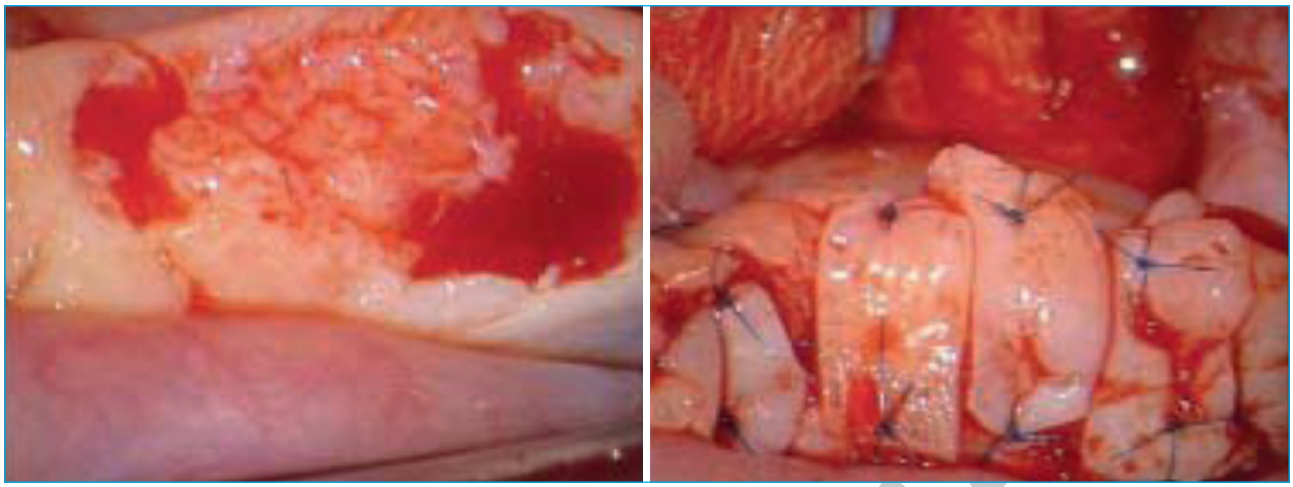

Figure 4. Techniques of orthotopic frozen-thawed ovarian cortex reimplantation. Ovarian tissue was reimplanted onto the remaining ovary after removal of the native cortex. In most cases, large strips of ovarian tissue were attached to the decorticated medulla with stitches.

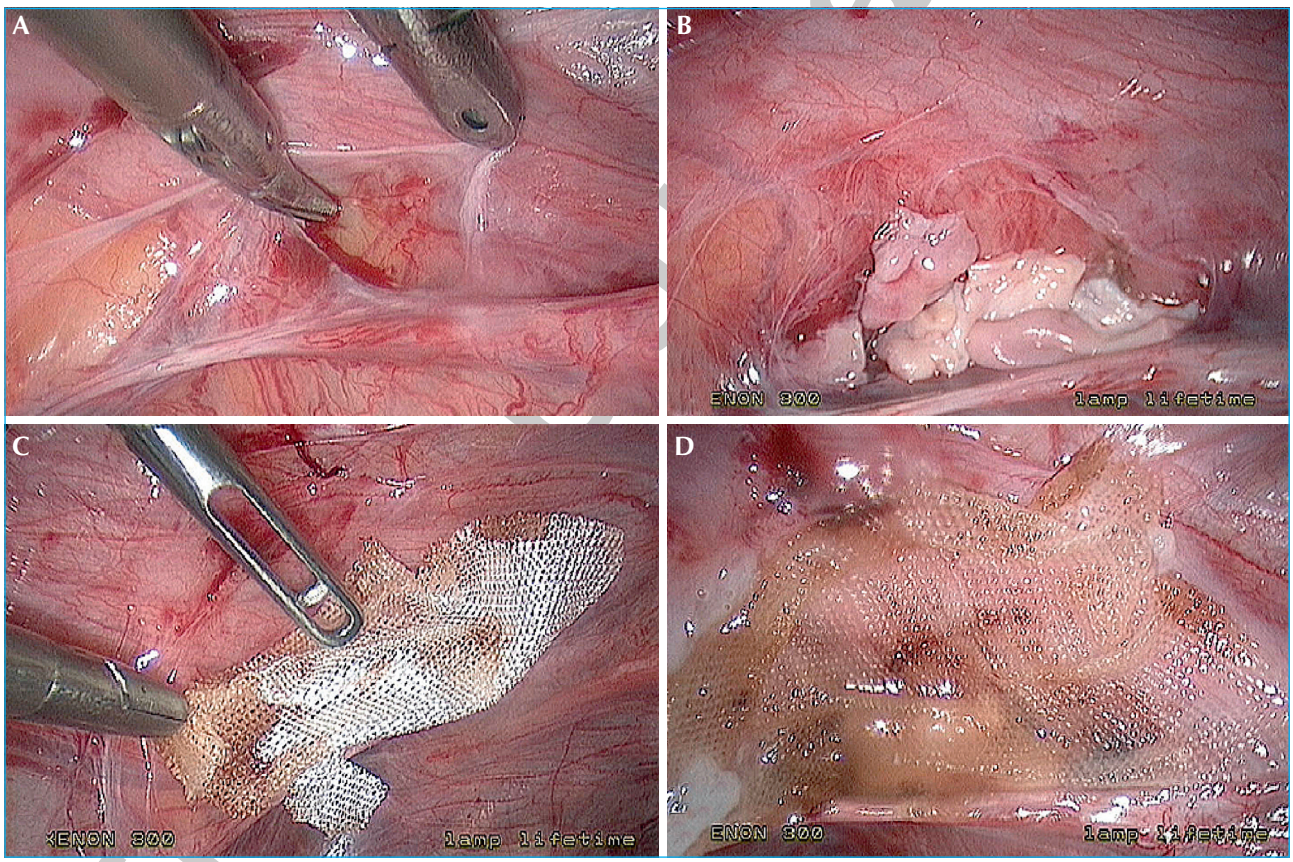

Figure 5. Surgical procedure. **A)** Creation of the peritoneal window in the anterior leaf of the broad ligament; **B)** Frozen-thawed ovarian fragments are placed in the peritoneal window; **C, D)** The ovarian cortical pieces are then covered with Interceed (Johnson and Johnson).

A recent investigation by Cobo *et al*. [33] showing an overall survival rate of 92.5% and ongoing pregnancy rate of 43.7% confirms the efficacy of oocyte vitrification.

Moreover, the incidence of congenital anomalies was not found to be increased in children born after oocyte cryopreservation compared with those conceived naturally [36, 37].

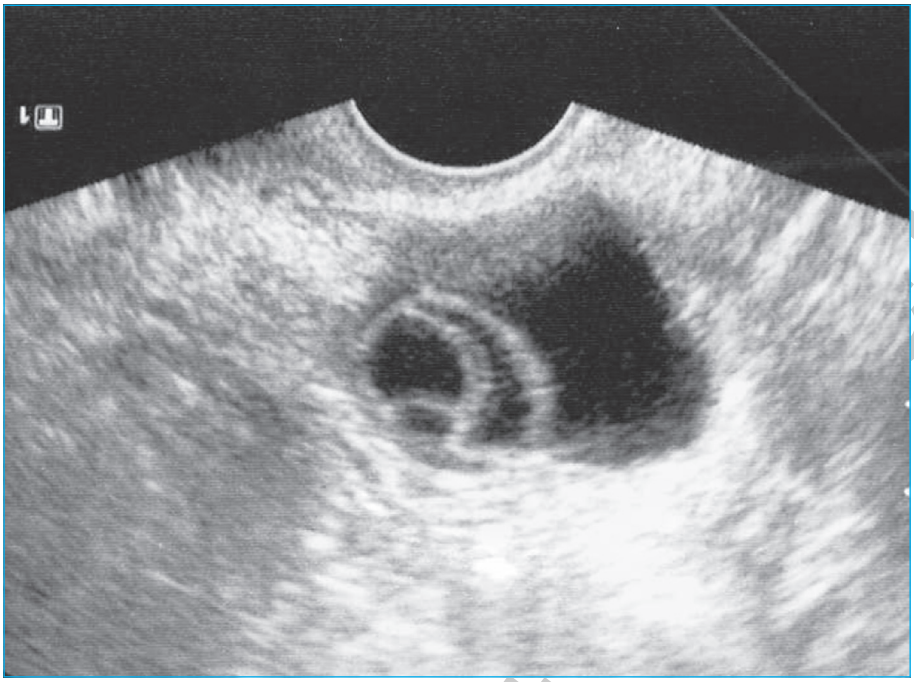

Figure 6. Ultrasonography of the broad ligament during the fifth ovarian stimulation attempt. Four follicles (26, 18, 15 and 9 mm in size) were observed on day 13.

Nevertheless, it should be stressed that 20 oocytes are required to have a 90% chance of having a baby.

In case of risk of POF, a combination of oocyte cryopreservation and ovarian tissue cryopreservation could increase the efficacy of the fertility preservation procedure and give patients an improved chance of future fertility [38].

Ovarian tissue cryopreservation

As fertility preservation is a priority in the treatment of endometriosis in patients at risk of impaired future fertility, cryopreservation of healthy ovarian tissue during surgery may be an option in case of severe endometriosis [29]. Recently, Donnez *et al.* described the first live birth after transplantation of frozen-thawed tissue after bilateral oophorectomy for endometriosis [39].

In our department, cryopreservation of ovarian tissue is proposed for various benign diseases, including severe endometriosis *(table 1)*. The age of the patient should be taken into consideration, since the follicular reserve of the ovary is age-dependent. Because a decline in fertility is now well documented after the age of 35 years, the procedure should probably be restricted to patients below this limit [28, 29, 31].

The aim of this strategy is to reimplant cortical ovarian tissue into the pelvic cavity (orthotopic site), or a heterotopic site like the forearm or abdominal wall in case of POF, in patients with severe and recurrent endometriosis. Since the first live birth back in 2004 [40], orthotopic transplantation of cryopreserved ovarian cortical fragments has been successfully used to restore ovarian function, resulting in > 35 live births to date [29, 31].

Transplantation of cryopreserved ovarian tissue

Orthotopic transplantation technique (for review see [28, 29])

Two techniques of orthotopic reimplantation (namely in the pelvic cavity) are available; which one is used depends on whether or not the patient still has an ovary. If an ovary is present, pieces of thawed ovarian cortex are fixed to the medulla after decortication of the ovary *(figure 4)*. If no ovary is present, the ovarian pieces are placed in a peritoneal window in an area where some small retroperitoneal vessels are visible *(figure 5)*. In our opinion, the pelvic cavity (orthotopic site) provides the optimal environment for follicular development compared with heterotopic sites, as temperature, pressure, paracrine factors and blood supply are more akin to those observed in a physiological situation. Even if transplanting ovarian tissue to heterotopic sites has some advantages, only one pregnancy has been reported following this procedure, making this approach somewhat questionable [41].

Transplantation results

So far, more than 35 live births have been described after orthotopic reimplantation of cryopreserved ovarian

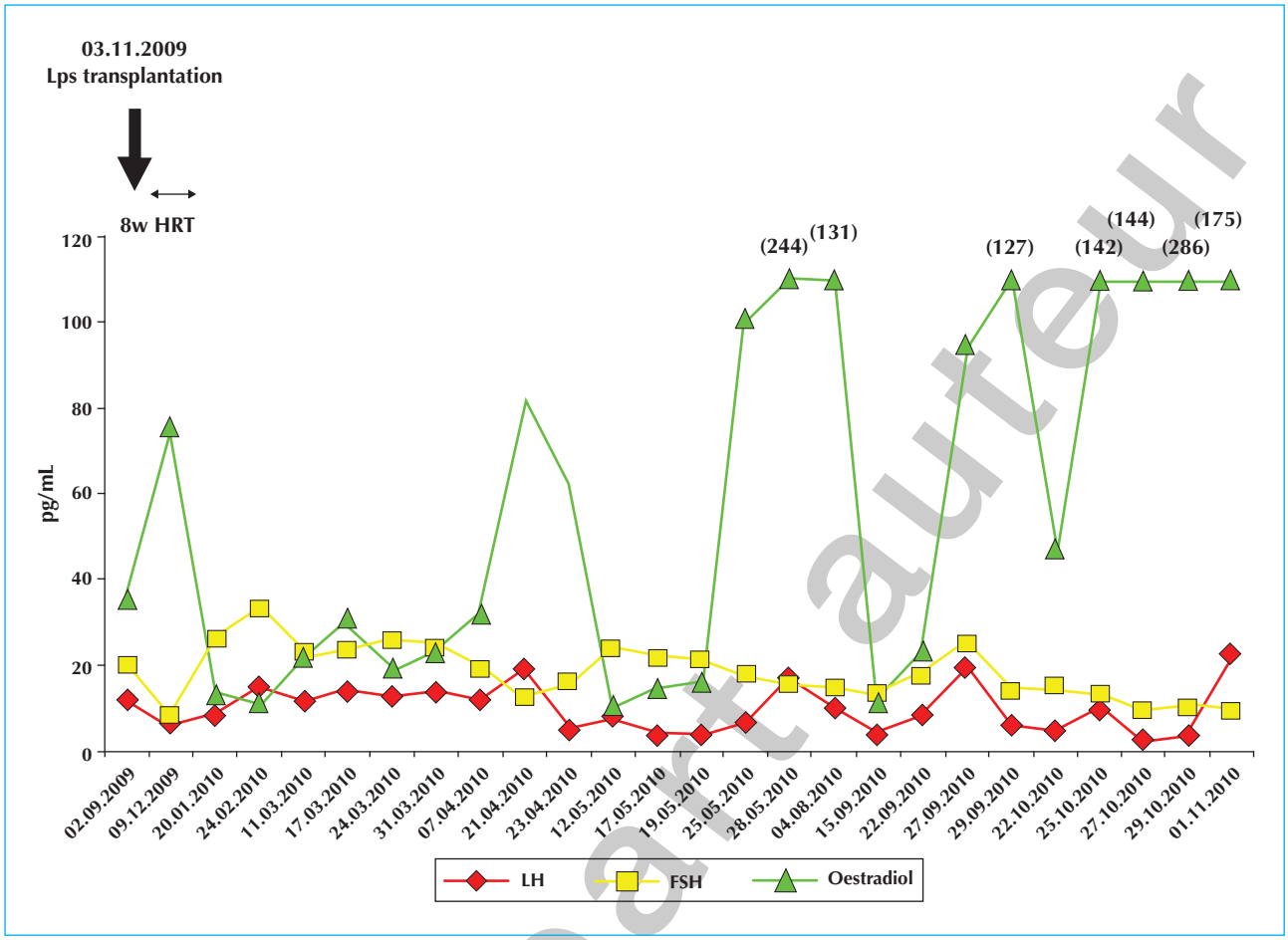

Figure 7. FSH, LH and 17-b estradiol concentrations before and after reimplantation of cryopreserved ovarian tissue.

tissue [28, 29, 31, 42]. Unfortunately, the number of reimplantations performed worldwide (the denominator) is not known. Results from three centers (in Denmark, Spain and Belgium) were collected to evaluate a series of 60 cases of orthotopic reimplantation [31]. Of the 60 patients, 51 had a follow-up of > 6 months. Of these women, 11 (21%) became pregnant and six have already delivered 12 healthy babies (follow-up 1–10 years). Restoration of ovarian activity was observed in 93% of the patients. In three patients, the absence of primordial follicles in their cryopreserved grafted tissue explained why ovarian function was not restored, highlighting the importance of evaluating follicular density before taking the decision to reimplant ovarian tissue. Restoration of ovarian activity occurred between 3.5 months and 6.5 months after grafting. This finding is consistent with follicle growth from the primordial to the antral stage, although some variations were observed that were mainly attributable to differences in follicular reserve at the time of cryopreservation [31].

First live birth after ovarian tissue cryopreservation and grafting in case of severe endometriosis [39]

The first pregnancy to occur after bilateral oophorectomy and ovarian cortex cryopreservation and grafting for benign ovarian pathology (recurrent bilateral abscesses on endometriomas) was reported in 2012 [39].

A number of papers have shown reduced AMH levels, a sign of decreased ovarian reserve, after ovarian cystectomy for endometriomas, especially in larger and bilateral cysts [8-10]. In young patients facing the prospect of such treatment, it may be wise to discuss fertility preservation options before the procedure.

Removal of ovarian cortex for cryopreservation can easily be performed during the surgical procedure. In case of endometriosis, one should bear in mind that the ovarian reserve may be reduced due to structural anomalies. Indeed, two of our studies showed lower follicular density in non-involved ovarian cortex of endometriotic ovaries [5, 6]. In case of severe pelvic inflammatory disease (PID)

and technically difficult surgery, freezing of a piece of ovarian cortex is also recommended. Despite it possibly being less successful than for oncological indications (because of the presenting ovarian pathology [5, 6]), a recently published case shows that it is worthwhile for endometriosis patients, especially if it is the only fertility preservation option available [39].

This was the first time that pregnancy was achieved after ovarian cryopreservation and grafting following bilateral oophorectomy. After the first reports of live births after transplantation of frozen-thawed ovarian cortex [39], doubts were cast on the validity of the procedure, and possible reactivation of the remaining native ovary was suggested. In our patient, both ovaries were completely removed at the time of surgery. Moreover, the frozen-thawed ovarian cortex was transplanted to the anterior leaf of the broad ligament *(figure 5)*, and follow-up by ultrasound clearly showed follicular development in the area of transplantation *(figure 6)*. Serum levels proved restoration of ovarian activity *(figure 7)*. This case therefore provides definitive proof that pregnancy can occur from transplanted ovarian cortex.

Conclusion

With respect to fertility preservation, the most important concern in endometriosis-associated infertility is ovarian surgery. Because surgery has to be effective (decrease the risk of recurrence) and protective (avoid normal ovarian tissue destruction), a new surgical procedure was proposed. The technique combines the best results of the stripping technique in terms of recurrence outcomes, since most of the cyst wall is excised, and the ablation technique, since the hilus area of the ovary is spared from surgical damage.

In the presence of severe endometriosis and/or recurrent endometriomas, normal residual ovarian tissue and/or ovarian vascularization may be compromised. In case of radical treatment (oophorectomy) in particular, but also conservative treatment as there is a risk of recurrence, oocyte vitrification and preservation of ovarian tissue should be considered alongside the procedure.

Disclosures : the authors have nothing to disclose.

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