FERTILITY PRESERVATION IN WOMEN WITH CERVICAL CANCER

ABSTRACT

Fertility preservation in women with cervical cancer is a demanding but evolving issue. Some remarkable achievements have been reached, in particular the improvement of primary and secondary prevention and the broadening of the indications for conservative surgery up to FIGO 2018 stage IB2. Natural pregnancy rate and the rate of obstetrics complications following conservative approach is satisfactory even if not optimal. On the other hand, the use of classic strategies for fertility preservation such as oocytes or ovarian cortex freezing is extremely limited, being the uterus compromised by treatment in a high proportion of cases. In fact, the availability of uterine surrogacy can play a role in the counseling and the decision-making process. The recent advent of uterus transplantation is fascinating but, at present, cannot be viewed as a realistic solution.

Key words: cervical cancer / fertility preservation / oocyte / surrogacy / uterus transplantation

INTRODUCTION

International guidelines recommend that patients with cancer should discuss with a specialist the possible consequences of their disease and its treatment on future fertility (Oktay et al., 2018; Ethics Committee of the ASRM, 2018). Together with fertility sparing surgical techniques, embryo/oocytes cryopreservation is a valid option to allow patients to preserve fertility. Although less investigated or validated, ovarian cortex cryopreservation, ovarian transposition and pharmacological protection of the gonads also deserve consideration (Oktay et al., 2018; Ethics Committee of the ASRM, 2018; Practice Committee of the ASRM, 2018).

Fertility preservation in cervical cancer represents a challenging issue (Boutas et al., 2014; Ghadjar et al., 2015; Sato et al., 2016; Tomao et al., 2016; McKenzie et al., 2018; Taylan and Oktay, 2019; Rosa et al., 2020; Floyd et al., 2020). Up to now, in patients interested in future pregnancies and with limited disease, the mainstay of clinical management has been centered in avoiding hysterectomy. Nonetheless, the scenario is more complex and multifaceted. Combined chemo-radiation or chemotherapy followed by surgery +/- chemotherapy can be used in patients with more advanced disease (Bhatla et al., 2018), but chemotherapy can harm the ovarian reserve and radiotherapy may impair the capacity of the uterus to bear a pregnancy. Ovarian transposition before radiotherapy may reduce follicle loss but, concomitantly, it distorts the pelvic anatomy and can interfere with natural fertility.

In this narrative review, we will discuss the several and intricate aspects of fertility preservation in women with cervical cancer. The ultimate aim is providing physicians with a complete and up-to-date vision of the topic in order to facilitate counseling and to consent affected patients to take wise, informed and shared decisions.

EPIDEMIOLOGY OF CERVICAL CANCER

Cervical cancer has a peculiar age-related incidence pattern: it increases rapidly with a peak at 40-50 years of age, followed by a plateau and a subsequent variable decline (Gustafsson et al., 1997). The age at peak incidence varies according to different countries, in relation to the different socioeconomic conditions. The presence of an early peak reflects Human Papilloma Virus (HPV) infection and persistence, a necessary condition to develop cervical cancer (Gustafsson et al., 1997). Overall, a large proportion of women are actually diagnosed during reproductive age, when they may have not yet fulfilled their wishes of motherhood.

The introduction of HPV screening programs and vaccination has led to a reduction in the incidence of cancer precursors and invasive lesions. A study conducted in England in 2019 has estimated that HPV testing resulted in increased detection of grade 3 cervical intraepithelial neoplasia and cervical cancer by approximately 40% and 30%, respectively, compared with liquid based cytology (Rebolj et al., 2019). A recent analysis conducted in UK has estimated that primary HPV testing could result in a 24% reduction of cervical cancer cases (Castanon et al., 2017).

Regarding vaccination, in 2007 Australia was one of the first countries to adopt a systematic program, reaching a high coverage in the target population. This has led to a substantial decrease in high grade cervical abnormalities in young women 3-5 years after vaccination (Tabrizi et al., 2012). According to a recent systematic review including 13 articles, the incidence of high grade intraepithelial lesions was decreased by 51% (Relative Risk-RR=0.49, 95%CI: 0.42-0.58) after 5-9 years of vaccination among screened girls aged 15-19 years and by 31% (RR=0·69, 95%CI: 0.57-0.84) among those aged 20-24 years (Drolet et al., 2019).

CONSERVATIVE SURGICAL TREATMENT

Standard treatment for patients with early stage cervical cancer is hysterectomy with pelvic lymphadenectomy (Sonoda et al, 2004). However, given that an increasing number of patients receive their diagnosis during childbearing age, fertility sparing surgery is becoming more common for patients with FIGO 2018 stage IB1 (tumor less <2 cm in greatest dimension) (Tomao et al., 2016; Bhatla et al., 2019; Feng et al., 2019; Machida et al., 2020). In a recent systematic review including more than 3,000 women treated conservatively, Bentivegna et al. found encouraging oncological outcomes with a recurrence rate <4% and a mortality rate of 1.2% (Bentivegna et al., 2016a). A recent independent but similar meta-analysis included a similar number of cases and confirmed these findings (Nezhat et al., 2020). Finally, in another subsequent meta-analysis exclusively focusing on women with Stage IA1 and IA2, progression free survival and overall survival were 99% and 98%, respectively, and fertility sparing surgery did not emerge as a risk factor for survival (Feng et al., 2018). Subsequent and more recent studies not included in these meta-analyses are in line with these findings (Matsuo et al., 2019; Gil-Ibanez et al., 2020)

Cervical cancer is known to spread locally to vagina, parametria and lymph nodes (LN). The negativity of pelvic LN is the first step to assess the feasibility of fertility sparing management. The risk of LN involvement increases with stage: this risk in stage IA1 without lymphovascular space invasion (LVSI) is less than 1%. Hence, in these cases, conization alone with negative cervical margins may represent a definitive treatment. For patients with stage IA1 and LVSI, pelvic LN dissection is recommended. For these patients, some Authors consider simple/radical trachelectomy as an option (Cibula et al., 2018; Marth *et al.*, 2018). Radical trachelectomy implies the excision of the entire cervix with the surrounding parametria, proximal to the cervical isthmus and then the suture of the uterus to the vagina; conversely, simple trachelectomy does not include parametria excision.

For stages IA2 to IB1, positivity of LN increases from 5%-7% up to 16%. In stage IA2, conization alone can be considered curative in case LVSI is negative. Radical or simple trachelectomy is an option for patients with positive LVSI, after assessment of negative nodal status (Cibula et al., 2018; Marth *et al.*, 2018)

According to ESGO guidelines, for stage IB1 tumors with negative nodes, radical trachelectomy is recommended in women wishing to preserve their fertility. It must be noted however that the risk of parametrial involvement in these cases is estimated to range between 0.4 and 0.6% (Wright et al, 2007; Frumovitz et al 2009; Reade 2013), thus these patients might benefit from a less radical approach, such as simple trachelectomy or conization, with a lower surgical and obstetrics morbidity (Tomao et al., 2017).

It has also been suggested that tumors between 2 and 4 cm (FIGO 2018 IB2) can be treated with neoadjuvant chemotherapy followed by conization or simple/radical trachelectomy (Pareja et al 2015; Tomao et al., 2016; Tesfai et al., 2020; Zusterzeel et al., 2020). Reported outcomes are comparable to those observed after standard treatment (recurrence rate 8.5%) (Fokom Domgue and Schmeler 2019). However, conservative surgical treatment for patients with IB2 tumors should be still considered experimental. More robust evidence on the best therapeutic options for conservative management will probably become available with the publication of the results of some pivotal ongoing trials (ConCerv, SHAOE, GOG278, CONTESSA).

NATURAL FERTILITY AFTER CONSERVATIVE SURGERY

The cervix plays a crucial role in defending the upper genital tract from infections. However, it also has an active role in ensuring fertility (Harris-Glocker and McLaren, 2013). The modification of the cervical mucus with sex steroids fluctuations functions as a gatekeeper, allowing spermatozoa to overcome this functional barrier only when ovulation approaches. In addition, the cervix has a role of sperm reservoir so that during the days preceding ovulation spermatozoa can be stored and gradually released to better cover the time of ovulation (Harris-Glocker and McLaren, 2013). On these bases, one may foresee that cervical cancer as well as its treatments could impair natural fertility. To note, a recent population-based study showed that cervical cancer was associated to the lowest chance of subsequent pregnancy compared to other tumors (Standardized Incidence Ratio-SIR=0.34, 95%Confidence Interval-CI: 0.31-0.37) (Anderson *et al.*, 2018).

On the other hand, it is essential to emphasize that this latter epidemiological evidence is too crude to draw definite information because it does not account for the desire of motherhood. Pregnancy rates have to be calculated with patients that attempted pregnancy after treatment as denominator. A first systematic review of the literature showed that among women with a history of stage I cervical cancer who attempted to become pregnant, 55% conceived, of whom 70% achieved a live birth (Bentivegna *et al.*, 2016b). The highest fertility rate (77%) and live birth rate (76%) were observed among women treated with neoadjuvant chemotherapy prior to surgery while the poorest outcome was documented in patient who underwent abdominal laparotomic radical trachelectomy (fertility rate of 44% and live birth rate of 68%) (Bentivegna *et al.*, 2016b). Simple trachelectomy or cone resection, Dargent procedure and laparoscopy-assisted radical trachelectomy gave intermediate results, the latter ~~latest~~ being the most promising. A second and more recent systematic review that included a similar number of cases generally confirmed these findings: conception rate was 55% and live birth rate 67%. Simple trachelectomy and radical vaginal trachelectomy were associated with higher rates of conception (Nezhat et al., 2020). However, this evidence comes from non randomized comparisons and has thus to be interpreted with caution. Of additional relevance here is that conservative surgery for cervical cancer is demanding and requires utmost expertise. For instance, in experience hands, radical vaginal trachelectomy was associated with a valuable pregnancy rate of 66%, that could be even higher if one considers that 20% of that cohort was already infertile before being diagnosed with cancer (Speiser *et al.*, 2011).

In the shared-decision making process leading to the choice of the most suitable therapeutic option for each woman, attention should be given to oncologic prognosis and desire of motherhood, but also to non-oncological aspects that may influence the fertility prognosis, including parity, age, ovarian reserve and inclination to egg donation. In addition, women should receive realistic and transparent information regarding the chances of live births after treatment. If possible, local Institutional data rather than evidence from the literature should be provided.

OBSTETRICAL COMPLICATIONS AFTER CONSERVATIVE SURGERY

When deciding to treat women of reproductive age conservatively, every effort should be made to balance the best reproductive and pregnancy outcomes with the oncological safety (Bentivegna *et al*., 2016b). Surgical procedures might cause the removal of a substantial portion of cervical connective tissue, thereby weakening the supportive function of the cervix as pregnancy progresses (Bevis *et al*., 2011). In addition, a shorter or absent cervix is less effective against ascending bacteria, thus facilitating intrauterine infections during pregnancy and subsequent preterm premature rupture of membranes (pPROM) (Robova *et al*., 2015).

According to a recent meta-analysis, the RRs (95%CI) for preterm birth among women treated with large loop excision or cold-knife conization were 1.7 (95%CI: 1.2-2.4) and 2.6 (1.8-3.7), respectively. A significantly higher risk of low birth weight (LBW) infants was also noted after both procedures (Kyrgiou *et al*., 2016). To note, the risk of preterm birth increased with increasing cone depth (and volume) and for techniques that remove or destroy larger parts of the cervix (Arbyn *et al*., 2008). However, a clear threshold of excision above which the risk of preterm birth becomes clinically relevant could not be drawn. Future investigation is needed to better define the population at greatest risk for preterm birth.

According to the meta-analysis of Bentiveglia *et al*. (2016b), the incidence of preterm birth may differ according the therapeutic approach chosen, being close to normality (15%) for women treated with simple trachelectomy or cone resection as well as for those treated with neoadjuvant chemotherapy. The rate was conversely higher for the Dargent procedure (39%), laparoscopy-assisted radical trachelectomy (50%) and laparotomic radical trachelectomy (57%) (Bentiveglia *et al*., 2016b).

Several strategies to prevent preterm birth and improve pregnancy outcome in women who underwent trachelectomy have been proposed. They include cervical cerclage (Kim *et al*., 2012), prophylactic antibiotics during pregnancy (Shepherd *et al*., 2006), corticosteroids to accelerate lung maturation of the fetus (Bernardini *et al*., 2003), routinely transvaginal monitoring of cervical length (Petignat *et al*., 2004) and placing the patient on strict bed rest with vaginal irrigation and tocolytics (Ishioka *et al*., 2007). Unfortunately, the available data are limited and no definitive recommendations can be drawn.

DETRIMENTAL EFFECTS OF RADIOTHERAPY

Radiotherapy represents an additional tool in the armamentarium for the management of cervical cancer. However, it further complicate the issue of fertility preservation (Ghadjar et al., 2015). Observational studies using ultrasound or Magnetic Resonance Imaging (MRI) assessment showed that uterine irradiation affects the myometrium (reducing uterine volume), the endometrium (reducing the endometrial thickness) and the uterine vasculature (impairing the uterine blood flow) (Arrive *et al*., 1989; Teh *et al*., 2014; Van de Loo *et al*., 2019). In exposed patients, reduced uterine volume and inappropriate uterine blood supply have been linked to poor obstetrical outcomes (Beneventi *et al*., 2015). An increased risk of mid-trimester miscarriages, premature delivery, LBW, stillbirth and fetal malpresentation has been reported (Chiarelli *et al*., 2000; Salloja *et al*., 2001; Green *et al*., 2002; Tough *et al*., 2003; Signorello *et al*., 2010).

A recent paper specifically investigated pregnancy outcome in women exposed to pelvic radiotherapy and highlighted a significantly increased probability of preterm birth and/or LBW (Van de Loo *et al*., 2019). However, the risk of small for gestational age (SGA) infants or miscarriage was not associated with pelvic radiotherapy. This implies that radiotherapy directed to the abdominal-pelvic area impairs the uterine ability to sufficiently expand and carry a pregnancy to term rather than impairing placental function.

Nonetheless, counseling women who were previously exposed to pelvic radiotherapy is challenging (Ghadjar et al., 2015). The precise threshold of radiation dose that causes a uterine damage not compatible with pregnancy is unknown. To date, evidence suggests that radiation doses to the uterus > 25 Gy during childhood may induce irreversible damage and doses > 45 Gy are incompatible with successful pregnancy (Larsen *et al*., 2004). It could be hypothesized that ultrasound or MRI may predict uterine impairment, but evidence aimed at identifying characteristics that could guide in the counseling are lacking.

DETRIMENTAL EFFECTS OF CHEMOTHERAPY ON OVARIAN AND UTERINE FUNCTION

The effects of platinum compounds on ovarian function have been studied in the mouse model and include oocyte-specific damages similar to those observed after the administration of alkylating agents (Morgan *et al.,* 2013; Allen *et al.,* 2020). Paclitaxel, a microtubule stabilizing agent, has low gonadotoxicity and modestly reduce AMH levels, at least in breast cancer patients where it has mostly been studied (Lambertini *et al.,* 2019). Few data are available about the protective effects of GnRH analogues co-administration during platinum/taxane-based chemotherapy in gynecological malignancies (Gilani *et al.,* 2007). Most evidences come from breast cancer patients, where the co-administration of GnRH analogues during alkylating chemotherapy reduces the risk of subsequent amenorrhea by approximately 60% (adjusted odds ratio-OR, 0.38; 95%CI: 0.26-0.57) (Lambertini *et al*., 2018).

Limited data is available about the impact of chemotherapy on the uterus. Van de Loo et al. (2019) reported that childhood cancer survivors treated with chemotherapy were more likely (OR 2.6) to have a small uterus (defined as <44.3 mL) and Beneventi et al. (2015) reported that in 21 patients treated with chemotherapy only, median uterine volumes were 39 mm^3 compared to 48 mm^3 in 64 control women ($p < 0.001$). Moreover, some studies show that prior chemotherapy exposure is associated to higher risks of preterm delivery and low birth weight infants (Black *et al*., 2017). Andersen et al. (2018) reported an altered profile of endometrial gene transcription after a single dose of doxorubicin in a sample of ovariectomized mice. However, it remains to be demonstrated whether this risk should be attributed to the reduced estrogen levels subsequent to ovarian damage after chemotherapy or to a direct endometrial effect.

Studies on embryo donation might help to clarify this issue. One study reported similar implantation rates following egg donation in a cohort of women previously exposed to chemotherapy, compared to control women who underwent egg donation but were not previously exposed to cancer therapy (38% versus 40%, respectively) (Munoz *et al*., 2015).

However, adult cancer survivors required more oocytes (11.5 versus 10.9 , p<0.05) and achieved significantly fewer pregnancies from the first transfer cycle (48 versus 58% pregnancy rate, p=0.029) (Munoz *et al.*, 2015). This evidence tends to support a possible detrimental role of chemotherapy on uterine receptivity, at least in some cases.

WHEN AND HOW PRESERVE FERTILITY IN YOUNG WOMEN WITH CERVICAL CANCER

When the diagnosis of cervical cancer is established, all young patients should be referred to an oncofertility team to have an extensive counselling. Several aspects have to be concomitantly taken into consideration in the decision-making (Table 1). In the balance of planning oocytes freezing and possible future heterologous methods, the oncologic prognosis deserves utmost consideration during the discussion and decision planning with the patient. This is particularly important in patients scheduled for radical surgery where the risk of recurrence is higher. In addition, the pros and cons should be also carefully balanced when no chemo or radiotherapy is performed.

Oocytes cryopreservation is an established procedure that offers a predictable likelihood of success based on the quantity of oocytes stored. However, cervical cancer is rarely mentioned as an indication for oocytes cryopreservation because of the need to face several critical issues (Table 1) (Alvarez and Ramanathan, 2018; Cobo et al., 2018; Creux et al., 2018; von Wolff et al., 2018). A first important question is the timing of oocytes retrieval according to the type of treatment. Different scenarios can be envisaged.

In **patients eligible for surgery** (fertility sparing or radical hysterectomy), it could be wiser to schedule oocytes pick-up after surgery when the tumour has been removed and the risk of malignant cells spillage is most likely negligible. If a hysterectomy is performed, these patients should be counseled regarding surrogacy, where this is permitted by law.

When there is an indication for neo-adjuvant chemotherapy or combined chemoradiation, we should consider oocytes cryopreservation before these treatments to avoid their potential gonadotoxicity. However, in this setting, the extent of the tumour besides the cervix implies an increased risk of spreading cancer cells. Available evidence on the effectiveness and safety of oocytes storage in women with cervical cancer is extremely scant (Table 1). A possible alternative strategy is ovarian tissue cryopreservation. In patients undergoing chemoradiation, we could consider a combined approach: the transposition of an ovary and the cryopreservation of the contralateral one. It is important to recognize that ovarian transposition may preclude future transvaginal oocyte retrieval if IVF is required. Transabdominal retrieval may be accomplished in some patients (Zinger et al., 2004). Moreover, there is a concern regarding the potential for reseeding tumor cells following ovarian tissue cryopreservation and transplantation procedures in cancer patients. The risk of ovarian involvement is known to be higher for non-squamous type cervical carcinomas. Cheng et al. (2019) reported that the incidence of ovarian metastases was 0% in stage IA, 2.8% in stage IB, 3.4% in stage IIA, and 11.8% in stage IIB cervical adenocarcinoma. They concluded that ovarian tissue cryopreservation in patients with FIGO 2018 stage IIB is not to be advised, due to the high risk of ovarian involvement (Cheng et al., 2019). It is unclear whether screening with histologic evaluation or with tumor markers is reliable and reduces the risk of reseeding tumor cells (Meirow et al., 2008).

Finally, in addition to iatrogenic ovarian injury, one may concomitantly consider the risk of injury to the uterus. Unfortunately, there is very little available evidence whether the irradiated uterus can successfully and safely carry a pregnancy (Griffiths et al., 2020).

FUTURE PERSPECTIVES: SURROGACY AND UTERUS TRANSPLANTATION

Until the recent advent of uterus transplantation, the only therapeutic option for women with absolute uterine factor infertility was gestational surrogacy (where legal), adoption or to lead a life without children (Sieunarine *et al*., 2005; Brännström *et al*., 2015).

The first cases of successful surrogacy for cervical cancer were reported in the late nineties (Meniru and Graft, 1997). However, since then, scientific evidence has been sporadic (Duska *et al*., 1998; Goldfarb *et al*., 2000; Giacalone *et al*., 2001; Zinger *et al*., 2004; Steigrad *et al*., 2005; Agorastos *et al*., 2009; Azem *et al*., 2013; Gordon *et al*., 2018). In this setting, the affected woman, commonly referred as "*intended mother*", becomes mother and raise the child with the partnership of a second woman ("*surrogate mother*") who becomes pregnant and gives birth to the child in her stead. This may occur by exploiting the natural fertility of the surrogate mother through artificial insemination with the intended father's sperm ("*traditional surrogacy*") or with the use of the intended mother's own eggs ("*gestational surrogacy*"). In this latter situation, conception is obtained with IVF and the surrogate mother has no genetic connection with the child. In these circumstances, the intended mother shares with the child her genetic background and this may be an important psychological comfort in modern Western culture (van den Akker, 2000; van den Akker, 2007). Anyway, only few case reports documented successful surrogate pregnancies in women who previously received radiotherapy or who previously underwent ovarian transposition (Giacalone et al., 2001; Steigrad et al., 2005; Agorastos et al., 2009; Azem et al., 2013). In these cases, women were all young (< 30 years), but response to hyper-stimulation was modest (≤ 5 oocytes) and retrieval was always done trans-abdominally. We failed to identify surrogate pregnancies obtained with ovarian cortex cryopreservation and replacement.

The first live birth following uterus transplantation was described in 2014. This event represented the proof of concept that the procedure could achieve the ultimate endpoint of a healthy live birth (Brännström *et al*., 2015). Since then, several uterus transplantation research projects have been implemented throughout the world with variations mainly regarding surgical techniques and donor selection (Johannesson *et al*., 2015; Tummers *et al*., 2019). There have been 15 reported live births, all through IVF (Tummers *et al*., 2019; Ejzenberg *et al*., 2019, Brännström *et al*., 2019a; Brännström *et al*., 2019b). Recently, a further important step was achieved in Brazil where the first healthy child born using a uterus transplanted from a deceased donor was reported (Ejzenberg *et al*., 2019). On these bases, the American Society of Reproductive Medicine (ASRM) has recognized uterus transplantation as a potential treatment for absolute uterine factor infertility but has also firmly stated that the procedure remains experimental (Practice Committee of the ASRM, 2018).

However, despite the current enthusiasm, uterus transplantation remains challenging. Rejection can occur and has to be promptly identified and treated. In addition, women should be frequently monitored during pregnancy because of the possible detrimental effects of immune-suppressive therapies and for the risk of preeclampsia and fetal growth retardation (Brännström *et al*., 2019a; Brännström *et al*., 2019b). Uterus transplantation is not intended for lifelong duration: the graft has to be removed after the birth of one or two healthy babies, according to recipient's motherhood desire, to limit immunosuppression period (Johannesson *et al*., 2014).

The vast majority of patients who underwent uterus transplantation had Mayer-Rokitansky-Kuester-Hauser Syndrome, a condition mainly characterized by uterus agenesis (Brännström *et al*., 2019b). Only one uterus transplantation has been performed in a woman who had previously undergone a radical hysterectomy for stage IB cervical carcinoma. No signs of tumor recurrence were reported and the patient had two regular pregnancies following uterus transplantation (Brännström *et al*., 2015). However, transplantation-related immunosuppression might increase the risk of cancer reactivation and might favor the development of new malignancies, such as cervical dysplasia, skin cancer and hematological malignancies (Piselli *et al*., 2014, Johannesson *et al*., 2015).

Uterine factor infertility in women with a past history of cervical cancer may be also the consequence of pelvic radiation. No uterus transplantation has been performed after radiotherapy and additional issues should be considered (Brännström *et al*., 2019b). Radiations impair both uterine and pelvic vascularization and vascular and anastomotic complications are frequent causes of uterus transplantation failure (Brännström *et al*., 2018; Brännström *et al*., 2019b).

In conclusion, uterine transplantation is an experimental procedure and it is currently unethical to consider the technique conceivable in a patient treated with radical hysterectomy for cervical cancer. Of note, the ASRM position statement has listed “the history of prior malignancy (excluding early-stage cervical cancer or other cancers at low risk for recurrence)” among the exclusion criteria for recipients of a uterus transplant (Practice Committee of the ASRM, 2018),

CONCLUSIONS

Fertility preservation in women with cervical cancer is evolving. Remarkable efforts and achievements have been reached in the prevention of infertility. Conservative surgery has overcome its traditional boundaries and more and more women can be effectively cured without hampering their chances of future pregnancies. On the other hand, the use of the classic techniques of fertility preservation, including oocyte and ovarian cortex freezing is still extremely limited, mainly because of the necessity to have access to surrogacy. Theoretically, oocytes cryopreservation could be proposed before treatment, but the indication and the timing for oocytes cryopreservation remain to be clarified. Despite some potential risks of tumor dissemination during oocytes harvesting, one may consider this option in women scheduled for neo-adjuvant therapy before conservative surgery. It may be also considered for those scheduled for hysterectomy but only in countries where surrogacy is allowed. Retrieval before the intervention may consent to obtain more oocytes but exposes the women to some unknown risks such as cancer spread. The advent of uterus transplantation may change the scenario but, to date, counseling patients based on this opportunity is not feasible. The procedure is highly experimental and a history of cervical cancer as an indication poses specific additional difficulties that remain to be addressed. Indeed, the anatomy can be radically subverted by previous surgery and/or radiotherapy and this may hamper the possibility of transplantation.

Overall, fertility preservation in women with cervical cancer is demanding. Important efforts are required. They should principally focus on better defining the indications for conservative treatment. The possible roles of uterine transplantation and maternal surrogacy also deserve clarification, even if their impact will presumably remain marginal.

CONFLICT OF INTEREST STATEMENT

The first author has received honoraria from Theramex, Merck-Serono and HRA. He also handles grants of research from Theramex, Merck-Serono and Ferring. All the other authors do not have any financial and non-financial competing interest to declare.

FUNDING

This paper was not funded

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Table 1. Points to consider when discussing oocytes cryostorage in women with cervical cancer

	Items	Egg freezing at the time of cancer diagnosis	Egg retrieval after the end of treatments	Comments
Cancer spread because of the transfixion of the malignant lesion at the time of egg retrieval.		Unlikely	Absent	Lack of scientific evidence. This risk is worrying but theoretical.
Cancer progression or recurrence because of hormonal-related growth.		Unlikely	Unlikely	Lack of clinical evidence. Cervical cancers are poorly responsive to sex steroids and a transient raise is unlikely to be detrimental.
Risks of egg retrieval	Planned hysterectomy	Normal	Increased	After hysterectomy, the anatomy can be subverted and transvaginal access to the ovaries can be more demanding.
	Planned radiotherapy	Normal	Increased	After radiotherapy, transvaginal retrieval may be complicated by the local diffuse fibrosis (increased risk of trauma).
	Planned chemotherapy	Normal	Normal	Chemotherapy is not expected to complicate the procedure of oocytes retrieval
	Planned ovarian transposition	Normal	Increased	After transposition, transvaginal retrieval may be demanding. Transabdominal retrieval can be done in these cases but it is more complex.
Ovarian responsiveness	Planned hysterectomy	Normal	Decreased	Vascularization of the ovary is damaged after hysterectomy and responsiveness of the ovaries can be reduced.
	Planned radiotherapy	Normal	Very decreased	Ovaries are in close proximity with the irradiation field and they can be severely damaged if not transposed.
	Planned chemotherapy	Normal	Decreased	Ovarian reserve is reduced following chemotherapy.
	Planned ovarian transposition	Normal	Decreased	Vascularization of the ovaries is damaged after transposition. Ovarian function typically resumes after surgery but responsiveness to stimulation is impaired.
Exposure to useless risks		Possible	Absent	Not all women who underwent oocytes cryopreservation prior to initiate cancer treatments will use their eggs

Wastage of resources	Possible	Absent	Not all women who underwent oocytes cryopreservation prior to initiate cancer treatments will use their eggs
Tayloring the number of COH cycles	Difficult	Possible	When done after the end of treatments, the number of cycles can be taylored to the necessity.

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