In vitro maturation of oocytes: uncommon indications

Michael Grynberg, M.D., Ph.D.,[a] Hady El Hachem, M.D.,[a] Astrid de Bantel, M.D.,[b] Julie Benard, M.D.,[a] Soizic le Parco, M.D.,[a] and Renato Fanchin, M.D., Ph.D.[a]

[a] Service de Gynécologie-Obstétrique et Médecine de la Reproduction, and [b] Service de Biologie de la Reproduction, Hôpital Antoine Béclère, Clamart, Universite Paris-Sud, Clamart, France

Retrieval of immature oocytes from unstimulated ovaries, followed by in vitro maturation (IVM) was initially proposed to avoid the risks and side effects of exogenous gonadotropin administration. Therefore, during the past decades, IVM was mainly offered to patients with polycystic ovary syndrome (PCOS) at high risk of ovarian hyperstimulation syndrome (OHSS). However, the development of fertility preservation has recently opened new perspectives in the field of IVM. The present review summarizes uncommon indications of IVM, which is a viable option to treat infertility in patients with ovarian resistance to FSH, but may also be considered to preserve fertility in leukemia as well as before ovarian transposition and endometrioma excision. (Fertil Steril® 2013;99:1182–8. ©2013 by American Society for Reproductive Medicine.)

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D uring the past 20 years, in vitro maturation (IVM) of oocytes has emerged as a reliable option in the strategy of infertility treatment. Since the first successful live birth obtained from IVM was described, advances in IVM protocols and improvements of the maturation method, as well as culture media, have led to satisfactory pregnancy rates (PR) in appropriately selected patient groups (1–3). In addition, the overwhelming majority of studies investigating the health risks of children conceived after IVM are reassuring (4–8).

Retrieval of immature oocytes without previous exogenous gonadotropin administration and subsequent culture in maturation medium was initially proposed to women with many antral follicles who were at risk of developing ovarian hyperstimulation syndrome (OHSS) (9). With time, the indications for IVM treatment have remarkably expanded, and include poor responders to controlled ovarian hyperstimulation (COH) (10) and oocyte donation (11). More recently, IVM has been proposed as an option for fertility preservation in women having to undergo gonadotoxic treatments (12, 13). Indeed, IVM not only allows mature oocyte cryopreservation when the fertility preservation is urgent and does not authorize exogenous gonadotropin administration, but also in estrogen (E)-sensitive cancers (13, 14).

The present article describes some uncommon indications of IVM, either as a treatment to infertility or in the field of fertility preservation.

OVARIAN RESISTANCE TO FSH

Ovarian resistance to FSH, also known as ovary resistant syndrome (15, 16), is a rare endocrine condition characterized by hypergonadotrophic hypogonadism and infertility (15–19). Patients often present with primary amenorrhea (15–19) with timely and spontaneous onset of secondary sexual characteristics (15–21). Biologically, serum gonadotropin levels are within menopausal range (15–23). As a consequence, these patients are frequently misdiagnosed with premature ovarian failure (POF). However, a pathognomonic characteristic of women suffering from ovarian resistance to FSH is the presence of an age-compatible number of small antral follicles. In addition, the remarkable normalcy of the antral follicle count is reinforced by hormonal markers of the follicular ovarian status, in particular inhibin B and antimüllerian hormone, which are within normal range (17, 23). Although genetic or immunologic abnormalities may explain antral follicle unresponsiveness to FSH, many patients with the ovarian resistance syndrome still remain with an undetermined diagnosis (17). Currently, given the inherent impossibility of obtaining mature follicles and oocytes from these patients due to their

defective response both to endogenous and exogenous FSH (17, 18, 22, 23), the only option for treating their infertility is egg donation (22, 23).

Taking into consideration the unfeasibility of obtaining satisfactory FSH-induced follicles and oocyte maturation in patients suffering from ovarian resistance to FSH and that they are normally endowed with small antral follicles, it was conceivable that IVM might constitute a useful approach for treating this type of infertility. We recently reported on two pregnancies achieved using IVM in two women whose ovaries were resistant to FSH (Grynberg et al. unpublished data). Patient characteristics and IVM outcome are provided in Table 1. The success of IVM proved that oocytes in this clinical situation are meiotically competent and healthy. Therefore, IVM may be the only viable alternative to egg donation for women suffering from gonadotropin resistance.

FERTILITY PRESERVATION

Advances in chemotherapy and radiation therapy have significantly improved cure rates for many young patients suffering from cancer (24). As a consequence, the number of long-term survivors is increasing and their future quality of life has become a major concern (25). However, loss of ovarian function and therefore, fertility, is one of the most common long-term adverse effects affecting premenopausal patients treated with chemotherapy and/or radiation therapy (26). For these patients, ensuring their reproductive capacity after oncologic treatment has become a major concern. Therefore, a number of strategies have been developed in recent years to enable these women to preserve their fertility and their ability to become genetic mothers. The field of fertility preservation has more recently been extended to non-oncologic diseases such as autoimmune diseases and premature ovarian insufficiency. Cryopreservation of oocytes and/or embryos after COH is currently the most established fertility preservation method. However, this strategy has two major limits. First, COH requires at least 10 days, which is not compatible when the initiation of cancer treatment is urgent. Second, the supraphysiologic serum E_2 levels obtained at the end of gonadotropin administration are theoretically contraindicated in E-sensitive diseases. To overcome these limits, cryopreservation of ovarian tissue has been proposed. However, this technique is still considered experimental, with a limited number of pregnancies reported to date (27, 28). More recently, IVM of oocytes has been proposed as an alternative approach for fertility preservation, as it does not require exogenous gonadotropin administration and is therefore associated with serum E_2 levels that are in the normal range. As a consequence, IVM represents an option for urgent fertility preservation, as well as in patients suffering from E-sensitive diseases (13, 29).

Although immature oocyte retrieval may be performed irrespective of the menstrual cycle phase, the procedure will be ideally proposed during the late follicular phase. This strategy allows one to obtain a mature oocyte from the dominant follicle in combination with immature oocytes. Lim et al. (30) reported acceptable PRs (40.4%) using natural IVF/IVM cycle in normo-ovulatory patients having more than seven small antral follicles counted on day 3.

Several lines of evidence indicate that zygote stage (31) or blastocyst stage (32, 33) embryos produced from an IVM cycle may be successfully vitrified, leading to pregnancies and live births. Cleavage stage, as well as blastocyst-vitrified embryos show high survival rates (85.5% and 92%, respectively) after thawing and acceptable PRs (25.0% and 43.8%, respectively) (34). Taken together, these results suggest that embryos produced from IVM cycles can be safely cryopreserved through vitrification. Aside from the established indications of IVM, other pathologies could be considered in fertility preservation.

Leukemia

Acute leukemia is the most common childhood cancer and advances in treatments have markedly improved the survival rates (>80%) (35). Patients suffering from leukemia are often candidates to hematopoietic stem cell transplantation and will experience permanent ovarian failure in 70%–90% of cases (36). Therefore, ovarian cortex cryopreservation before gonadotoxic chemotherapy has been proposed to enable these patients to possibly recover endocrine ovarian function and fertility potential (28, 37, 38). However, one major concern raised by the ovarian cortical fragment cryopreservation in cancer patients is the possible risk that the frozen-thawed ovarian tissue might harbor malignant cells that could induce a recurrence of the disease after grafting. Overall, the magnitude of the risk of reimplanting malignant cells by autotransplantation of ovarian tissue is currently completely unknown. However, in the case of leukemia, this risk may be high as the disease affects the bone marrow and blood. As a consequence, malignant cells may be present in all blood-filled organs, including the ovaries. Animal studies previously showed that transplantation of testicular cells from leukemic donor rats transmits acute leukemia to healthy recipients (39). In line with this, Dolmans et al. (40), using a model of immunodeficient mice transplanted with ovarian cortex from patients with leukemia, reported a contamination of the ovarian cortex by leukemic cells in 5 of 18 cases. In addition, small traces of disease-specific fusion transcripts have been found by quantitative real time polymerase chain reaction (qRT-PCR) in the ovarian cortex of patients suffering from leukemia. Given these data, it is recommended that any harvested tissue from patients with leukemia should not be used for autotransplantation because of the high risk of malignant cell reintroduction (41). Recently, Greve et al. (42) failed to find any signs of viable malignant cells in fragments of ovarian tissue obtained from leukemic patients in remission. These results, obtained using histologic, immunohistochemical, and qRT-PCR studies after transplantation of frozen/thawed human ovarian cortex to nude mice, may open the possibility of future ovarian tissue grafting in leukemic patients after complete disease remission using tissue that had undergone cryopreservation. However, further studies are still needed to consider this procedure safe enough for common clinical practice.

TABLE 1

Clinicobiological characteristics and IVM outcome in two patients suffering from ovarian resistance to gonadotropins.

	Age (y)	FSH (mIU/mL)	LH (mIU/mL)	AMH (ng/mL)	Antral follicle count	Total no. of immature oocytes retrieved	No. of oocytes matured after 24 h	No. of oocytes matured after 48 h	No. of embryos obtained	IVM outcome
Patient 1	29	40.3	35.7	4.5	23	14	12	0	7	Live birth
Patient 2	31	54.1	33.5	4.2	26	10	3	1	2	Clinical pregnancy

Note: AMH = antimüllerian hormone; IVM = in vitro maturation.

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At present, as leukemia represents a contraindication to ovarian cortex transplantation, follicle culture with IVM may be a solution (43, 44). Another option could be isolated follicle grafting, enzymatically purified from frozen-thawed ovarian tissue (45, 46). Further research in this field is needed to develop safe options to restore fertility in leukemic patients from cryopreserved ovarian tissue.

Currently, IVM constitutes the only reliable option that could be offered to preserve fertility in patients suffering from leukemia. Usually, these women have already had an induction cure, before the request of fertility preservation. This treatment aims at removing most malignant cells from the blood, but may not eliminate malignant cells in the bone marrow. In addition, the chemotherapy used for induction cures usually does not include alkylating agents (47–49) and is therefore considered at low risk of follicular toxicity (50). As a consequence, patients seeking fertility preservation may be offered immature oocyte retrieval followed by IVM and subsequent mature oocyte or embryo cryopreservation. Because in vitro matured oocytes are, by definition, devoid of any leukemic cells, IVM offers patients a reliable opportunity to become genetic mothers without any risk of recurrence of the disease. In addition, IVM may be combined with ovarian tissue cryopreservation (14). We performed this double procedure in five patients (Table 2). All patients had previously undergone induction chemotherapy. We were able to recover a significant number of immature oocytes that were meiotically competent and therefore suitable for cryopreservation. Usually, immature oocytes are retrieved by the conventional transvaginal aspiration method, before oophorectomy. However, the possibility of collecting immature oocytes ex vivo, in a human reproduction laboratory, after oophorectomy has also been reported (51). These investigators obtained approximately three oocytes from each of the four patients undergoing this method, with maturation rates of 79% on average. Our team achieved the retrieval of seven and six immature oocytes from the two patients who required this approach (Grynberg et al. unpublished data). A major concern of the ex vivo strategy is the quality of oocytes frozen after IVM. Immature follicles are aspirated from the ovarian tissue suspended into a culture medium at 4°C, the ideal temperature for dissection of cortical strips. Although oocyte maturation rates are encouraging, the risk of meiotic disturbance due to temperature fluctuations cannot be neglected (52, 53). As a consequence, we consider that transvaginal oocyte retrieval before oophorectomy should be preferred, as immature oocytes are kept at optimal temperature. In addition, immature oocyte aspiration may be more efficient when it is performed under ultrasound guidance in comparison with recovery by aspiration of all visible antral follicles from an oophorectomy piece.

Given the current knowledge, we consider that, from an ethical standpoint, IVM should at least be proposed to leukemic patient candidates for ovarian cortex preservation, as it represents the only current option for restoring the fertility in these women. However, patients should be aware of the remarkable lack of data regarding the actual potential of frozen-thawed oocytes matured in vitro.

TABLE 2

In vitro maturation and cryopreservation of oocytes retrieved from seven patients with cancer facing imminent gonadotoxic treatment who were unable to undergo hormonal ovarian stimulation for fertility preservation.

	Age (y)	Disease	Chemotherapy before IVM	Other method of fertility preservation	Antral follicle count	Total no. of oocytes retrieved	No. of MII oocytes at retrieval	No. of oocytes matured after 24 h	No. of oocytes matured after 48 h	No. of MII oocytes cryopreserved
Patient 1	30	ALL	Yes	OTC	22	11	0	3	3	6
Patient 2	25	AML	Yes	No	20	9	0	8	1	9
Patient 3	36	ALL	Yes	OTC	10	1	0	1	0	1
Patient 4	24	ALL	Yes	OTC	15	4	0	4	0	4
Patient 5	20	AML	Yes	OTC	19	3	0	3	0	3
Patient 6	20	AML	Yes	OTC	20	15	0	14	0	14
Patient 7	32	Rectum cancer T3N0M0	No	Oophoropexy + OTC	15	5	0	1	0	1

Note: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; IVM = in vitro maturation; MII = meiosis II; OTC = ovarian tissue cryopreservation.

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Endometriosis

Endometriosis is one of the most frequently encountered benign diseases in women of reproductive age. It is usually associated with dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. Although complete resolution of endometriosis is not yet possible, medico-surgical treatment aims at reducing pain, preserving and improving fertility. Surgery often includes ablation of endometriotic implants or excision of ovarian endometrioma. However, several lines of evidence indicate that normal ovarian tissue may be excised with the endometriomal wall, therefore reducing the ovarian reserve (54–56). Thus, women having undergone ovarian endometrioma excision show reduced response to COH (57) as well as earlier menopausal transition (58). In addition, some cases of postsurgical ovarian failure have been documented in women operated for bilateral endometriomas (59, 60).

As a consequence, preserving fertility in patients with endometriosis scheduled for endometrioma excision, has become a major concern. Therefore, it has been recommended that experienced surgeons should perform the procedure. In addition, some investigators have proposed the use of more "active" methods of fertility preservation (61). Because endometriosis is an E-related disease, it is conceivable that preoperative administration of exogenous gonadotropins for oocyte or embryo cryopreservation may be harmful. Another option could be the excision of ovarian cortical strips and further cryopreservation (61). However, this strategy implies a retrieval of safe ovarian tissue and therefore a reduction of the ovarian reserve. In vitro maturation may constitute an interesting alternative for preserving fertility in patients with endometriosis as it offers the opportunity to freeze eggs or embryos without the administration of exogenous FSH and the subsequent increase of serum E_2 levels. In particular, the possibility of performing IVM irrespective of the menstrual cycle phase (29, 62) avoids delaying surgery. However, the quality of in vitro matured oocytes obtained from patients with endometriosis remains to be objectively established.

Ovarian Transposition

It is now clearly established that radiation therapy to the female pelvis will invariably lead to ovarian damage and/or failure if no intervention is taken. The effects of radiation on the ovary are age and dose dependent. Irreversible ovarian failure is certain at delivery doses to both ovaries of 4–7 Gy in women older than 40 years. The ovaries are more resistant in prepubertal girls, and ovarian failure is therefore not predictable. Nevertheless, it has been reported that with a wide range of doses (12–50 Gy), primary amenorrhea occurred in 68% of cases treated at a mean age of 6.9 years (63).

Transfixing ovaries out of radiation fields before therapy has been proposed to avoid ovarian irradiation damage (64). Oophoropexy can be performed laparoscopically, with the objective of sparing ovarian function and enabling women of reproductive age to become pregnant (65–67). However, the effectiveness of ovarian transposition to preserve ovarian function remains debated (68). In addition, some investigators suggest that bilateral transposition will require subsequent assisted reproductive technologies (ART)

because of the potential damage to the ovaries and the fallopian tubes (69).

Because the potential of fertility of women having undergone oophoropexy may be difficult to objectively predict, additional techniques of fertility preservation have been proposed. The surgical procedure of ovarian transposition enables a portion of an ovary to be obtained for cryopreservation (67, 70). Like ovarian transposition, this procedure aims at restoring both hormonal function and infertility after transplantation if ovarian failure occurs (71). However, as the ovarian tissue graft still has undetermined success rates, some investigators have proposed to recover immature oocytes from all visible antral follicles before preparing ovarian strips for cryopreservation. Aspirated oocytes at the germinal vesicle stage may be matured in vitro and vitrified at the mature stage or after fertilization (71, 72). This strategy offers the opportunity to have three different fertility preservation treatments using only one surgical procedure. This multiple strategy of fertility preservation raises two points. First, IVM is currently the only way to offer patients oocyte or embryo cryopreservation before radiation therapy. Although COH should ideally be performed when considering oocyte or embryo cryopreservation, it is associated with anatomic modifications of ovaries that could make the oophoropexy difficult. Second, as previously discussed, we consider that the IVM procedure should be performed "in vivo," before initiating the laparoscopic procedure. Three cases of IVM before ovarian transposition and ovarian tissue cryopreservation have already been performed in our center. Patient characteristics and IVM data are reported in Table 2.

At present, IVM and subsequent oocyte or embryo cryopreservation should be considered in the strategy of fertility preservation in women of reproductive age before pelvic radiation. However, it is important to keep in mind that whatever technique of fertility preservation is chosen, endometrial damage after radiotherapy may preclude successful natural as well as medically assisted pregnancies (73).

In conclusion, marked improvements of the clinical and laboratory aspects of IVM treatment have led to better clinical outcomes. The recent development of fertility preservation has extended the indications of IVM beyond patients at risk of OHSS. In particular, IVM may represent a viable option in patients suffering from ovarian resistance to FSH, whose ovaries are endowed with a normal number of antral follicles. Because IVM may be performed without exogenous gonadotropin administration, therefore avoiding supraphysiologic serum E_2 levels, it is applicable in emergency situations as well as in patients suffering from E-sensitive diseases. Given the simplicity and the safety of the IVM procedure and the possibility to combine immature oocyte retrieval with ovarian cortex cryopreservation, and given the risk of disease recurrences after grafting in some cases, we consider that IVM should systematically be offered to candidates undergoing ovarian tissue freezing. In leukemic patients, IVM currently represents the only viable option of fertility preservation as transplantation of cryopreserved ovarian tissue is still contraindicated.

REFERENCES

1. Chian RC, Gülekli B, Buckett WM, Tan SL. Priming with human chorionic gonadotropin before retrieval of immature oocytes in women with infertility due to the polycystic ovary syndrome. N Engl J Med 1999;341:1624–6.
2. Chian RC, Buckett WM, Tulandi T, Tan SL. Prospective randomized study of human chorionic gonadotrophin priming before immature oocyte retrieval from unstimulated women with polycystic ovarian syndrome. Hum Reprod 2000;15:165–70.
3. Söderström-Anttila V, Mäkinen S, Tuuri T, Suikkari AM. Favourable pregnancy results with insemination of in vitro matured oocytes from unstimulated patients. Hum Reprod 2005;20:1534–40.
4. Cha KY, Chung HM, Lee DR, Kwon H, Chung MK, Park LS, et al. Obstetric outcome of patients with polycystic ovary syndrome treated by in vitro maturation and in vitro fertilization-embryo transfer. Fertil Steril 2005;83:1461–5.
5. Mikkelsen AL. Strategies in human in-vitro maturation and their clinical outcome. Reprod Biomed Online 2005;10:593–9.
6. Söderström-Anttila V, Salokorpi T, Pihlaja M, Serenius-Sirve S, Suikkari AM. Obstetric and perinatal outcome and preliminary results of development of children born after in vitro maturation of oocytes. Hum Reprod 2006;21:1508–13.
7. Shu-Chi M, Jiann-Loung H, Yu-Hung L, Tseng-Chen S, Ming IL, Tsu-Fuh Y. Growth and development of children conceived by in-vitro maturation of human oocytes. Early Hum Dev 2006;82:677–82.
8. Buckett WM, Chian RC, Holzer H, Dean N, Usher R, Tan SL. Obstetric outcomes and congenital abnormalities after in vitro maturation, in vitro fertilization, and intracytoplasmic sperm injection. Obstet Gynecol 2007;110:885–91.
9. Chian RC. In-vitro maturation of immature oocytes for infertile women with PCOS. Reprod Biomed Online 2004;8:547–52.
10. Child TJ, Abdul-Jalil AK, Gulekli B, Tan SL. In vitro maturation and fertilization of oocytes from unstimulated normal ovaries, polycystic ovaries, and women with polycystic ovary syndrome. Fertil Steril 2001;76:936–42.
11. Holzer H, Scharf E, Chian RC, Demirtas E, Buckett W, Tan SL. In vitro maturation of oocytes collected from unstimulated ovaries for oocyte donation. Fertil Steril 2007;88:62–7.
12. Cao YX, Chian RC. Fertility preservation with immature and in vitro matured oocytes. Semin Reprod Med 2009;27:456–64.
13. Berwanger AL, Finet A, El Hachem H, Le Parco S, Hesters L, Grynberg M. New trends in female fertility preservation: in vitro maturation of oocytes. Future Oncol 2012;8:1567–73.
14. Huang JY, Chian RC, Gilbert L, Fleiszer D, Holzer H, Dermitas E, et al. Retrieval of immature oocytes from unstimulated ovaries followed by in vitro maturation and vitrification: a novel strategy of fertility preservation for breast cancer patients. Am J Surg 2010;200:177–83.
15. De Moraes-Ruehsen M, Jones GS. Premature ovarian failure. Fertil Steril 1967;18:440–61.
16. Jones GS, de Moraes-Ruehsen M. A new syndrome of amenorrhae in association with hypergonadotropism and apparently normal ovarian follicular apparatus. Am J Obstet Gynecol 1969;104:597–600.
17. Huhtaniemi I, Alevizaki M. Gonadotrophin resistance. Best Pract Res Clin Endocrinol Metab 2006;20:561–76.
18. Van Campenhout J, Vauclair R, Maraghi K. Gonadotropin-resistant ovaries in primary amenorrhea. Obstet Gynecol 1972;40:6–12.
19. Talbert LM, Raj MH, Hammond MG, Greer T. Endocrine and immunologic studies in a patient with resistant ovary syndrome. Fertil Steril 1984;42:741–4.
20. Koninckx PR, Brosens IA. The "gonadotropin-resistant ovary" syndrome as a cause of secondary amenorrhea and infertility. Fertil Steril 1977;28:926–31.
21. Jequier AM. Conception in the resistant ovary syndrome occurring during hormone replacement therapy: a report of 2 cases. Aust N Z J Obstet Gynaecol 1990;30:176–8.
22. Koumantakis E, Matalliotakis I, Livas V, Neonaki M, Papavasiliou E. Gonadotrophin-resistant ovary syndrome (Savage syndrome). J Obstet Gynaecol 1997;17:208.

23. Arici A, Matalliotakis IM, Koumantakis GE, Goumenou AG, Neonaki MA, Koumantakis EE. Diagnostic role of inhibin B in resistant ovary syndrome associated with secondary amenorrhea. Fertil Steril 2002;78:1324–6.

24. Ries LAG. Childhood cancer mortality. In: Ries LAG, Smith MA, Gurney JG, et al. editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975-1995. Bethesda, Maryland: National Cancer Institute; 1999:165–9. Available: http://seer.cancer.gov/publications/childhood/mortality.pdf. Last accessed January 27, 2013.

25. Jemal A, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, et al. Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. Cancer 2004;101:3–27.

26. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? Lancet Oncol 2005;6:209–18.

27. Silber SJ. Ovary cryopreservation and transplantation for fertility preservation. Mol Hum Reprod 2012;18:59–67.

28. Grynberg M, Poulain M, Sebag-Peyrelevade S, le Parco S, Fanchin R, Frydman N. Ovarian tissue and follicle transplantation as an option for fertility preservation. Fertil Steril 2012;97:1260–8.

29. Maman E, Meirow D, Brengauz M, Raanani H, Dor J, Hourvitz A. Luteal phase oocyte retrieval and in vitro maturation is an optional procedure for urgent fertility preservation. Fertil Steril 2011;95:64–7.

30. Lim JH, Yang SH, Xu Y, Yoon SH, Chian RC. Selection of patients for natural cycle in vitro fertilization combined with in vitro maturation of immature oocytes. Fertil Steril 2009;91:1050–5.

31. Hashimoto S, Murata Y, Kikkawa M, Sonoda M, Oku H, Murata T, et al. Successful delivery after the transfer of twice-vitrified embryos derived from in vitro matured oocytes: a case report. Hum Reprod 2007;22: 221–3.

32. Son WY, Yoon SH, Park SJ, Yoon HJ, Lee WD, Lim JH. Ongoing twin pregnancy after vitrification of blastocysts produced by in-vitro matured oocytes retrieved from a woman with polycystic ovary syndrome: Case report. Hum Reprod 2002;17:2963–6.

33. Son WY, Lee SY, Chang MJ, Yoon SH, Chian RC, Lim JH. Pregnancy resulting from transfer of repeat vitrified blastocysts produced by in-vitro matured oocytes in patient with polycystic ovary syndrome. Reprod Biomed Online 2005;10:398–401.

34. Son WY, Tan SL. Laboratory and embryological aspects of hCG-primed in vitro maturation cycles for patients with polycystic ovaries. Hum Reprod Update 2010;16:675–89.

35. Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009;360:2730–41.

36. Wallace WH. Oncofertility and preservation of reproductive capacity in children and young adults. Cancer 2011;117:2301–10.

37. Donnez J, Dolmans MM, Demylle D, Jadoul P, Pirard C, Squifflet J, et al. Live birth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004;364:1405–10.

38. Andersen CY, Rosendahl M, Byskov AG, Loft A, Ottosen C, Dueholm M, et al. Two successful pregnancies following autotransplantation of frozen/thawed ovarian tissue. Hum Reprod 2008;23:2266–72.

39. Jahnukainen K, Hou M, Petersen C, Setchell B, Söder O. Intratesticular transplantation of testicular cells from leukemic rats causes transmission of leukemia. Cancer Res 2001;61:706–10.

40. Dolmans MM, Marinescu C, Saussoy P, van Langendonckt A, Amorim C, Donnez J. Reimplantation of cryopreserved ovarian tissue from patients with acute lymphoblastic leukemia is potentially unsafe. Blood 2010;116: 2908–14.

41. Practice Committee ISFP, Kim SS, Donnez J, Barri P, Pellicer A, Patrizio P, Rosenwaks Z, et al. Recommendations for fertility preservation in patients with lymphoma, leukemia, and breast cancer. J Assist Reprod Genet 2012;29:465–8.

42. Greve T, Clasen-Linde E, Andersen MT, Andersen MK, Sorensen SD, Rosendahl M, et al. Cryopreserved ovarian cortex from patients with leukemia in complete remission contains no apparent viable malignant cells. Blood 2012;120:4311–6.

43. Hovatta O. Cryopreservation and culture of human ovarian cortical tissue containing early follicles. Eur J Obstet Gynecol Reprod Biol 2004;113:S50–4.

44. Telfer EE, McLaughlin M, Ding C, Thong KJ. A two-step serum-free culture system supports development of human oocytes from primordial follicles in the presence of activin. Hum Reprod 2008;23:1151–8.

45. Dolmans MM, Martinez-Madrid B, Gadisseux E, Guiot Y, Yuan WY, Torre A, et al. Short-term transplantation of isolated human ovarian follicles and cortical tissue into nude mice. Reproduction 2007;134:253–62.

46. Dolmans MM, Yuan WY, Camboni A, Torre A, van Langendonckt A, Martinez-Madrid B, et al. Development of antral follicles after xenografting of isolated small human preantral follicles. Reprod Biomed Online 2008;16:705–11.

47. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Engl J Med 2006;354:166–78.

48. Estey E, Döhner H. Acute myeloid leukaemia. Lancet 2006;368:1894–907.

49. Schmiegelow K, Forestier E, Hellebostad M, Heyman M, Kristinsson J, Söderhäll S, et al. Nordic Society of Paediatric Haematology and Oncology. Long-term results of NOPHO ALL-92 and ALL-2000 studies of childhood acute lymphoblastic leukemia. Leukemia 2010;24:345–54.

50. Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, et al. American Society of Clinical Oncology. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol 2006;24:2917–31.

51. Huang JY, Tulandi T, Holzer H, Tan SL, Chian RC. Combining ovarian tissue cryobanking with retrieval of immature oocytes followed by in vitro maturation and vitrification: an additional strategy of fertility preservation. Fertil Steril 2008;89:567–72.

52. Pickering SJ, Braude PR, Johnson MH, Cant A, Currie J. Transient cooling to room temperature can cause irreversible disruption of the meiotic spindle in the human oocyte. Fertil Steril 1990;54:102–8.

53. Almeida PA, Bolton VN. The effect of temperature fluctuations on the cytoskeletal organisation and chromosomal constitution of the human oocyte. Zygote 1995;3:357–65.

54. Gupta S, Agarwal A, Agarwal R, Loret de Mola JR. Impact of ovarian endometrioma on assisted reproduction outcomes. Reprod Biomed Online 2006; 13:349–60.

55. Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. Fertil Steril 2007;88:1568–72.

56. Ragni G, Somigliana E, Benedetti F, Paffoni A, Vegetti W, Restelli L, et al. Damage to ovarian reserve associated with laparoscopic excision of endometriomas: a quantitative rather than a qualitative injury. Am J Obstet Gynecol 2005;193:1908–14.

57. Somigliana E, Benaglia L, Viganó P, Candiani M, Vercellini P, Fedele L. Surgical measures for endometriosis-related infertility: a plea for research. Placenta 2011;32:S238–42.

58. Coccia ME, Rizzello F, Mariani G, Bulletti C, Palagiano A, Scarselli G. Ovarian surgery for bilateral endometriomas influences age at menopause. Hum Reprod 2011;26:3000–7.

59. Busacca M, Riparini J, Somigliana E, Oggioni G, Izzo S, Vignali M, et al. Post-surgical ovarian failure after laparoscopic excision of bilatéral endometriomas. Am J Obstet Gynecol 2006;195:421–5.

60. Di Prospero F, Micucci G. Is operative laparoscopy safe in ovarian endometriosis? Reprod Biomed Online 2009;18:167.

61. Donnez J, Squifflet J, Jadoul P, Lousse JC, Dolmans MM, Donnez O. Fertility preservation in women with ovarian endometriosis. Front Biosci (Elite Ed) 2012;4:1654–62.

62. Grynberg M, Even M, Hesters L, Trèves R, Fanchin R, Frydman N. Similar in vitro maturation (IVM) and fertilization rates of oocytes retrieved either at the follicular or the luteal phase of the cycle offers flexible options for urgent fertility preservation (FP) [oral communication]. ASRM Annual Meeting San Diego, California, October 20–24, 2012.

63. Bhatia S, Blatt J, Meadows TA. Late effects of childhood cancer and its treatment. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology. Philadelphia: Lippincott Williams & Wilkins; 2006: 1490–514.

64. McCall ML, Keaty EC, Thompson JD. Conservation of ovarian tissue in the treatment of carcinoma of the cervix with radical surgery. Am J Obstet Gynecol 1958;75:590–600.

65. Williams RS, Littell RD, Mendenhall NP. Laparoscopic oophoropexy and ovarian function in the treatment of Hodgkin disease. Cancer 1999;86:2138–42.

66. Bisharah M, Tulandi T. Laparoscopic preservation of ovarian function: an underused procedure. Am J Obstet Gynecol 2003;188:367–70.

67. Gershenson DM. Fertility-sparing surgery for malignancies in women. J Natl Cancer Inst Monogr 2005;34:43–7.

68. Levitt GA, Jenney ME. The reproductive system after childhood cancer. Br J Obstet Gynaecol 1998;105:946–53.

69. Kuohung W, Ram K, Cheng DM, Marcus KJ, Diller LR, Laufer MR. Laparoscopic oophoropexy prior to radiation for pediatric brain tumor and subsequent ovarian function. Hum Reprod 2008;23:117–21.

70. Oktay K, Nugent D, Newton H, Salha O, Chatterjee P, Gosden RG. Isolation and characterization of primordial follicles from fresh and cryopreserved human ovarian tissue. Fertil Steril 1997;67:481–6.

71. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, et al. Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med 2005;353:318–21.

72. Elizur SE, Tulandi T, Meterissian S, Huang JY, Levin D, Tan SL. Fertility preservation for young women with rectal cancer—a combined approach from one referral center. J Gastrointest Surg 2009;13:1111–5.

73. Farber LA, Ames JW, Rush S, Gal D. Laparoscopic ovarian transposition to preserve ovarian function before pelvic radiation and chemotherapy in a young patient with rectal cancer. MedGenMed 2005;7:66.