CASE REPORT

First pregnancy and live birth from ex vivo-retrieved metaphase II oocytes from a woman with bilateral ovarian carcinoma: a case report

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Objective: To report pregnancy and live birth resulting from intracytoplasmic sperm injection of ex vivo-retrieved mature oocytes from a woman with bilateral ovarian carcinoma.
Design: Case report.
Setting: Fertility clinic.
Patient: A 34-year-old nulliparous woman with bilateral ovarian tumor, with a risk of malignancy of 96.1% according to International Ovarian Tumor Analysis Group recommendations for adnexal tumors, who desired fertility preservation before definitive surgical treatment.
Intervention(s): Cryopreservation of ex vivo-retrieved mature metaphase II oocytes is followed by fertilization with donor sperm and embryo transfer to a gestational carrier.
Main Outcome Measure(s): Fertility preservation.
Results: After controlled ovarian stimulation, 12 metaphase II oocytes were retrieved from oophorectomized specimens and vitrified. Intracytoplasmic sperm injection with donor sperm was performed in remission, resulting in 9 cleavage-stage embryos, 2 of which were transferred to a gestational carrier, resulting in a normal, healthy singleton pregnancy, and the live birth of a healthy infant.
Conclusion(s): Ex vivo oocyte retrieval after oophorectomy may be a safe alternative to standard oocyte retrieval for fertility preservation in women with ovarian malignancies. (Fertil Steril® 2024;■:■–■. ©2024 by American Society for Reproductive Medicine.)
Key Words: Fertility preservation, egg freezing, oncofertility, ex vivo mature oocytes retrieval, ovarian cancer

Given the potential gonadotoxicity of cancer treatment and the significant improvements in survival rates for children, adolescents, young adults, and premenopausal women, the pursuit of medical counseling and options for fertility preservation has been growing. Advances available in routine include the following: the development and establishment of random-start gonadotropin-releasing hormone antagonist controlled ovarian stimulation protocols, allowing clinicians to start treatment regardless of the menstrual cycle phase; the use of aromatase inhibitors to suppress serum estradiol elevation or selective estrogen receptor modulators during controlled ovarian stimulation for women with estrogen-sensitive tumors; the cryopreservation of the ovarian cortex, mainly for the pediatric population; and fertility-sparing surgical approaches, allowing surgeons to preserve the reproductive organs of women with less aggressive or early-stage gynecological tumors (1–6).

Conventionally, vitrification of unfertilized metaphase II (MII) oocytes has been well recognized for fertility preservation in female patients with cancer of reproductive age (7). However, MII

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oocytes are usually retrieved after gonadotropic stimulation of the ovaries and transvaginal follicular aspiration, which may be unsafe in the presence of ovarian malignant neoplasia. In addition to the postponement of cancer treatment, there is a hypothetical risk of neoplastic transformation and stimulation by the administration of exogenous gonadotropins (8–10) and a real risk of tumor capsule rupture and/or cell spillage resulting from ovarian puncture.

Because of the abovementioned reasons, fertility preservation in advanced ovarian cancer (OC) remains challenging and underresearched. Preliminary studies have led researchers to develop effective gonadal bioprosthetics in mice (11, 12), and efforts have been made toward the possibility of recovering mature oocytes after in vitro culture of human ovarian follicles (13). Although such findings remain experimental, the obvious way to minimize the risks should be, then, the aspiration of small ovarian follicles from nonstimulated oophorectomized specimens, aiming to collect immature oocytes for in vitro maturation (IVM). It is true that a few reports of ex vivo-retrieval of immature oocytes have been well succeeded (14–19), and 2 live births (LBs) have been documented to date (9, 10). However, general outcomes of IVM are far from being sufficiently good for its use as the first choice in assisted reproductive technologies (ARTs) (20).

In the light of scientific knowledge, vitrification of MII oocytes would be, unequivocally, the ideal fertility preservation option for all female patients with cancer of reproductive age. To date, a few reports have documented gonadotropic stimulation for ex vivo retrieval of MII oocytes in OC, revealing an intriguing strategy apparently without additional neoplastic stimulation or the risk of massive discharge of malignant cells because of follicular puncture (21–25). However, no pregnancy or birth has been reported to date. In this article, we report the first pregnancy and LB resulting from intracytoplasmic sperm injection of ex vivo retrieved MII oocytes from a woman with bilateral high-grade serous ovarian carcinoma in a gestational carrier.

CASE REPORT

A 34-year-old single nulligravida, body mass index of 21.37 kg/m^2, without family history of cancer, was referred to the oncology center because of the finding of bilateral adnexal multilocular masses with solid components and dense echoes of mucinous appearance; on the right, the entire lesion measured 85 mm × 69 mm × 85 mm and the solid component measured 69 mm × 28 mm × 30 mm, Doppler score 4; on the left, the entire lesion measured 68 mm × 29 mm × 39 mm, with papillary projections measuring 9 mm × 6 mm and 17 mm × 11 mm, Doppler score 4 (Fig. 1). The risk of malignancy was 96.1%, according to International Ovarian Tumor Analysis Group recommendations for adnexal tumors (IOTA-ADNEX, Fig. 2) (26). Total abdominal magnetic resonance imaging with diffusion-weighted imaging confirmed bilateral solid-cystic masses with diffusion restriction and intense paramagnetic contrast intake infiltrating the uterine posterior wall. There was no evidence of thoracic disease. Cancer antigen 125 levels were 978 U/mL.

The patient had a strong desire for fertility preservation; thus, she was referred for oncofertility counseling, receiving information about the possibility of attempting ex vivo MII oocyte retrieval and its risks. Informed consent was obtained after proper counseling, including the experimental nature of the approach.

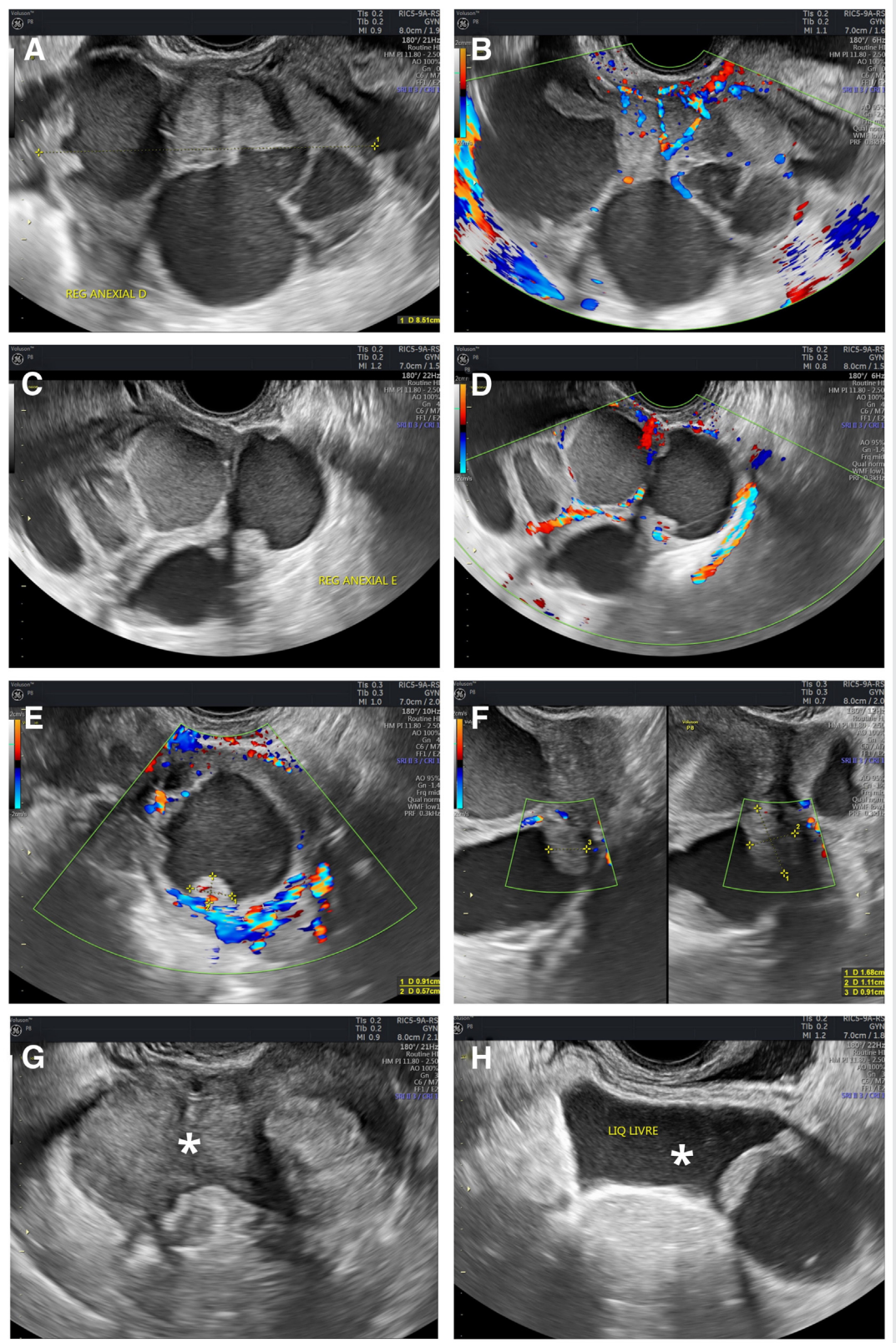
On natural subsequent cycle day 2, after confirming normal ovarian reserve by counting 11 antral follicles, a subcutaneous injection of corifollitropin alfa 150 μg (Elonva, NV Organon Oss, the Netherlands) was administered, complemented by a daily subcutaneous injection of follitropin beta 100 IU/d (Puregon, NV Organon Oss), from stimulation day 5 to stimulation day 7. From day 8 onward, stimulation was continued using a daily subcutaneous injection of follitropin beta 200 IU/d (Puregon, NV Organon Oss). Daily subcutaneous injections of ganirelix acetate 0.25 mg (Orgalutran, NV Organon Oss) were added from stimulation days 9–13. An ultrasound scan was performed on stimulation days 1, 5, 8, 10, and 12. After agreement with the oncology team, it was decided to induce follicular maturation on stimulation day 13, when the leading follicle reached the mean diameter of 16 mm. Follicular maturation was triggered by a single dose of choriogonadotropin alfa 250 μg (Ovidrel, Merck Serono S.p.A. Bari, Italy).

Surgery was planned so that the oophorectomized specimens reached the hands of the oocyte retrieval team approximately 36 hours after the maturation trigger. A diagnostic laparoscopy revealed a minimal amount of ascites, no upper abdominal or omental carcinomatosis, and a bilateral ovarian mass with infiltration of the uterus and rectosigmoid. Frozen section was evaluated by a pathologist, and it was consistent with a malignant tumor presenting with marked atypia and a probable diagnosis of high-grade serous ovarian carcinoma. A modified posterior pelvic exenteration was performed using laparotomy. The integrity of the infundibulopelvic ligament was kept until the end of the dissection to minimize ischemia, and the oophorectomized specimens were handled by the oncofertility team.

An ex vivo oocyte retrieval set was enabled inside the surgery room. The specimens were placed over a sterile surgical cloth at room temperature. Follicular aspiration was performed with a standard aspiration single lumen 17G 330 mm needle (Wallace, Smiths Medical International, United Kingdom) in a closed system connected directly to the tubes, which were placed in a tube warmer preheated to 35.6 °C. Follicular aspiration was performed with a maximum ischemia time of 31 minutes. All enlarged follicles were punctured and aspirated under ultrasound guidance, using a 6–13 MHz linear probe applied directly to the specimens (Fig. 3). A total of 21 ovarian follicles were aspirated. The transport of follicular fluids was performed in a thermal container, taking 5 minutes to cover a path of 220 meters between the hospital and the ART laboratory. Thirteen oocytes were yielded, 12 of which were MII and vitrified using the Cryotech method (Reprolife Inc., Shinjuku-ku, Tokyo).

The retroperitoneum was explored, and 3 enlarged lymph nodes were resected from the external iliac vessels bilaterally. There were no enlarged para-aortic nodes. A complete cytoreduction was achieved. The final pathology was consistent

FIGURE 1



Bilateral adnexal mass, presents a 96.1% risk of malignancy (77.2% risk for stage II–IV ovarian cancer), according to International Ovarian Tumor Analysis Group recommendations for adnexal tumors (IOTA-ADNEX) (19). Multilocular masses with solid components and dense echoes of mucinous appearance on the right (**A**), Doppler score 4 (**B**), and on the left (**C**), Doppler score 4 (**D**); in the left ovary, papillary projections measuring 9 mm × 6 mm (**E**) and 17 mm × 11 mm (**F**); metastatic uterine involvement (**G**, asterisk); free fluid in the pelvic cavity (**H**, asterisk).

de Carvalho. Birth from ex vivo retrieved MII oocytes. Fertil Steril 2024.

with high-grade serous ovarian carcinoma with infiltration of the muscularis propria of the rectosigmoid and 3 positive pelvic nodes, FIGO 2014 Stage IIIC. Adjuvant chemotherapy with 6 cycles of carboplatin and paclitaxel was prescribed, and maintenance was performed with olaparib. During the follow-up, a comprehensive mutational analysis of *BRCA*1/2 genes was employed using next-generation sequencing, detecting the *BRCA*1 variant c.1865C>T p.(Ala622Val), which is classified as benign.

Seventeen months after surgery, the patient returned with the tumor in remission, desiring to become a mother with her sister as the gestational carrier. Oocyte warming was also performed according to the Cryotech method. Intracytoplasmic sperm injection with nonidentified donor sperm was performed in the 12 warmed MII oocytes, resulting in the normal development of 9 embryos (Supplemental Fig. 1, available online), cultured in the EmbryoScope Plus time-lapse incubator (Vitrolife A/S, Denmark). Two top-quality day 3 embryos (score 5, according to the morphokinetic-based artificial intelligence KIDScore Day 3) were transferred to the gestational carrier after endometrial preparation using transdermal estradiol (Oestrogel, Besins Manufacturing Drogenbos, Belgium) from day 2 of the menstrual cycle and luteal phase support using vaginal micronized natural progesterone 600 mg/d (Utrogestan, Besins Manufacturing Drogenbos), beginning on treatment day 9, 3 days before the embryo transfer day. A positive pregnancy test was achieved 12 days later, and treatment led to a normal, healthy singleton pregnancy, an uneventful prenatal follow-up, and the LB of a healthy 46, XX infant at 3,770 kg, 51 cm, using cesarean section.

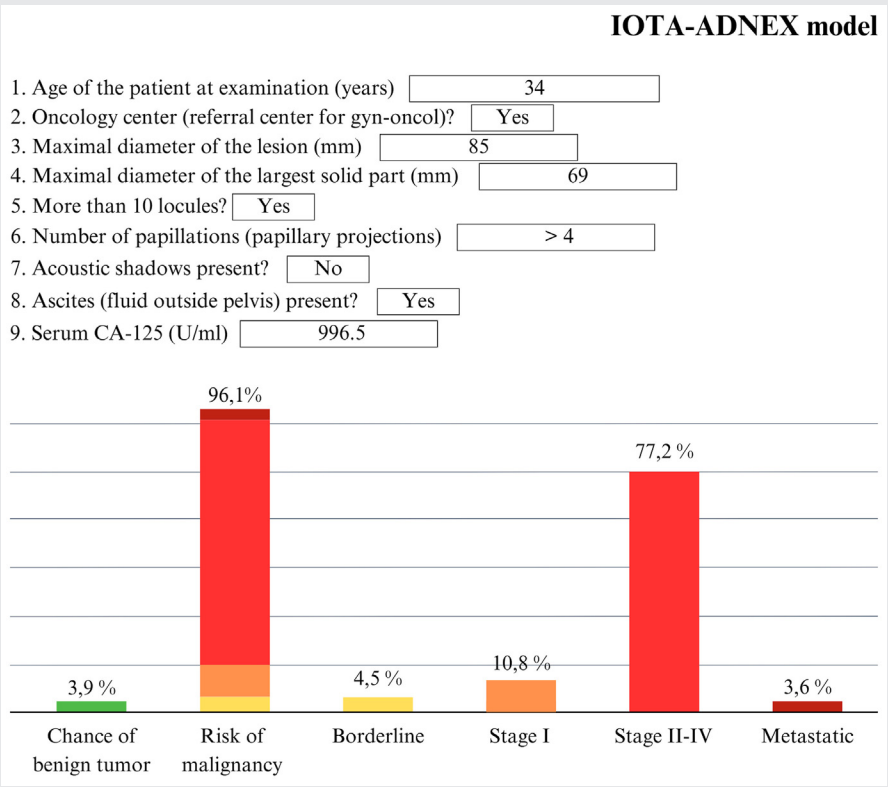
After 30 months of ovarian stimulation and surgery, tumor marker levels remained within normal limits (cancer antigen 125: 8.09 U/mL, carcinoembryonic antigen: 1.69 ng/mL). This case report was approved by the Institutional Review Board (statement CAAE 74035823.8.0000.0023), and the patient signed a written informed consent form authorizing publication.

DISCUSSION

This is the first report of a successful pregnancy and LB after transfer of embryos obtained from intracytoplasmic sperm injection of MII oocytes harvested from oophorectomized specimens after conventional gonadotropic stimulation, thus suggesting it as a feasible and possibly safe approach for fertility preservation in women with OC.

Ovarian cancer is a particularly challenging issue in the oncofertility scenario, and comprehensive care for this specific group of women demands more discussion on the opportunities to reach their family-building desire as an aspect of quality of life beyond the disease. Cryopreservation of mature oocytes has been increasingly used worldwide with the aim of preserving the fertility of women with malignancies (5, 27). However, it is noteworthy that conventional MII oocyte

FIGURE 2



Risk of malignancy, according to International Ovarian Tumor Analysis Group recommendations for adnexal tumors (IOTA-ADNEX).

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FIGURE 3

Ex vivo oocyte retrieval set, inside the surgery room, where the ovaries were placed over a sterile surgical cloth, at room temperature, and ultrasound-guided follicular aspiration was performed with a standard aspiration single lumen needle, in a closed system connected directly to the tubes, which were placed in a tube warmer preheated to 35.6 °C.

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retrieval, which is performed using follicular puncture through the vaginal fornix after ovarian stimulation with gonadotropins, may carry the risk of cancer stimulation and rupture of the tumor capsule, leading to malignant cell spillage. Thus, the aspiration of small follicles from no stimulated or mildly stimulated oophorectomized specimens has been broadly tested as an effort toward elimination of the abovementioned risks, obtaining immature oocytes that are subsequently matured in vitro (14, 16, 17, 28–32), with a maturation rate of approximately 35% (16, 31, 32).

Nevertheless, even being widely studied, IVM has not been demonstrated to evolve significantly since early studies, and reproductive outcomes are far below expectations, even for in vivo retrieved immature gametes. Concerns about the IVM of immature oocytes lay in the possibility of incomplete cytoplasmic maturation and developmental competence, lacking the accumulation of factors that prepare the gamete for fertilization and embryonic development (20). In addition, diminished early cleavage and blastulation rates in IVM-derived zygotes have been demonstrated, as well as multinucleation and elevated rates of direct cleavage from 1–4 cells (33). Recent data also show that IVM may lead to lower implantation and cumulative LB rates per complete ART treatment cycle than conventional treatments (20, 34), and such a context supports different reproductive medicine societies to recognize that more research is needed to increase the efficiency of the technique for clinical application (20). For these reasons, developing protocols and interventions to efficiently retrieve in vivo matured oocytes without changing the oncological prognosis would mean a great advance for fertility preservation in ovarian malignancies.

Our report is novel in that prior case reports of ex vivo retrieval of MII oocytes after ovarian stimulation did not result in a LB (21–25) (Table 1). The pioneer case studies from Fatemi et al. (21) (2011) and Bocca et al. (22) (2011) both reported the strategy in women before the age of 30 years, leading to the recovery of satisfactory amounts of MII oocytes but aspirating the follicles exclusively identified by the external view, then assuming the possibility of leaving mature follicles behind. The de la Blanca et al. (24) report introduced the use of an adapted transvaginal ultrasound probe directly applied to the specimens, aiming to facilitate access to all potential mature follicles. Finally, in 2021, we published the first Brazilian report of the use of the technique, from which 12 MII and 3 IVM oocytes were vitrified, proposing the use of a 6–13 MHz ultrasound linear probe directly applied to the oophorectomized specimens (25).

A point of concern to be raised in the case we present is the possible role of follicle-stimulating hormone (FSH) in ovarian epithelial tumorigenesis. Despite the fact that this association is inconclusive to date, one should not deny that the incidence of epithelial OC is elevated in postmenopausal years, when the circulating serum FSH level is expected to be 10–20 times higher than in reproductive years (8–10). Additionally, there are studies demonstrating that FSH may affect signaling pathways, gene expression, tumor proliferation, invasion, angiogenesis, and adhesion in epithelial OC (10), supporting the hypothesis of a short term potential oncologic risk from exposure to supraphysiologic FSH serum levels.

As a counterpart, data from 2 recent meta-analyses on gonadotropin use during fertility treatments vs. OC are reassuring. According to Rizzuto et al. (35) (2019), available studies are not strong enough to support concerns about a higher risk of OC in women treated with fertility drugs, because of low quality, short follow-up periods, and important confounding factors. Additionally, infertility alone may be considered a risk factor for OC, and its association with infertility drugs needs to be adjusted to age, body mass index, parity, and genetic factors (35). The meta-analysis of Barcroft et al. (36) (2021) draws attention to the intertwinement between infertility itself and fertility treatments, challenging researchers to define when an eventual greater incidence of ovarian tumors is because of fertility drugs or when it is just a spotlight over an at-risk population.

TABLE 1

Summary of case reports using ex vivo retrieval of mature oocytes in ovarian tumors.

Reference	Age (y)	Type of tumor	Marital status; parity; brief medical history	Controlled ovarian stimulation protocol	Surgery type	Ultrasound guidance (yes/no)	Total MII oocytes yielded	Total in vitro matured oocytes
Fatemi et al. (21), 2011	27	Papillary serous adenocarcinoma (recurrence)	Not mentioned; nulliparous; previous infertility reported; previous laparoscopic left salpingo-oophorectomy; papillary serous adenocarcinoma; ovarian reserve not mentioned.	rFSH 200 IU/d; ganirelix acetate, 0.25 mg/d, from d 6; maturation trigger with urinary hCG 10,000 IU	Laparotomy	No	13[a]	0
Bocca et al. (22), 2011	25	Serous borderline tumor	Single; nulliparous; previous laparoscopic left salpingo-oophorectomy; serous borderline ovarian tumor; AFC approximately 10	rFSH 200 IU/d; ganirelix acetate, 0.25 mg/d from d 7–10; maturation trigger with rhCG 250 μg on d 10	Laparoscopy, approximately 34–35 h after maturation trigger[b]	No	14	0
Pereira et al. (23), 2017	37	Not mentioned	Single; nulliparous; AFC approximately 14	rFSH 300 IU/d + HP-hMG 150 IU/d + letrozole 5 mg/d; rFSH reduced to 150 IU/d from d 8–11; ganirelix acetate, 0.25 mg/d; maturation trigger with rhCG 250 μg on d 12	Laparotomy, approximately 34 h after maturation trigger	No	7	0
de la Blanca et al. (24), 2018	31	Struma ovarii	Single; nulliparous; previous laparoscopic left salpingo-oophorectomy; mature teratoma; AFC unfeasible; AMH 1.1 ng/mL	Corifollitropin alpha 150 μg, rFSH 200 IU/d from d 8–9; ganirelix acetate, 0.25 mg/d, from d 6–10; maturation trigger with rhCG 250 μg on d 10	Laparoscopy, approximately 35 h after maturation trigger	Yes	5	0

de Carvalho. Birth from ex vivo retrieved MII oocytes. Fertil Steril 2024.

TABLE 1

Continued.

Reference	Age (y)	Type of tumor	Marital status; parity; brief medical history	Controlled ovarian stimulation protocol	Surgery type	Ultrasound guidance (yes/no)	Total MII oocytes yielded	Total in vitro matured oocytes
de Carvalho et al. (25), 2021	28	Serous borderline tumor, bilateral	Married; nulliparous; AFC 27	Corifollitropin alpha 150 μg, rFSH 250 IU/d from treatment d 8–10; ganirelix acetate, 0.25 mg/d, from d 6–11; maturation trigger with triptorelin acetate 0.2 mg on d 10	Laparoscopy, approximately 36 h after maturation trigger	Yes	12	3

Note: AFC = antral follicles count; AMH = antimüllerian hormone; hCG = human chorionic gonadotropin; HP-hMG = highly purified human menopausal gonadotropin; MII = metaphase II; rFSH = recombinant follicle-stimulating hormone; rhCG = recombinant human chorionic gonadotropin.

[a] Intracytoplasmic sperm injection was proceeded, and seven top-quality zygotes were vitrified.

[b] Informed by the first investigator.

de Carvalho. Birth from ex vivo retrieved MII oocytes. Fertil Steril 2024.

In conclusion, ex vivo retrieval of MII oocytes may be an interesting strategy for fertility preservation in women with OC, and this is the first report pointing to the most important reproductive outcome measure, the birth of a live and healthy child. However, the few reports to date do not support ex vivo mature oocyte retrieval for routine use, and it must be considered an experimental approach. Larger series and further well-designed studies are needed to reinforce our findings, offering reliable information on the feasibility and safety of gonadotropic stimulation in patients with OC, as well as confronting risks vs. chances of reproductive success.

CRediT Authorship Contribution Statement

Bruno R. de Carvalho: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Georgia F. Cintra:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Íris O. Cabral:** Writing – review & editing, Supervision, Investigation. **Taise M. Franceschi:** Writing – review & editing, Methodology, Investigation. **Leandro S.A. Resende:** Writing – review & editing, Methodology. **Janina F.L. Huguenin:** Writing – review & editing, Methodology. **Andrea Tatiane O.S. Barros:** Writing – review & editing, Methodology.

Declaration of Interests

B.R.D.C. is speaker ad hoc Corifollitropin alfa for Organon Brasil. G.F.C. has nothing to disclose. I.O.C. has nothing to disclose. T.M.F. has nothing to disclose. L.S.A.R. has nothing to disclose. J.F.L.H. has nothing to disclose. A.T.O.S.B. has nothing to disclose.

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