Human Reproduction, Vol.29, No.2 pp. 276–278, 2014
Advanced Access publication on December 9, 2013 doi:10.1093/humrep/det420

human reproduction

CASE REPORT *Infertility*

First pregnancy and live birth resulting from cryopreserved embryos obtained from *in vitro* matured oocytes after oophorectomy in an ovarian cancer patient

E.B. Prasath[1,4,*], M.L.H. Chan[1], W.H.W. Wong[1], C.J.W. Lim[1], M.D. Tharmalingam[1], M. Hendricks[1,4,5], S.F. Loh[1,2,4,5], and Y.N. Chia[3,6]

[1] Department of Reproductive Medicine, KKIVF Centre, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore [2]Duke-NUS Graduate Medical School, Singapore [3]Department of Gynaecological Oncology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore
[4]Present address: Thomson Fertility Centre, 8 Sinaran Drive, Singapore 307470
[5]Present address: The O&G Specialist Clinic, Thomson Medical Centre, 339 Thomson Road, Singapore
[6]Present address: Department of Gynae-Oncology, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore

*Correspondence address. Tel: +6563941026; Fax: +6562918135; E-mail: balaivf@yahoo.com

Submitted on May 1, 2013; resubmitted on October 19, 2013; accepted on October 28, 2013

ABSTRACT: *In vitro* maturation (IVM) of immature oocytes retrieved from surgically resected ovaries has been proposed as a method of fertility preservation in ovarian cancer patients undergoing definitive surgery. While there had been several reports of successful derivation of mature oocytes and or embryos, there have been no reports as yet of successful pregnancies. In this case report, we present a pregnancy and live birth from a young patient, with stage IIIC ovarian cancer, who had undergone fertility sparing surgery. The immature oocytes recovered after oophorectomy were fertilized after IVM. The embryos obtained were cryopreserved and later transferred to achieve a singleton healthy pregnancy leading to a live birth.

Key words: *in vitro* maturation / ovarian cancer / IVF / fertility preservation / cryopreservation

Introduction

In vitro maturation (IVM) of oocytes harvested from ovaries in cases of cancer forms an integral part of fertility preservation. Oocytes harvested from ovaries *ex vivo* have been reported, with successful vitrification of matured oocytes. Although an attempt at transferring embryos from obtained frozen–thawed *in vitro* matured oocytes has been reported (Fadini *et al.*, 2012), there had been no pregnancies reported to date. Here we present a case report of a successful pregnancy and live birth after the transfer of frozen–thawed embryos obtained from oocytes which had been recovered from a cancerous ovary after oophorectomy, matured *in vitro* and fertilized by ICSI. This approach was used in the context of ovarian cancer in a young woman with recurrent ovarian tumours.

Case report

A 21-year-old nulliparous woman presented in April 2009 with bilateral large pelvic masses, peritoneal disease and ascites, and raised serum CA125 of 1279 U/ml. Intra-operatively, both ovaries were noted to be replaced by papillary tumours with seedings over the omentum and pelvic peritoneum in addition to a large amount of ascites. A frozen histological section of the right ovarian tumour showed a borderline serous pathology. A fertility sparing right salpingo-oophorectomy and left ovarian cystectomy, infragastic omentectomy and resection of invasive implants on the rectal serosa and bladder and right pelvic lymph node dissection was performed. The final histological report revealed bilateral borderline serous tumours with foci of well-differentiated serous carcinoma, invasive implants in the omentum and bladder serosa and one

pelvic lymph node showing metastatic serous carcinoma. Her final diagnosis wa micropapillary serous carcinoma of the ovary, FIGO Stage IIIC Grade 1. Post-operatively, she received six cycles of adjuvant carboplatin and paclitaxel chemotherapy. Seven months after completion of adjuvant chemotherapy, she was noted to have rising CA 125 on a routine follow-up. Magnetic resonance imaging of the abdomen and pelvis showed a 7.1 cm complex cyst in her remaining left ovary, suggestive of isolated recurrent disease.

At this point, she was referred to our centre for discussion regarding fertility preservation. Stimulation of the ovary was avoided due to shortage of time and potential concern about using agents for ovarian stimulation (Lobo, 2005). The *in vivo* collection and subsequent preservation of immature oocytes or ovarian tissue was not considered in order to avoid infection and transmission of disease in the future. Therefore, a left salpingo-oophorectomy was performed on Day 5 of her menstrual cycle with left pelvic lymph dissection and preservation of the uterus. The oophorectomy specimen was transferred to the IVF laboratory within 20 min in HEPES buffered HTF medium (Irvine Scientifc, USA) and all visible follicles were aspirated with an 18G needle attached to a 10 ml syringe. The aspirates were placed in HEPES-buffered HTF medium, and the presence of oocyte–cumulus complexes was sought. Four immature GVoocytes were retrieved, all of which matured within 24 h in IVM medium (Origio, Denmark) supplemented with recombinant FSH (Puregon, MSD) and HCG (MSD). As the patient was married, matured MII oocytes were fertilized through ICSI of the husband's sperm, resulting in three high-grade embryos which were cryopreserved on Day 2 by controlled slow freezing. Embryo cryopreservation was chosen over cryopreservation of oocytes because, in our hands at the time, the survival rate of cryopreserved embryos was better than that of cryopreserved oocytes.

Histology of the left ovarian tumour showed a borderline serous tumour with metastatic deposits noted in 4 out of 10 left pelvic lymph nodes. She declined further chemotherapy. Her CA 125 normalized at 4 months after the second surgery and she remained disease free on follow-up.

Fourteen months after her second surgery, the patient requested to have her frozen embryos transferred after extensive discussion with both her oncologist and the fertility team. Two embryos were thawed and replaced in an artificial frozen-embryo transfer cycle after three cycles of combined oral contraceptive pill treatment. This produced a normal healthy singleton pregnancy resulting in the live birth of a healthy baby boy at 2.580 kg.

The patient has given consent for publication of this report. Institutional ethical approval was not required as this was case report.

Discussion

Borderline ovarian tumours typically occur in younger women, who tend to present in early stages of the disease. In particular, for early stage tumours, fertility sparing surgery has been proposed, although recurrence and malignancy may still recur (Cadron *et al.*, 2007). In these cases, because of high rates of recurrence of up to 45% with conservative surgery, such as a cystectomy (Cadron *et al.*, 2007), the generation of oocytes for vitrification or embryo generation is now becoming an option for fertility preservation (Huang *et al.*, 2007; Fatemi *et al.*, 2011).

In this case, the final histology included foci of well-differentiated micro-papillary serious carcinoma in the largely borderline serous tumour. Despite adjuvant chemotherapy, she had a recurrence involving her other ovary, necessitating its removal. The option for fertility preservation in this context was thus limited to obtaining oocytes for either cryopreservation through vitrification or the generation of embryos, as ovarian tissue cryopreservation has a theoretical risk of re-implantation of the cancer or multi-foci neo-carcinogenesis in the remaining tissues (Cadron *et al.*, 2007).

To date, there are five other reports on the *ex vivo* harvest of oocytes in the context of borderline ovarian tumours. Revel *et al.* (2004) reported a similar approach as ours in an endometrial cancer patient. However, embryo transfer was not done as the patient had to look for surrogacy as she also had hysterectomy. Another approach involved the use of IVM of immature oocytes harvested at the time of oophorectomy and vitrification of resulting oocytes (Huang *et al.*, 2007). A different approach utilized controlled hyperstimulation of the ovaries, and retrieval of mature oocytes at oophorectomy either through laparotomy (Fatemi *et al.*, 2011) or laparoscopy (Bocca *et al.*, 2011), with subsequent vitrification of the oocytes. Similar to Huang *et al.*, Fadini *et al.* (2012) cryopreserved oocytes after IVM then performed ICSI and transferred two resulting embryos in a patient with ovarian adenocarcinoma. However, this did not result in a pregnancy. To our knowledge, this case reported here is the first successful pregnancy and live birth reported, from the transfer of frozen–thawed embryos derived from *ex vivo* harvested oocytes, after IVM and ICSI, thus validating this important approach in fertility preservation in suitable candidates, ovarian cancer patients in particular. Our approach is feasible only when the patient has a partner at the time of surgery.

Authors' roles

E.B.P. was responsible for the study conception and design, the harvesting and *in vitro* maturation of oocytes and the preparation of the manuscript. M.L.H.C., W.H.W.W., C.J.W.L., D.M.T. were responsible for the embryology work and the interpretation of data. M.H. was responsible for clinical work and the preparation of the manuscript. S.F.L. was responsible for the study conception and design, clinical work, supervision and the preparation of the manuscript. Y.N.C. was responsible for the study conception, clinical work and the preparation of the manuscript.

Funding

No external funding was received.

Conflict of interest

There are no conflicts of interest to be declared.

References

Bocca S, Dedmond D, Jones E, Stadtmauer L, Oehninger S. Successful extracorporeal mature oocyte harvesting after laparoscopic oophorectomy following controlled ovarian hyperstimulation for the purpose of fertility preservation in a patient with borderline ovarian tumor. *J Assist Reprod Genet* 2011;**28**:771–772.

Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I. Management of borderline ovarian neoplasms. *J Clin Oncol* 2007;**25**:2928–2937.

Fadini R, Dal Canto M, Renzini MM, Milani R, Fruscio R, Cantù -, Brambillasca F, Coticchio G. Embryo transfer following in vitro maturation and cryo-preservation of oocytes recovered from antral follicles during conservative surgery for ovarian cancer. *J Assist Reprod Genet* 2012;**29**:779–781.

Fatemi HM, Kyrou D, Al-Azemi M, Stoop D, De Sutter P, Bourgain C, Devroey P. Ex-vivo oocyte retrieval for fertility preservation. *Fertil Steril* 2011;**95**:1787, e15–1787.e15

Huang JY, Buckett WM, Gilbert L, Tan SL, Chian RC. Retrieval of immature oocytes followed by in vitro maturation and vitrification: a case report on a new strategy of fertility preservation in women with borderline ovarian malignancy. *Gynecol Oncol* 2007;**105**:542–544.

Lobo RA. Potential options for preservation of fertility in women. *N Engl Med* 2005;**353**:64–73.

Revel A, Safran A, Benshushan A, Shushan A, Laufer N, Simon A. In vitro maturation and fertilization of oocytes from an intact ovary of a surgically treated patient with endometrial carcinoma: case report. *Hum Reprod* 2004;**19**:1608.