Double oocyte retrieval in a cancer patient for emergency fertility preservation: A case report

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Fertility preservation

Fertility preservation(FP) has emerged as a new discipline within the past decade

Fertility preservation

- The overall increase in long term survival for cancer pts
- Concerning quality of life
- Improving the ART technologies

- Patients
- Oncologists
- Fertility specialists

such a new and important discipline

Fertility preservation

- Embryo cryopreservation → standard
- Oocyte cryopreservation → standard
- Ovarian cryopreservation → experimental
- Ovarian transposition → standard

ASCO guideline

- Adult Females
- Present both embryo and oocyte cryopreservation as established fertility preservation methods
- Discuss the option of ovarian transposition when pelvic radiation is performed as cancer treatment
- Inform patients of conservative gynecologic surgery and radiation options
- Inform patients that there is insufficient evidence regarding the effectiveness of ovarian suppression (GnRH agonists) as a fertility preservation method, and these agents should not be relied on to preserve fertility
- Inform patients that other methods (e.g.ovarian tissue cryopreservation, which does not require sexual maturity, for the purpuse of future transplantation) are still experimental

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ASCO SPECIAL ARTICLE

Fertility Preservation for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

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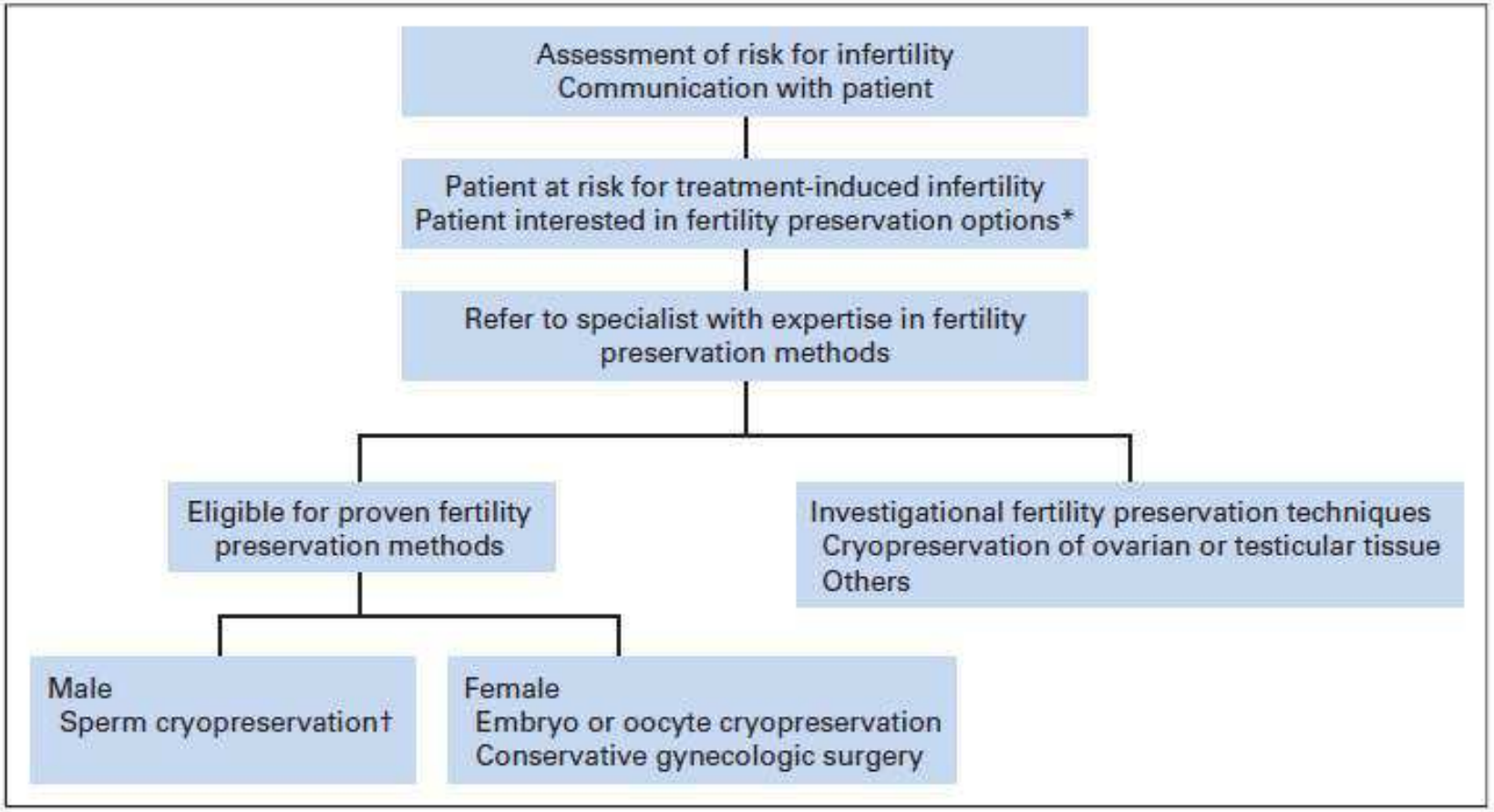


Ovarian stimulation

- One of the most important challenge is the time required to complete the OI in oncological patients
- Conventionally stimulation with GnRH antagonist is initiated at the beginning of the follicular phase
- This may require 2-6 weeks, depending on the patient's cycle day

Double oocyte retrieval in the same menstruel cycle for emergency FP

Purpose;

To report the double oocyte retrieval procedure where late follicular and luteal phase (in combined with ovarian stimulation) oocyte recovery was performed for emergency fertility preservation.

Double oocyte retrieval in the same menstruel cycle for emergency FP

- A patient aged 33 years diagnosed with invasive ductal carcinoma
- The patient was on her 7^{th} day of menstrual cycle and baseline ultrasound showed a 12 mm follicle in the right ovary
- E2=95 pg/ml,
- FSH=5.8 IU/L, and
- LH =3.3 IU/L
- The first plan was suppressing the dominant follicle by using a GnRH antagonist for a few days following random start of letrozole (5 mg/day) plus recombinant FSH for the ovulation induction.

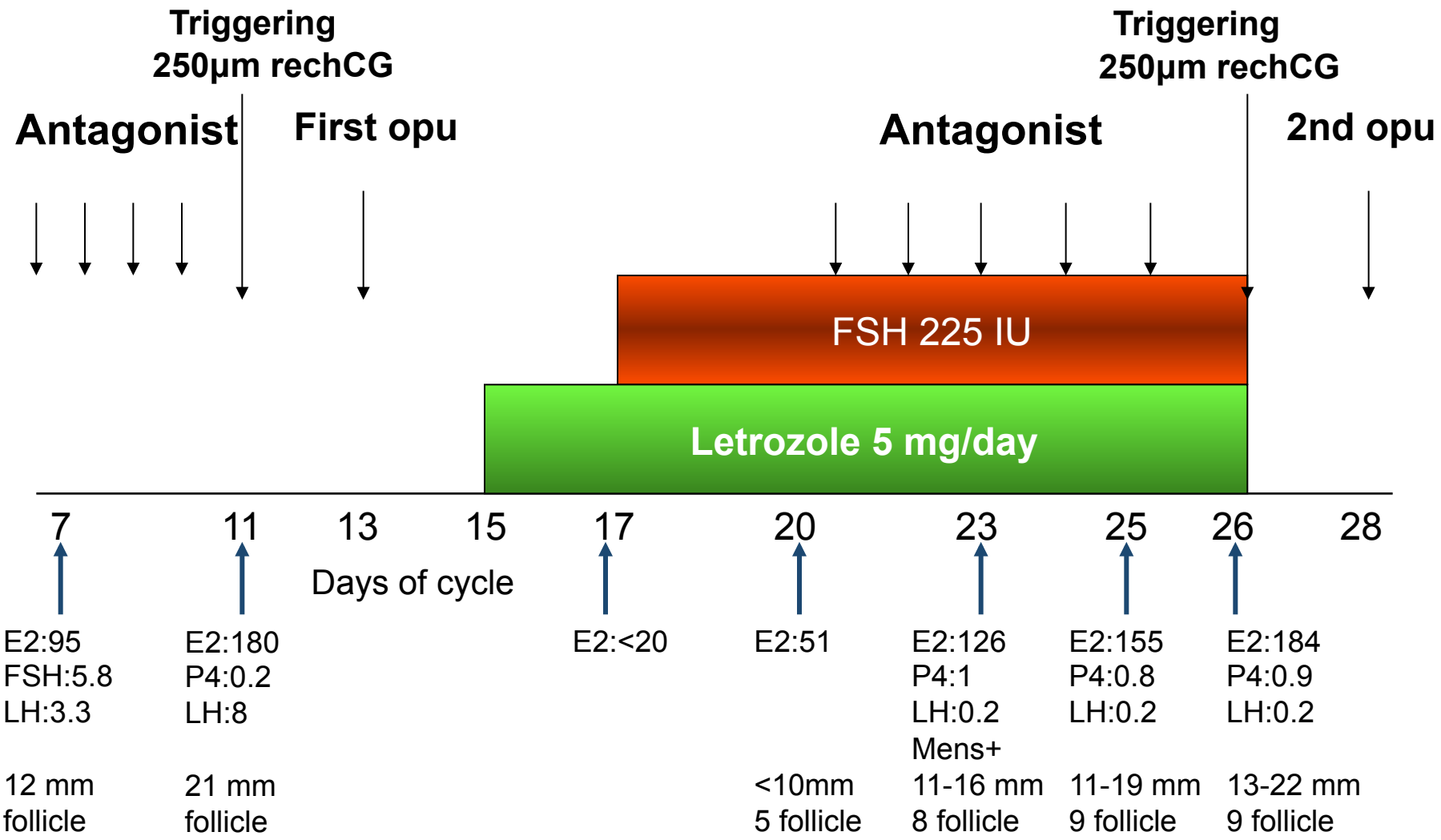
Double oocyte retrieval in the same menstruel cycle for emergency FP

- After 4 days injection of GnRH antagonist, usg revealed a dominant follicle in 21 mm diameter with E_2 level=180 pg/ml, LH= 8 IU/L and progesterone level = 0.2 ng/ml
- Ovulation was triggered with 250µm rec hCG
- First opu was performed 36 h after, one mature oocyte was obtained, ICSI was performed and 4-cell, grade 1 embryo was vitrified on day 2

Double oocyte retrieval in the same menstruel cycle for emergency FP

- Second stimulation was started 2 days later with letrozole 5 mg/day plus recFSH 225 IU/day , a GnRH antagonist was added on 5th day of FSH stimulation
- Total duration of luteal phase stimulation was 12 days
- At the 13th day of induction ultrasound showed 5 follicles within ≥17 mm diameter.
- Serum peak E2 =184 pg/ml, LH= 0.2 IU/L, progesterone= 0.9 ng/ml
- Totally 8 oocytes were harvested resulting in 5 embryos (3 cell-I-II, 4 cell-I, 6 cell-I, 8 cell-I/II, 10 cell-I) to be frozen. One additional embryo was frozen from the first attempt.

Double oocyte retrieval in the same menstruel cycle for emergency FP



Discussion

- For women whose cancer treatment cannot be delayed, there is a narrow window for egg collection
- The conventional approach requires approximately 2 weeks of ovulation induction from the beginning of the menstrual cycle
- This may require 2-6 weeks, depending on the patient's cycle day

Random start ovulation induction

- Different protocols have been described
- Initiating luteolysis followed by COS with menses
- Inducing luteolysis with simultaneus COS
- Performing a random start COS irrespective of phase

Random start ovulation induction

- **Anderson et al. (1999);** CL breakdown induced by GnRH antagonist, 4 days later COS started, 6 and 4 mature oocytes obtained

- **vonWolff et al.(2009);** random start IVF study; compared (n=40) cycle outcomes of follicular or luteal phase start groups

  Cancer pts in lutal phase (n=12) started GnRH antagonist and recFSH simultaneously

  Duration of stimulation, mean number of retrieved oocytes, MII oocytes and fertilization rates were similar

  High progesterone levels in the luteal phase group did not affect oocyte quality

  This protocol allowed oocyte retrieval in cancer patients within 2 weeks irrespective of menstrual cycle day

- **Bedoschi et al (2010):** Two pts with OI started in **luteal phase**, GnRH antagonist and gonadotropins simultaneusly started , 12 oocytes obtained

- **Sönmezer et al (2011):** Random start OI (**day 11,14,17**) with letrozole and recFSH in three breast ca pts, total duration of COH ranged 9-12 days and resulted 7-10 embryos for cryopreservation

- **Nayak et al.(2011):** Four pts with cancer, random start OI (**day 10-17**), recFSH+GnRH antagonist protocol, GnRH agonist trigger. Duration of COH ranged 8-13 days and total of 14-40 oocytes resulted 5-20 embryos

- **Keskin et al (2014):** Random start OI in three pts with cancer (**Day 5,8,15**). Duration of COH ranged 7-8 days resulted in 4-9 mature oocytes. Time saved to start cancer treatment was 16 to 26 days

Random start ovulation induction

- **Çakmak et al. (2013)** ; Random (n=35) vs conventional-start COS (n=93)
- The number of oocytes retrieved (14.4 vs 14.5) , maturation rates, fertilization rates were similar
- In random start group: the length of COS was longer (9.3 vs 10. 9 day) and total gonadotropin used was higher
- **Follicular development patterns and E_2 rise were similar**
- **In luteal phase-start cycles, CL regression and decreasing P_4 levels were observed**
- Random start COS is as effective as conventional-start COS in fertility preservation. This protocol would minimize delays and allow more pts to have a chance for FP.

Random start ovulation induction

- **Rashidi et al (2014);** 7 pt with random start vs 7 pt with conventional stimulation. Duration of stimulation (7.8 vs 8.7), dose of gonadotropins, no of oocytes (5.8 vs 7.8)
- **Kim et al. (2015);** 22 pts with random start OI vs 44 women with conventional start. The number of oocytes was higher (11.5 vs 7.4) and duration of stimulation (11.4 vs 10.3) was longer in random start group
- **Simi et al. (2015);** Retrospective analysis of follicular (n=13) or late follicular/luteal phase OI (n=12)

  Days of stimulation, doses of gonadotropins, peak E2 levels, number of mature oocytes were found similar

Random start ovulation induction

- **Von Wolff et al.(2016);** Analysis of 684 women's OI outcomes
- Cycle day 1-5 (69%)
- Cycle day 5-14 (15%)
- Cycle day >14 (15%)

Days of stimulation: 10.8-10.6- 11.5

Dose of gonadotropins:2496-2529-2970 IU

no of retrieved oocytes: 11.6-13.9-13.6

'**stimulation can be started at any phase of the cycle before gonadotoxic treatment, including the luteal phase** '

Random start ovulation induction

- Multiple waves of follicular reqruitment within a single interovulatory period (*Baerdwald et al.2003*)
- Antral follicles observed in luteal phase may not be atretic
- Luteal phase oocyte retrieval and IVM provides evidence that oocytes obtained at luteal phase can be competent to mature and fertilized (*Oktay K et al.2008*, *Demirtas et al.2008, Maman et al. 2011*)

Future viability? Pregnancy rates?

- Prospective study: 242 luteal phase stimulation outcomes were analyzed (Kuang et al.2014)
- COS protocol: Letrozole 2.5 mg+HMG 225 IU/day **after spontan ovulation**, agonist trigger
- Average number of oocytes:13.1
- Average number of high qualty embryos: 4.8
- In FET cycles: CPR 55.4%, ongoing PR 48.9%

  IR: 40.3%

  Luteal-phase ovarian stimulation is feasible for producing competent oocytes/embryos, with optimal pregnancy outcomes in FET cycles

Future viability? Pregnancy rates?

- Martinez et al. (2014) performed two ovarian stimulations of the same donor (Cycle day 2 start and cycle day 15 start)
- Similar mature oocyte number (14 vs 16)
- Similar fertilization rates (77.3 vs 76.5%)
- Similar pregnancy rates (62.5 vs 58.3%)
- Similar implantation rates (41.6 vs 45%) in recipients

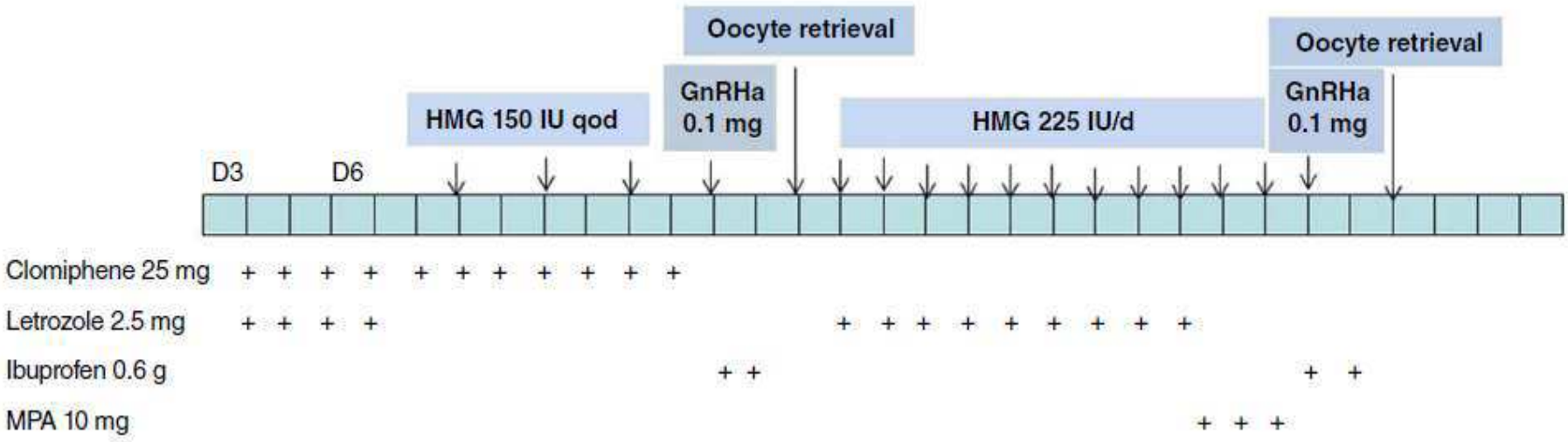
Double ovarian stimulation

- A case report of a patient with POR
- Two oocyte retrievals within the follicular and luteal phase of the same menstrual cycle
- Minimal stimulation with agonist trigger
- One mature oocyte obtained from luteal phase, and resulted into a 8-cell embryo

Xu et al. 2013, RMB online

Double ovarian stimulation

- A pilot study evaluated the efficacy of double ovarian stimulation during the follicular and luteal phase in poor responders (Kuang et al.2014) (Shanghai protocol)
- 38 women enrolled, 30 women underwent second stimulation, 26 had one to six viable embryos
- More oocytes/embryos could be obtained in a shorter period



Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation

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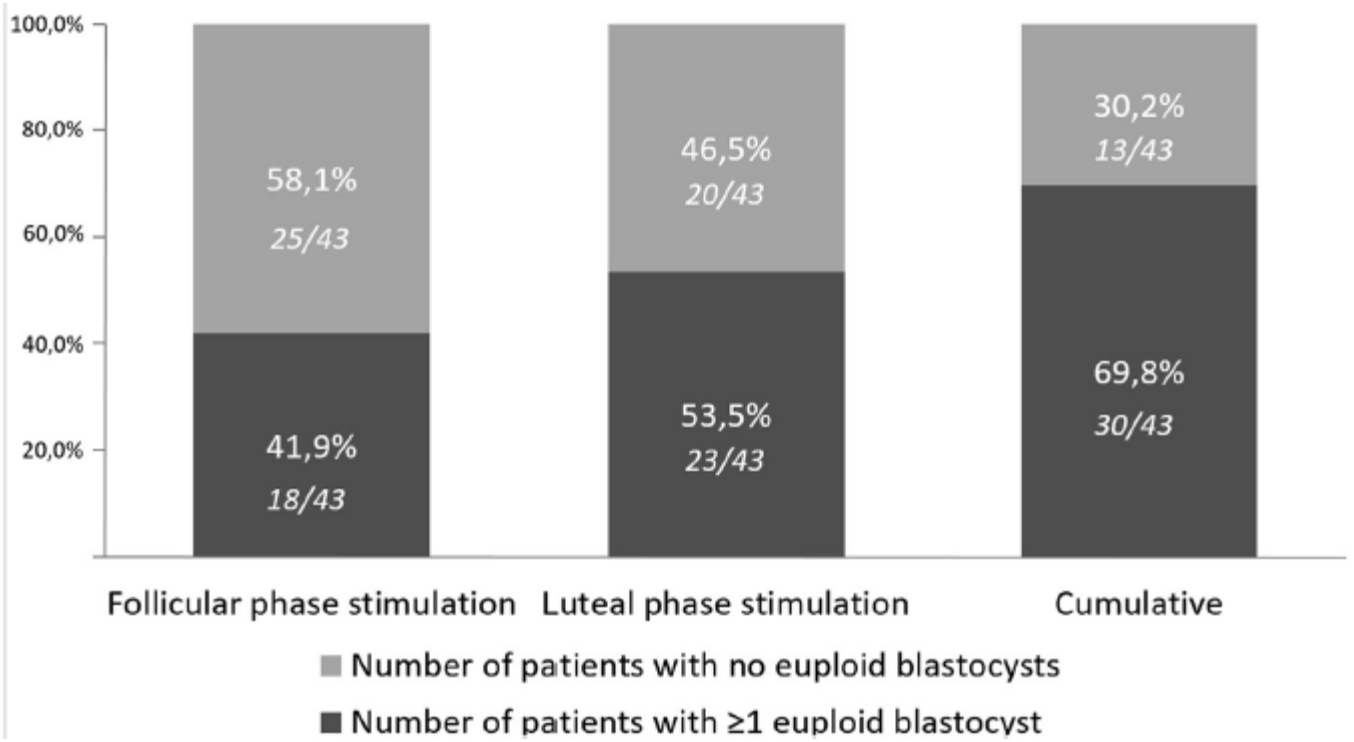

Fertility Steriliy, 2016

Double ovarian stimulation

- DuoStim in the same menstrual cycle could provide an opportunity to retrieve more oocytes
- DuaStim well tolerated by women and provides twice as many oocytes and embryos as a regular antagonist protocol in less than 30 days (Moffat et al. 2014)
- The short overall duration of these approaches (<30 days) is valuable for cases of fertility preservation (Moffat et al.)

Conclusion

- Starting COS anytime of menstrual cycle is an established method in oncological patients
- In order to obtain much more oocyte/ embryos; double stimulation might be a feasible option for selected patients.

THANK YOU,,,

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