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Fertility Preservation

Fertility preservation

- Improvements in treating cancer have enabled many younger persons with cancer to survive.
- 5year survival rates with testicular cancer, hematologic malignancies, breast cancer, and other cancers that strike young people may be as much as 90% to 95%.
- Treatment of these cancers is often highly detrimental to both male and female reproductive function.
- Fertility preservation before gonadal damage is emerging as a discipline in itself

U.S. National Institutes of Health, National Cancer Institute, Division of Cancer Control and Population Sciences. Surveillance, Epidemiology, and End Results Program, 1975–2000

- Patients receiving potentially gonadotoxic therapies should be given options for fertility preservation and future reproduction before starting such treatment
- Established methods of fertility preservation include embryo and oocyte cryopreservation prior to gonadotoxic therapy.
- Experimental procedures such as cryopreservation of ovarian tissue in girls should be offered only in a research setting.
- The data on the use of GnRH agonist for ovarian suppression have been conflicting; until definitive proof of efficacy is established, other fertility preservation options should be offered with GnRH agonist.
- Ovarian transposition is an option to reduce gonadal damage prior to pelvic radiotherapy with variable results.
- All available options should be offered and can be performed alone or in combination, often without delay to cancer treatment.

Fertility preservation in women

Indefinite procedures

Definite procedures

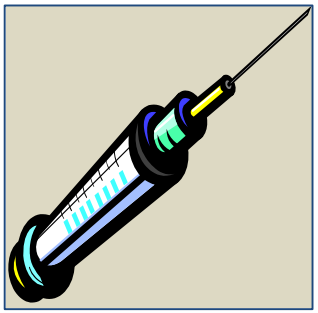
GnRH a depot for ovarian suppression

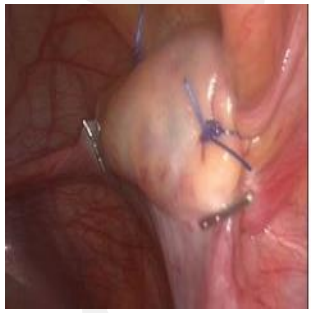
Ovario-pexy & ovarian trans-position

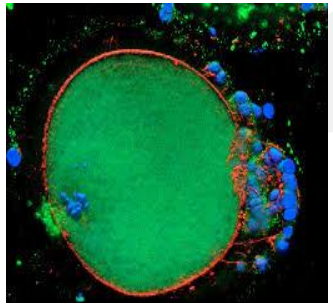
Embryo/ oocyte cryo-preserva-tion

IVM of oocytre cumulus complex

Ovarian tissue cryo-preservat ion

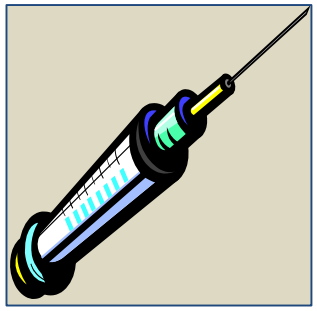






GnRHa depot protects ovarian function by returning it to the pre-pubertal state

GnRH a depot for ovarian suppression



Proposed mechanisms:

- Central suppression of gonadotropin secretion
- Suppresses gonadotropin receptors on ovary
- Decreases ovarian metabolism and blood flow
- Up-regulates gonadal protective molecules
- Prevents apoptosis? Possible protection of germ line stem cells?

Prevention of Early Menopause Study (POEMS)-S0230

Phase III trial of LHRH analog during chemotherapy to reduce ovarian failure in early stage, hormone receptor-negative breast cancer: an international Intergroup trial of SWOG, IBCSG, ECOG, and CALGB (Alliance)

Halle C.F. Moore, Joseph M. Unger, Kelly-Anne Phillips, Frances Boyle, Erika Hitre, David Porter, Prudence A. Francis, Lori Minasian, Richard D. Gelber, Lori J. Goldstein, Henry L. Gomez, Carlos S. Vallejos, Ann H. Partridge, Shaker R. Dakhil, Silvana Martino, William E. Barlow, Carol J. Fabian, Frank L. Meyskens, Gabriel N. Hortobagyi, Kathy S. Albain

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Halle Moore at 2014 ASCO Annual Meeting

Goserelin Administration

- Goserelin 3.6 mg SubQ every 4 weeks
- Started at least 1 week prior to first chemotherapy dose
- Continued for duration of chemotherapy
  - Last goserelin administered within 2 weeks of (before or after) the final chemotherapy dose

Endocrine Toxicity

	Standard Chemotherapy n=111	Chemotherapy + Goserelin n=103	
Grade II-IV	27(24%)	49 (48%)	p=.0006
Grade III-IV	6 (5%)	7 (7%)	p=.89
Grade IV	0	1	

Most common added toxicities with goserelin were hot flashes, mood changes, vaginal dryness, and headache.
Only grade IV toxicity was a thromboembolic event.

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POEMS Ovarian Failure

	Standard Chemotherapy	Chemotherapy + Goserelin
Ovarian failure at 2 years	15/69 = 22%	5/66 = 8%

Logistic Regression Results:

Analysis	Odds Ratio	95% CI	p-value	
			One-sided	Two-sided
Univariate	0.30	0.10 – 0.87	p=.01	p=.03
Stratified*	**0.30**	**0.09 – 0.97**	**p=.02**	**p=.04**
Multivariate*	0.36	0.11 – 1.14	p=.04	p=.08

*Accounting for age and regimen through stratification ("Stratified") or covariate ("Multivariate") adjustment, respectively

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POEMS

LIMITATIONS

- Did not meet full accrual
- Missing endpoint data for 38% of patients
  - However, no evidence that patterns of follow-up by arm significantly differed with respect to stratification variables
- Not stratified for disease risk factors
  - Stage, HER2, nodal status
  - However, stage adjustment did not alter DFS or OS

STRENGTHS

- Largest randomized study of LHRH agonist for ovarian protection addressing 2 year endpoints
- Consistent evidence of benefit across multiple endpoints
- Most informative study with respect to pregnancy outcomes

VOLUME 30 · NUMBER 5 · FEBRUARY 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial Using Gonadotropin-Releasing Hormone Agonist Triptorelin for the Preservation of Ovarian Function During (Neo)Adjuvant Chemotherapy for Breast Cancer

Pamela N. Munster, Amy P. Moore, Roohi Ismail-Khan, Charles E. Cox, Mensura Lacevic, Margaret Gross-King, Ping Xu, W. Bradford Carter, and Susan E. Minton

- Premenopausal women age 44 years or younger were randomly assigned to receive either triptorelin or no triptorelin during (neo)adjuvant chemotherapy and were further stratified by age (35, 35 to 39, 39 years), estrogen receptor status, and chemotherapy regimen
-

When stratified for age, estrogen receptor status, and treatment regimen, amenorrhea rates on triptorelin were comparable to those seen in the control group.

  - six cycles of fluorouracil, epirubicin, and cyclophosphamide.

- Menstruation resumed in 19 (90%) of 21 patients in the control group and in 23 (88%) of 26 in the triptorelin group
- *Menses returned after a median of 5.8 months (range, 1 to 19 months)* after completion of chemotherapy in the triptorelin versus 5.0 months (range, 0 to 28 months) in the control arm.
- *Two patients (age 26 and 35 years at random assignment) in the control* group had spontaneous pregnancies with term deliveries.

Ovariopexy & ovarian transposition

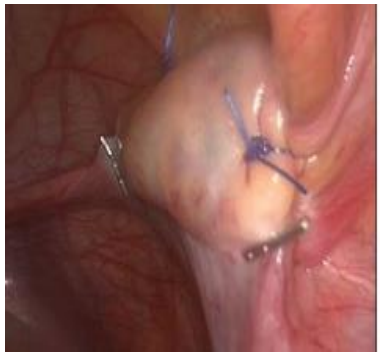
Bisharah & Tulandi, 2003; Cowles et al., 2007; Jadoul et al., 2007

Procedure used before radiotherapy to displace ovaries from radiation field.

Techniques used

- **Lateral fixation of Ovary**: Craniospinal irradiation, ovary fixed laterally as far as possible from the spine. Anatomic relations of ovary with Fallopian tube and uterus maintained thus natural fertility can be preserved.
- **High fixation of Ovary**: For pelvic irradiation ovary is anchored, as high as possible, to anterior abdominal wall, laterally in the paracolic gutter by resection of the utero-ovarian ligament and Fallopian tube. Titanium clips placed on the two opposite borders of ovary allow radiological identification prior to radiotherapy

Ovario-pexy & ovarian trans-position



Success of ovarian function preservation 16 to 90%

Success rates affected by

- **Degree of scatter radiation**
- **Vascular compromise**
- **Patient age**
- **Radiation dose**
- **No benefit with concomitant chemotherapy**

Abdominal transposition

- **No spontaneous pregnancy**
- **2nd procedure needed to relocate ovaries to the pelvis**
- **OCR for IVF technically more challenging.**

Candidates for ovarian transposition should be selected carefully, taking into account all variables that may affect success rate.

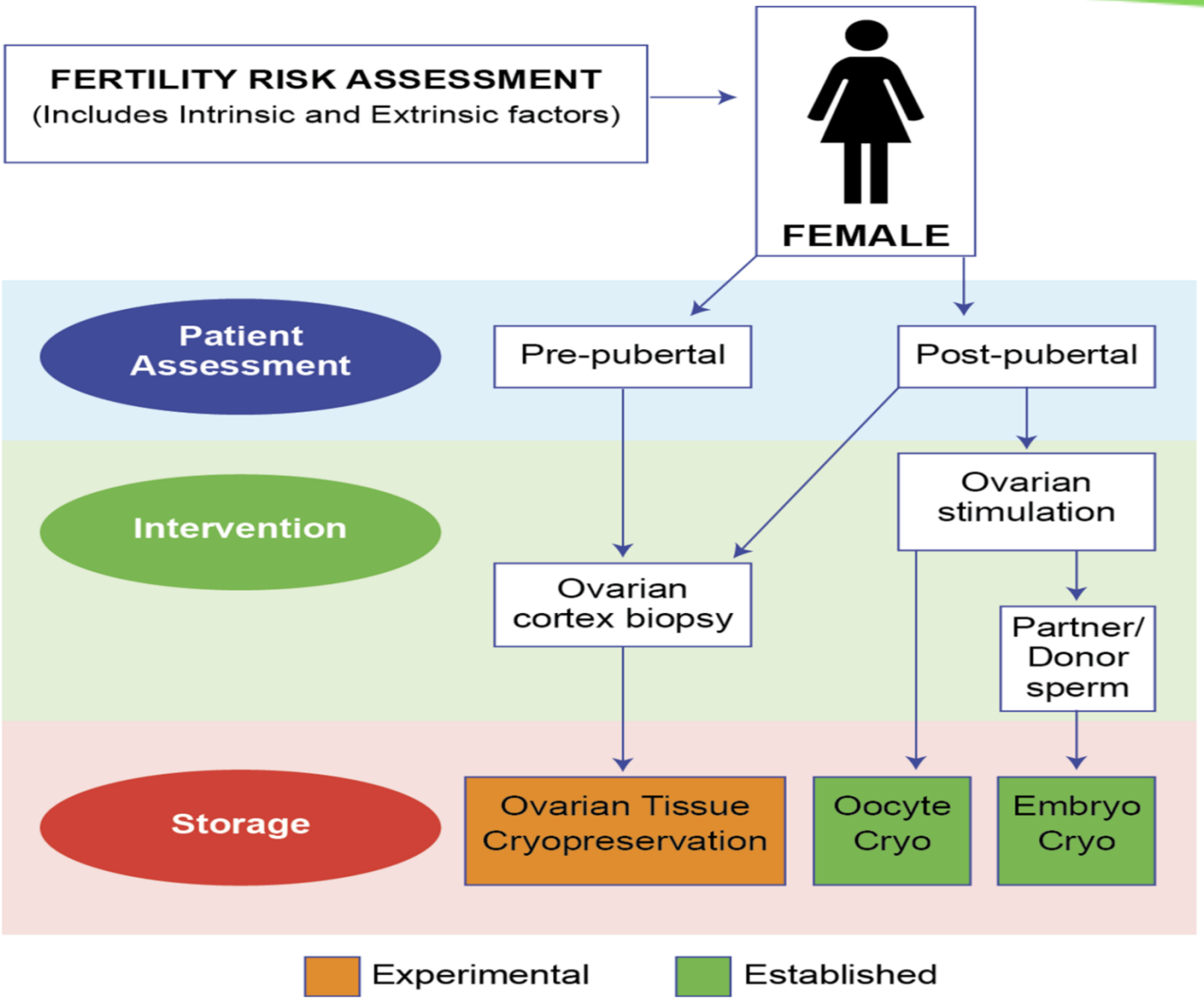
Thibaud et al., 1992; Morice et al., 2000; Aubard et al., 2001; Scott and Schlaff, 2005

Established methods of fertility preservation include embryo & oocyte cryopreservation prior to gonadotoxic therapy.

Embryo/ oocyte cryo-preserva-tion

Aim for Cancer patients:

- Collect as many oocyte or embryos before chemo or radiotherapy
- Shortage of time thus start whenever the patient comes even if it is late follicular phase or luteal phase
- Follicular phase stimulation OCR followed by stimulation in the same cycle luteal phase can be done to maximize oocyte numbers



From: Ovarian tissue cryopreservation for fertility preservation: clinical and research perspectives, Hum Reprod Open. 2017;2017(1).

Protocols for ovarian stimulation in patients with a small time line

The emergence of these protocols occurred with data coming from researchers which fuelled the concept that OS for IVF can be dissociated from the follicular phase and its hormonal environment, as long as no fresh ET takes place. Oocyte yields of these protocols were found to equal those of OS started in the early follicular phase.

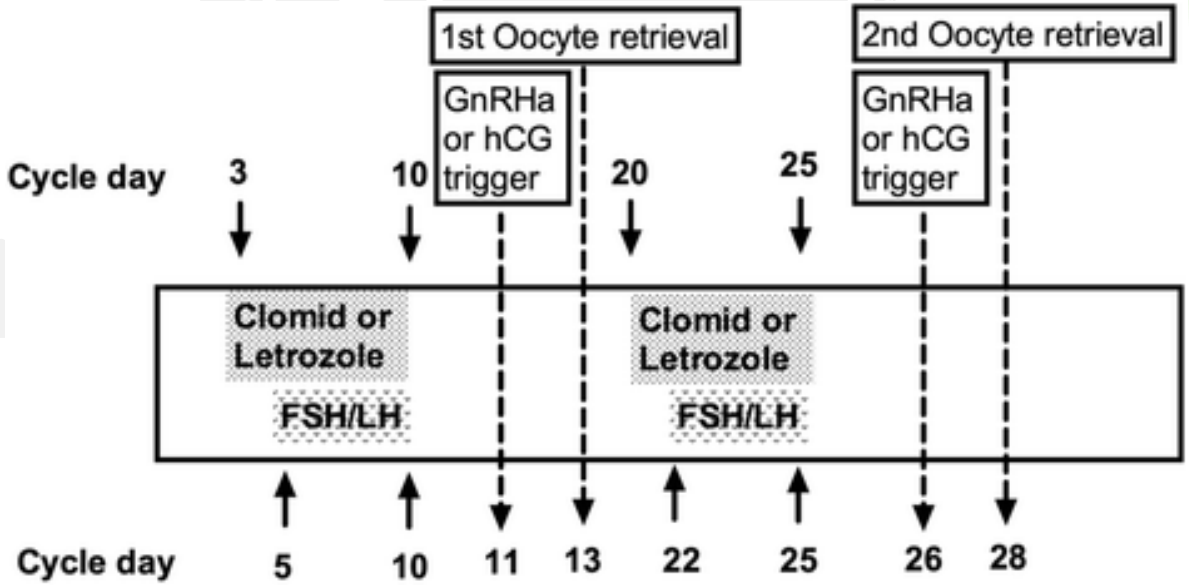
1. Duo-stimulation protocols ‘Duplex protocol’
2. Random start protocols

Shanghai protocol

Dual stimulation
Follicular & luteal stimulation with GnRHa trigger in first stimulation

Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim)

results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation



Hum Reprod. 2018 Jun 15. doi: 10.1093/humrep/dey217. [Epub ahead of print]

Luteal phase anovulatory follicles result in the production of competent oocytes: intra-patient paired case-control study comparing follicular versus luteal phase stimulations in the same ovarian cycle.

Cimadomo D[1], Vaiarelli A[1], Colamaria S[1], Trabucco E[2], Alviggi C[3,4], Venturella R[5], Alviggi E[2], Carmelo R[2], Rienzi L[1,2], Ubaldi FM[1,2].

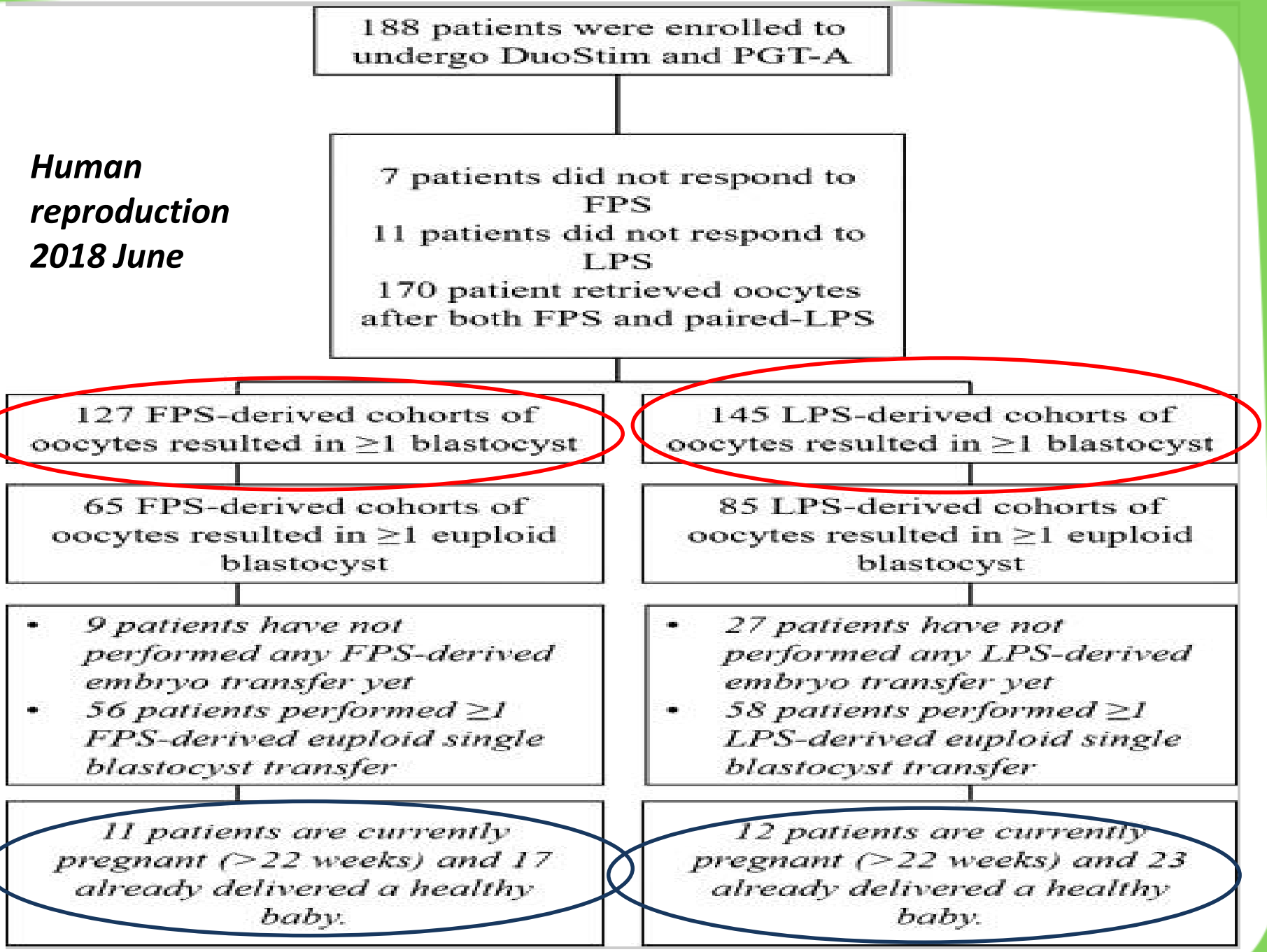
Abstract

STUDY QUESTION: Are the mean numbers of blastocysts obtained from sibling cohorts of oocytes recruited after follicular phase and luteal phase stimulations (FPS and LPS) in the same ovarian cycle similar?

SUMMARY ANSWER: The cohorts of oocytes obtained after LPS are larger than their paired-FPS-derived cohorts and show a comparable competence, thus resulting in a larger mean number of blastocysts.

STUDY DESIGN, SIZE, DURATION: This case-control study was conducted with paired follicular phase- and luteal phase-derived cohorts of oocytes collected after stimulations in the same ovarian cycle (DuoStim) at two private IVF clinics between October 2015 and December 2017.

Human reproduction 2018 June

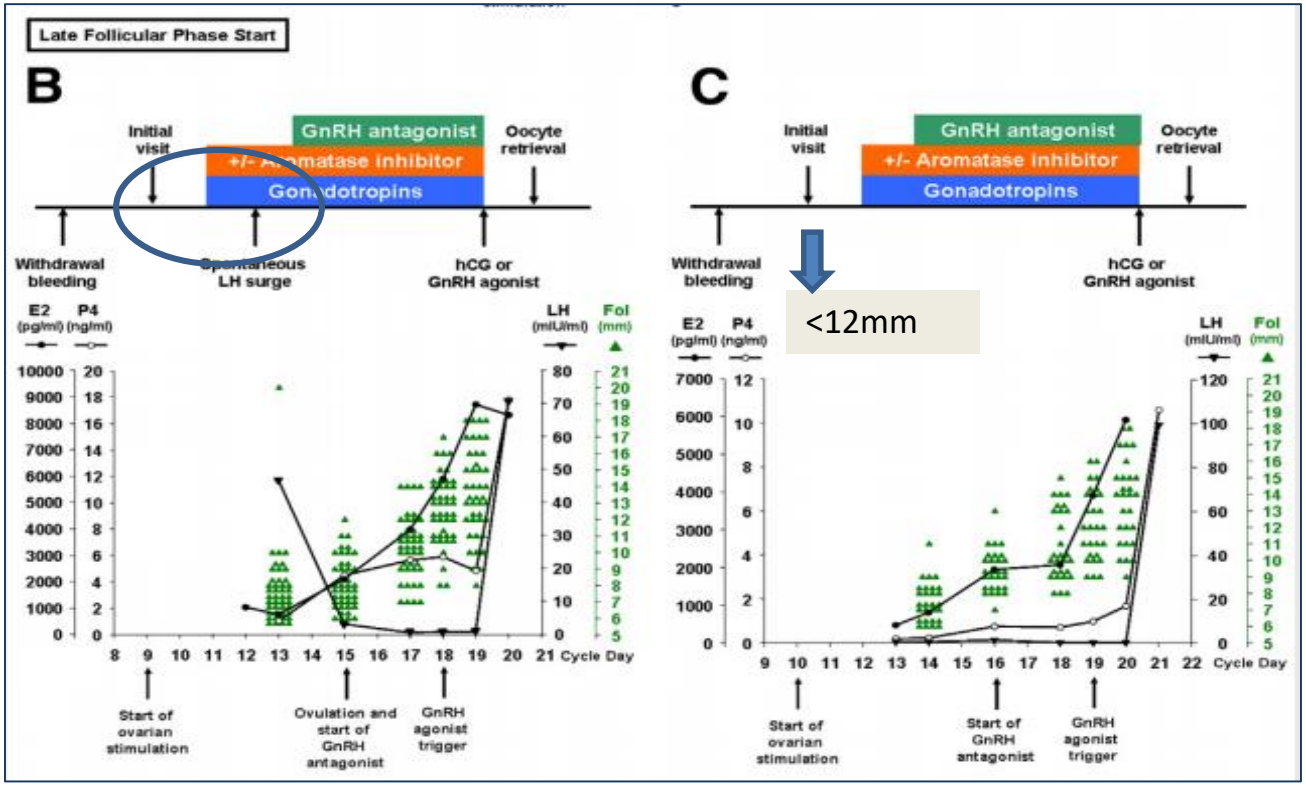


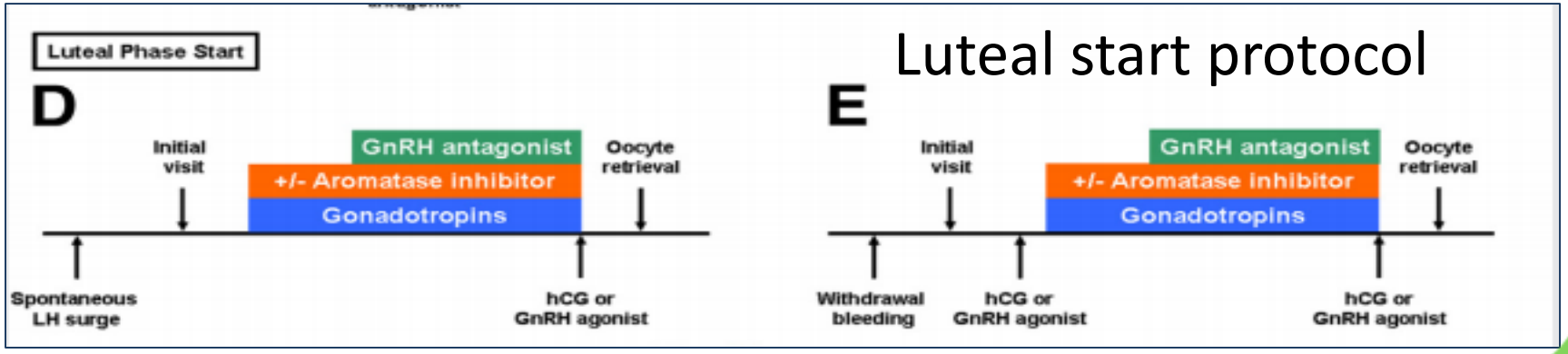
Random start protocols:

Patient presenting in late follicular phase or luteal phase following COS plans are used:

I. Late follicular phase:
    I. lead follicle >12 mm: COS with letrozole and gonadotropin started without antagonist till spontaneous LH surge for that single follicle, continue COS till the secondary follicle cohort reaches 12 mm. Add GnRH antagonist till trigger.
    II. Lead follicle <12 mm before starting COS, start COS and add antagonist from 12 mm cohort size, continue till trigger.
II. Luteal phase COS: Start in 5 to 7 days after hCG or GnRH agonist trigger. Ignore menstruation if happens between stimulation and use antagonist when cohort 12 mm or start progesterone from day of stimulation MPA or DYG till trigger

Late follicular phase start





Luteal start protocol

Ovarian stimulation in cancer patients

Hakan Cakmak, M.D. and Mitchell P. Rosen, M.D.

Department of Obstetrics, Gynecology, and Reproductive Sciences, Division of Reproductive Endocrinology and Infertility, University of California, San Francisco, California

Comparison of characteristics and outcomes of conventional and random start antagonist IVF cycles in cancer patients.

	Conventional start (n = 87; 101 cycles)	Random start (n = 24; 24 cycles)	*P* value
Age (y)	33.9 ± 5.2	34.6 ± 5.0	NS
AFC	13 (9–19)	11.5 (6–16)	NS
Days of ovarian stimulation	9 (8–10)	11 (10–12)	<.001
Total dose of gonadotropins (IU)	3,386 ± 1,085	4,201 ± 1,147	.001
Follicles ≥13 mm	12 (6–17)	10 (8–15.5)	NS
Oocytes retrieved	15 (9–23)	12.5 (9–20.5)	NS
Mature oocytes (MII) retrieved	11 (6–16)	9 (5–14.5)	NS
Oocyte/AFC ratio	1.1 (0.8–1.7)	1.2 (0.9–1.7)	NS
Mature oocyte/AFC ratio	0.8 (0.5–1.1)	0.8 (0.6–1.2)	NS
Fertilization rate after ICSI (2PN/MII)	0.77 ± 0.22	0.87 ± 0.15	NS

Note: Data are presented as mean ± SD or median (interquartile range) (32). 2PN = two pronuclei; AFC = antral follicle count; ICSI = intracytoplasmic sperm injection; MII = metaphase II; NS = not significant.

Cakmak. Ovarian stimulation in cancer patients. Fertil Steril 2013.

JKMS
JOURNAL OF KOREAN MEDICAL SCIENCE
jkms.org

J Korean Med Sci. 2015 Mar; 30(3): 290–295.
Published online 2015 Feb 16. doi: [10.3346/jkms.2015.30.3.290]
PMCID: PMC4330484
PMID: 25729252

Efficacy of Random-start Controlled Ovarian Stimulation in Cancer Patients

Jee Hyun Kim,[1] Seul Ki Kim,[1,2] Hee Jun Lee,[1,2] Jung Ryeol Lee,[✉1,2] Byung Chul Jee,[1,2] Chang Suk Suh,[1,2] and Seok Hyun Kim[2]

	Early follicular Phase (n = 6)	Late follicular Phase (n = 11)	Luteal Phase (n = 5)	P value
Duration of ovarian stimulation (days)	11.8 (10-13)	10.7 (9-14)	12.3 (11-13)	0.088
Total dose of gonadotropins (IU)	1,500[a,b] (1,050-3,000)	1,725[a] (1,200-3,600)	2,100[b] (1,950-2,700)	0.048
Total oocytes	11.5 (3-17)	18 (3-27)	9.0 (4-17)	0.340
Mature oocytes	4.5 (1-16)	9 (1-20)	6 (2-14)	0.343
Oocyte maturity rate (%)	55.2 (37/67)	67.8 (118/174)	68.8 (33/48)	0.156
Cryopreserved oocytes	10 (1-16)	15.5 (3-22)	5.0 (2-14)	0.275

COS using tamoxifen or letrozole with gonadotropin may be safer for women with ER+tumor compared to gonadotropins alone

Letrozole with gonadotropins

Letrozole 5 mg from day 2 till hCG trigger with inj. FSH conventional doses with antagonist protocol in cOS.

Estradiol levels can be kept to almost physiological levels by increasing letrozole dose.

Tamoxifen with gonadotropins

60 mg tamoxifen with inj. FSH conventional doses with antagonist protocol in COS.

E2 levels on day of hCG significantly higher, but effect of estrogen on breast tissue blocked at receptor sites.

Recurrence rates do not seem to be increased by tamoxifen, but the letrozole protocol may be preferred because it results in lower peak E2 levels.

Oktay K, et al.. Reprod Biomed Online. 2010;20:783–8.

Oktay K, Buyuk E, Libertella N, Akar M, Rosenwaks Z. J Clin Oncol. 2005

Ovulation trigger: GnRH agonists versus hCG

Agonists trigger achieved a greater and faster decline of the estradiol levels in luteal phase without reducing number of mature oocytes or fertilization rate for women with breast cancer undergoing fertility preservation by aromatase inhibitor and FSH stimulation.

Oktay K, et al. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod Biomed Online. 2010;20:783–8.

Presently ~100 babies born following this procedure & numbers increasing all the time.

Ovarian tissue cryo-preservation

How effective is ovarian tissue cryopreservation?

- First successful pregnancy after replacement of cryopreserved ovarian tissue reported by Donnez in 2004.
- Analysis of 60 tissue replacements carried out in Belgium, Denmark and Spain demonstrated that over 90% of women showed some evidence of ovarian activity, in a median of 4 months after transplantation
  - 18% of these women achieved pregnancy,
  - Majority natural conception
  - 12 live births from 6 women.

(Donnez et al., 2013).

Criteria for ovarian tissue banking (by S. Samuel Kim)

1. Communication with oncologists: cancer treatment plan and prognosis
2. Age: > 37 & ovarian function present by FSH, AFC or AMH
3. When delaying cancer treatment is not acceptable, hormonal stimulation is not permitted, ART is not allowed.
4. Prepubertal girls with no other options or high risk for POF
5. Informed consent from adult patients or guardians for minors
6. Physically and mentally healthy enough for surgery
7. Desires to have a child in the future
8. Counselling on surgical nature of procedure and how to use cryo-banked ovarian tissue for fertility restoration
9. Should understand experimental nature and potential risks of cancer cell transmission

J Assist Reprod Genet (2015) 32:1167–1170
DOI 10.1007/s10815-015-0544-9

FERTILITY PRESERVATION

Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice

Jacques Donnez[1] · Marie-Madeleine Dolmans[2]

J Pediatr Surg. 2007 May;42(5):862-4.

Laparoscopic ovarian tissue preservation in young patients at risk for ovarian failure as a result of chemotherapy/irradiation for primary malignancy.

Feigin E[1], Abir R, Fisch B, Kravarusic D, Steinberg R, Nitke S, Avrahami G, Ben-Haroush A, Freud E.

CONCLUSIONS: Laparoscopy for ovarian tissue retrieval for cryopreservation is safe in young cancer patients. Based on reports of successful cryopreservation of human ovarian tissue containing primordial follicles, we believe that this approach holds promise for female cancer survivors.

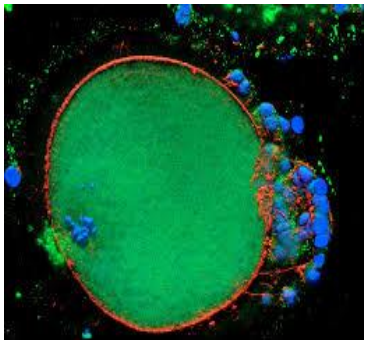
Ovarian cortex vitrification vs slow freezing?

Fertility preservation using aspiration and maturation of oocyte cumulus complexes to produce oocytes that can form developmentally normal embryos for vitrification is now establishing with increasing success across ART centres.

Reproductive Bio-Medicine Online Oct 2010 , Alak et al., 1998; Cha and Chian, 1998; Mikkelsen et al., 1999; Cavilla et al., 2008; Chian et al., 2013

IVM of oocyte cumulus complex

Immature oocyte retrieval can be done both in the follicular phase & luteal phase and both can be successfully matured in vitro.



If time is insufficient prior to adjuvant chemotherapy this is the best method.

Reproductive Bio-Medicine Online Oct 2010 Vol 21, I

In Vitro Maturation

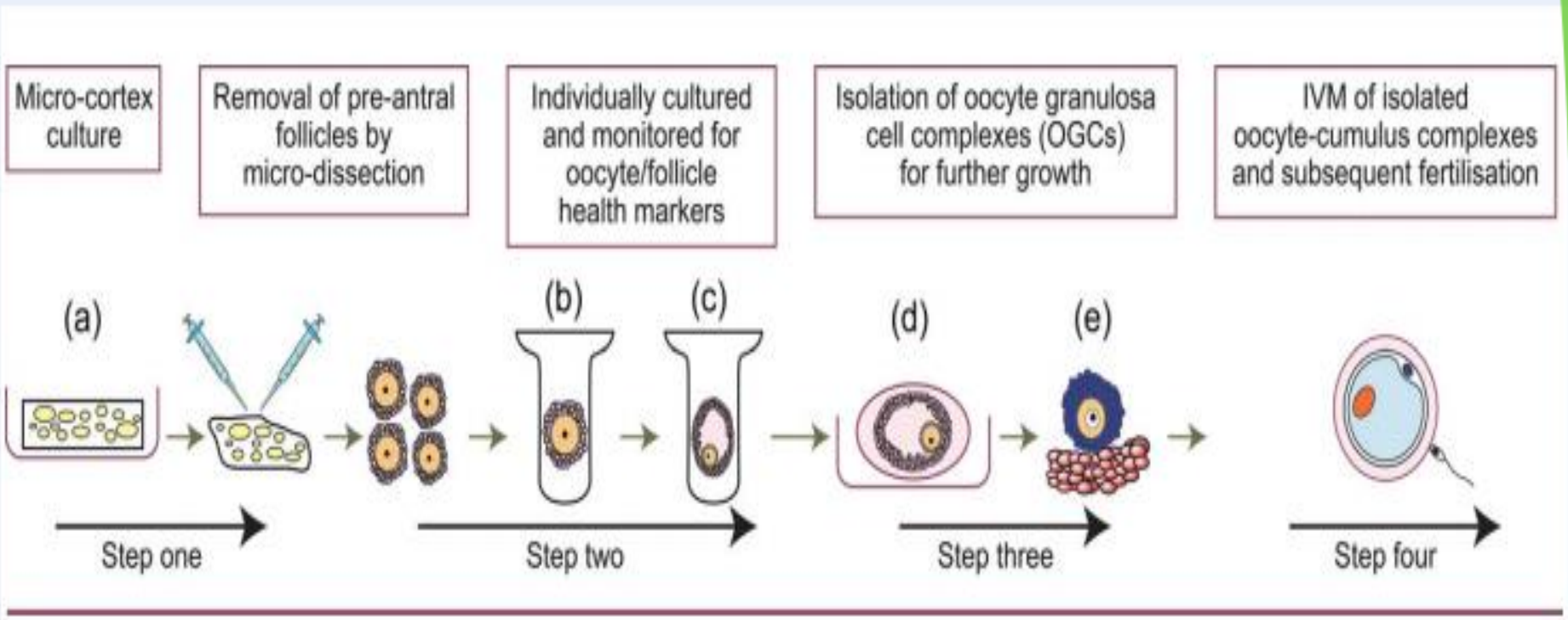


Figure 3 Multistep culture system for activation of human primordial follicles and subsequent follicle/oocyte development. Primordial follicles can be activated or held dormant within ovarian cortical tissue (**a**). Once activated preantral stages can be isolated (**b**), they are grown individually to antral stages (**c**). These can be further grown, for example, within an alginate bead (**d**) to obtain fully grown oocytes (**e**), then competence to undergo maturation and fertilization is tested.

Drawbacks of IVM

- Accepted fact till now that only 40–80% of immature human oocytes can successfully complete IVM and fertilization.
- Rate of maturation of immature oocytes is well below that of oocytes harvested from stimulated ovaries.
- Either protocols are suboptimal or many of the harvested oocytes are intrinsically unable to undergo maturation ***Chang et al., 2014***

To conclude

Concerns about welfare of resulting offspring not sufficient reasons to deny treatments assistance in reproduction.

Parents may decide to preserve fertility of minors if the intervention is likely to provide potential benefits to the child.

Instructions must specify about disposition of stored gametes, embryos, or gonadal tissue in the event of patient's death or unavailability.

PGD to avoid the birth of offspring with a high risk of inherited cancer is ethically acceptable

Thank you