

Stopping the Biological CLOCK!

Jeff Roberts M.D.

Co-Director
Pacific Centre for Reproductive Medicine
Vancouver, British Columbia
jroberts@pacificfertility.ca

COI Disclosures

In compliance with accreditation, we require the following disclosures to the session audience:

Research Support/P.I.	N/A
Employee	N/A
Consultant	N/A
Shareholder	Pacific Centre for Reproductive Medicine
Speakers Bureau	N/A
Honoraria	N/A
Scientific Advisory Board	N/A

Egg Freezing Patients

Elective (social) egg freezing

- Cryopreservation of mature oocytes on an elective basis for the purpose of delaying childbearing

Cancer patients

- Cryopreservation of mature oocytes, embryos, ovarian tissue prior to sterilizing medical treatments

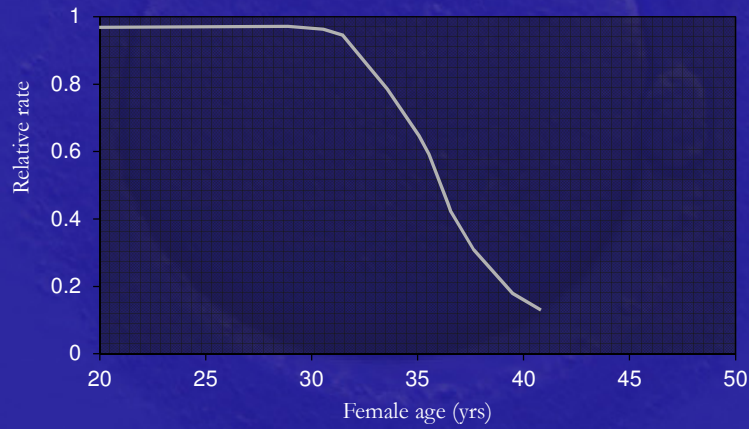
Anticipated Gamete Exhaustion (AGE) Banking

Young Egg Freezing Patient

- Infertility distress can affect overall mood and cause symptoms of PTSD¹
- Psychological stress level of infertility ranks with that of cancer²
- Lack of knowledge about their own reproduction and existing reproductive technologies
- 75% of childless women want children in the future^{3,4}

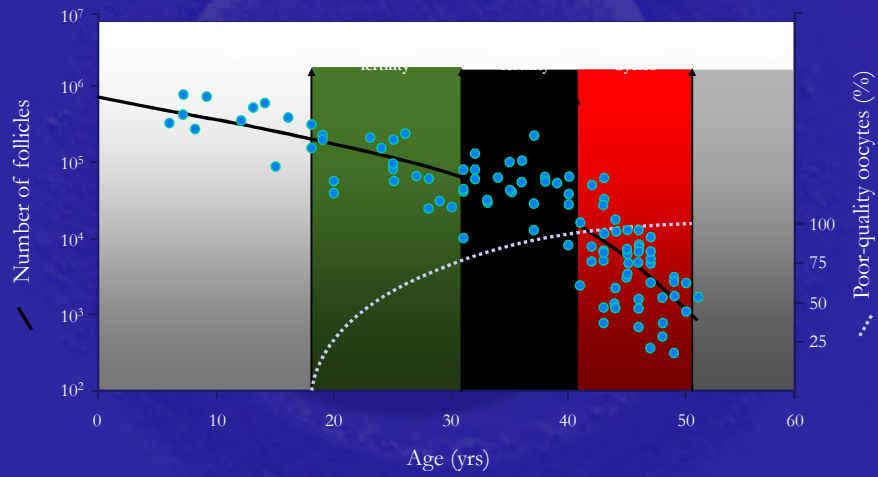
1. Schover LR et al. *Pediatr Blood Cancer*. 2009;53:281-284
2. Domar et al *J Psychosom Obstet Gynaecol* 1993;14 Suppl:45-5
3. Schover LR et al. *Cancer*. 1999;86:697-709.
4. Schover LR et al. *J Clin Oncol*. 2002;20:1880-1889.

Fecundity Declines With Age



van Noord-Zaadstra BM et al. *Brit Med J* 1991;302:1361-65.

Increasing Maternal Age and Decline in Follicle Number and Oocyte Quality



Adapted from Klinkert ER, 2005 PhD Thesis, University of Utrecht.

Prevalence of Aneuploidy

Franasiak et al. Fertil Steril 2014; 101:656-63

Origins of Aneuploidy

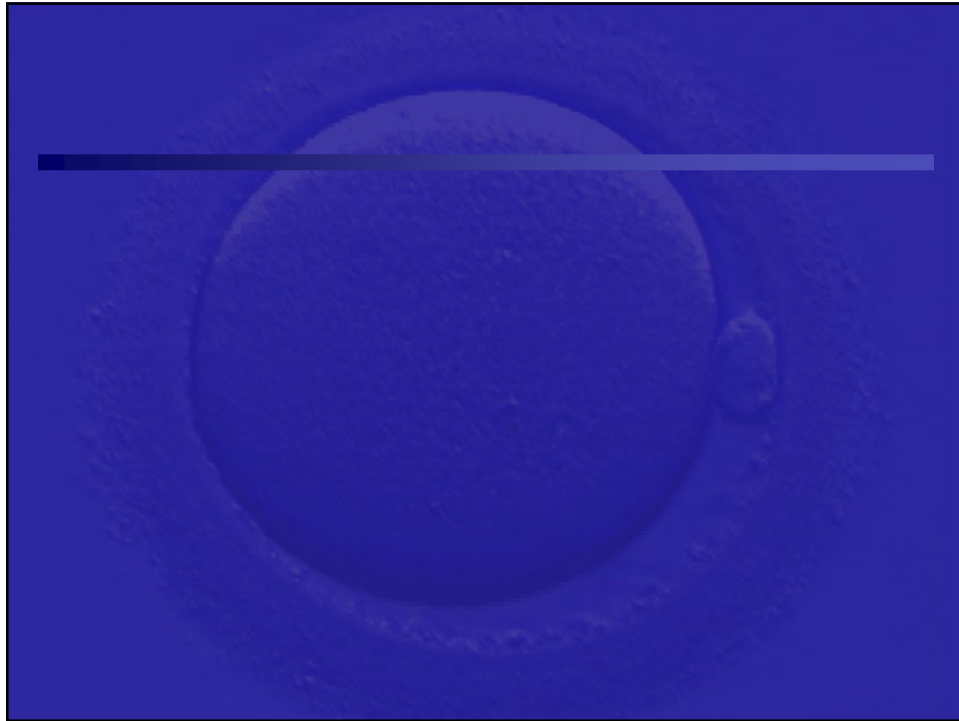
Paternity confusion hypothesis

- Males uncertain of which are their children were more likely to care for them equally
- Not every egg works and humans don't physically advertise when they are ovulating

Grandmother hypothesis

- Non-pregnant grandparents benefit the community/raise children, allowing parents can hunt/gather
- Childbirth at older ages was also dangerous

1. McCoy et al Science 2015;348:234-38
2. Hawkes et al Evol Anthrol 2013;22:294-302



Female Reproductive Lifespan How much time do I have?

- Egg population at birth is individual
- Velocity of egg loss is individual
 - Age-related (individual variation, genetic, familial)
 - Iatrogenic (chemotherapy, surgical)
 - Lifestyle (smoking, ?stress, lower SES)
 - Medical condition (lymphocytic oophoritis)
- Age-related decline in egg "quality" universal

Women are having children older?

<http://www.cdc.gov/nchs/data/databriefs/db152.htm>

Chemotherapy Accelerates Egg Loss

Destruction of Ovarian Follicle

- Pre-granulosa cell apoptosis and swelling
- Increased recruitment and depletion of PF pool (Burnout Theory)
- Disappearance of oocyte
- DNA damage

Pre-ovulatory follicles → Temporary Amenorrhea

Primordial and early follicles →

1. Malformation (short term)
2. Diminished ovarian reserve
Infertility
Early menopause
3. Ovarian failure

1. Philosof-Kalich I, et al. ESHRE 2009.
2. Rosendahl M et al. *Fertil Steril*. 2010;94:155-156.
3. Meirou D et al. *Clin Obstet Gynecol*. 2010;53(4):727-739.

Ovarian Failure Risk by Class of Chemotherapeutic Agent

Damario et al, 2001

Chemotherapy-related Acute Ovarian Failure

Acute Ovarian Failure

- Female survivors age 18 – 40
- N=2532 survivors
- Survey on reproductive hx

Letourneau et al. Cancer 2012;188:1933-9

Acute Ovarian Failure Underestimates Reproductive Impairment

Infertility

- Female survivors age 18 – 40
- N=2532 survivors
- Survey on reproductive hx

Letourneau et al. Cancer 2012;188:1933-9

Regular Cycles ≠ Fertile

- <10% of ovarian mass required to maintain menstrual function
- Increased risk of early menopause after treatment with alkylating agents¹
- Relative survival of cancer patients treated with standard chemotherapy protocols will at the least shorten the patient's reproductive life-span^{2,3}
- All measures of ovarian reserve affected by chemotherapy⁵
- Fertility treatment success limited using eggs exposed to chemotherapy⁶

1. Partridge et al. Eur J Cancer 2007;43:1646-1653, 2. Sklar et al. JNCI 2006;98:890-896, 3. Blumenfeld Z. *Best Pract Res Clin Obstet Gynaecol.* 2012;26;379-390, 4. Kil et al. Breast Cancer Res Treat 2006;96:245-250, 5. Anderson et al. Hum Reprod 2006;21:2583-2592, Dolmans et al. Fertil Steril 2005;83(4):897-901

Assisted

Reproductive

Technologies

Goals of Egg Freezing

- Hope for motherhood
- Increased probability of pregnancy in future
- For cancer
 - NOT affect cure
 - Positive distraction

Testing Ovarian Reserve - Day 3 FSH

- Pituitary gonadotropin closely linked to ovarian reserve and egg quality
- Low in the early follicular phase
- Often used for predicting IVF success rates
 - Pregnancy OR 0.58 when ≥ 10 IU/L¹
 - Sensitivity 7% and PPV 90+%²

1. Yanushpolsky EH, et al. Fertil Steril 2003. 80:111-115
2. Jain T et al. Fertil Steril 2004. 82: 180-185

IVF Delivery Rates and Basal FSH

Scott RT et al. Fertil Steril (2008) 89:868-78

Testing Ovarian Reserve - Antimullerian Hormone (AMH)

- Secreted from granulosa cells of growing follicles
- AMH is the "follicular gatekeeper" that limits the size of the cohort available to respond to pituitary gonadotropins each month¹⁻²
- Cycle day independent - dominant follicle and corpus luteum do not secrete
- Clinically more versatile and predictive than FSH

1. Dewailly D et al. Oxford University Press; 2014 May;20(3):370-85. 2. Durlinger AL, et al. Endocrinology. 1999 Dec;140(12):5789-96.

Testing Ovarian Reserve - Antimullerian Hormone (AMH)

Predictive for:

- Ovarian response to gonadotropins^{1,2}
- Live birth rates after IVF³
- Age of menopause⁴

NOT predictive for:

- Natural fertility - high AMH actually predictive of lower⁵
- Miscarriage

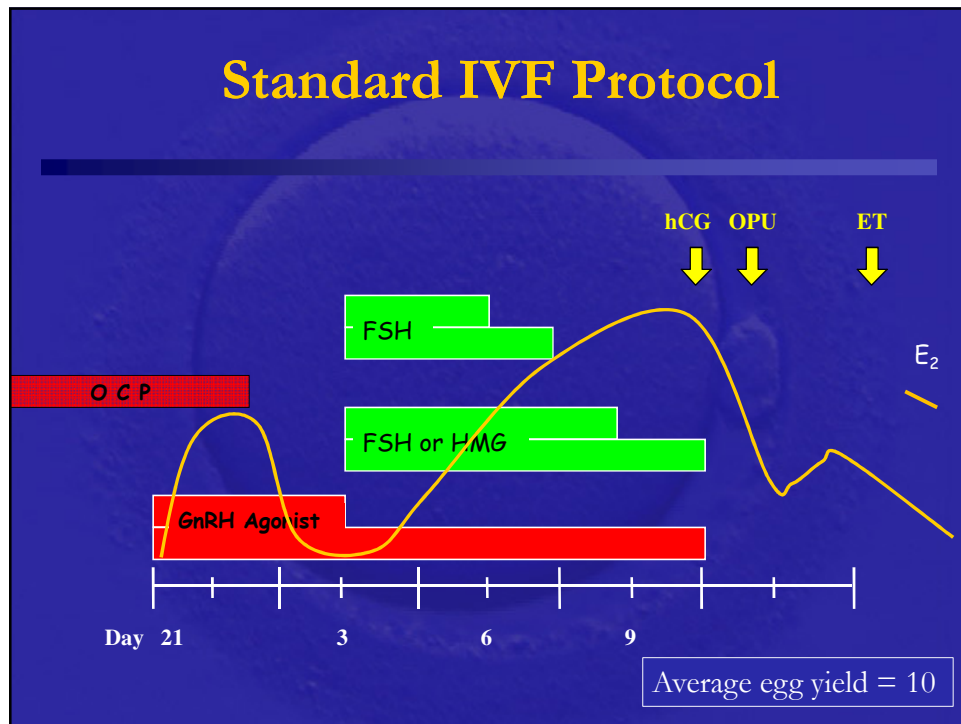
1. Arce JC et al. Fertil Steril 2013;99(6):1644-53, 2. Riggs RM et al. Am J Obs Gyn 2008;199(2):202, 3. Brodin T et al. J Clin Endo Metab 2013;98(3):1107-14, 4. Depmann M, et al. Hum Reprod; 2016 Jul;31:579-87. 5. Hagen CP et al. Ferti Steril 2012 Dec;98(6):1602-2.

Testing Ovarian Reserve - Antral Follicle Count (AFC)

- Performed early follicular phase by transvaginal ultrasound
 - Antral follicle = 2-9 mm
 - Normal values: 4-10 per ovary
- Declines with age

Before age of 37:	4.8% per year
After age of 37:	11.7% per year
- Valuable screening tool for IVF

Scheffer GJ et al. Fertil Steril 1999, 72: 845-51



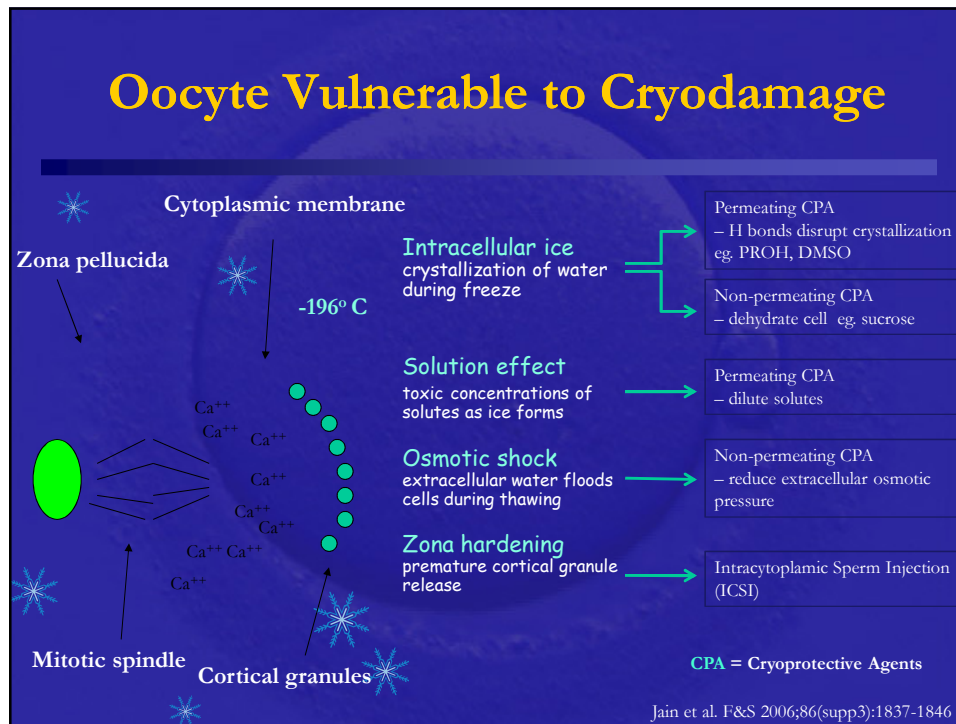
Embryo Cryopreservation

- Most established fertility preservation technique for women with cancer
- Requires sperm
- Requires IVF
- Millions of babies born

Oocyte Cryopreservation

- ASRM/ASCO guidelines - no longer consider oocyte cryopreservation experimental
- Requires IVF
- No sperm required
- Lower pregnancy compared to embryo cryopreservation
- Fewer than 20,000 babies born of this technology

1. Practice Committee of the American Society for Reproductive Medicine. *Fertil Steril* 2013;99:37-43.
2. Loren AW, et al. *J Clin Oncol*. epub ahead of print May 28, 2013



Cryopreservation - Vitrification

- Vitrification directly solidifies an egg/embryo and surrounding solution to a glasslike (vitreous) state, minimizing the formation of intracellular and extracellular ice crystals
- Meta-analysis of 6 RCTs¹
 - Vitrification, as compared with slow freezing, appears to be better in terms of post-thawing survival rates, both for cleavage-stage embryos.
 - No significant difference in clinical pregnancy rates per transfer could be detected between the two cryopreservation methods"

Kolibianakis et al, Curr Opin Obstet Gynecol 2009; 21(3):270-74

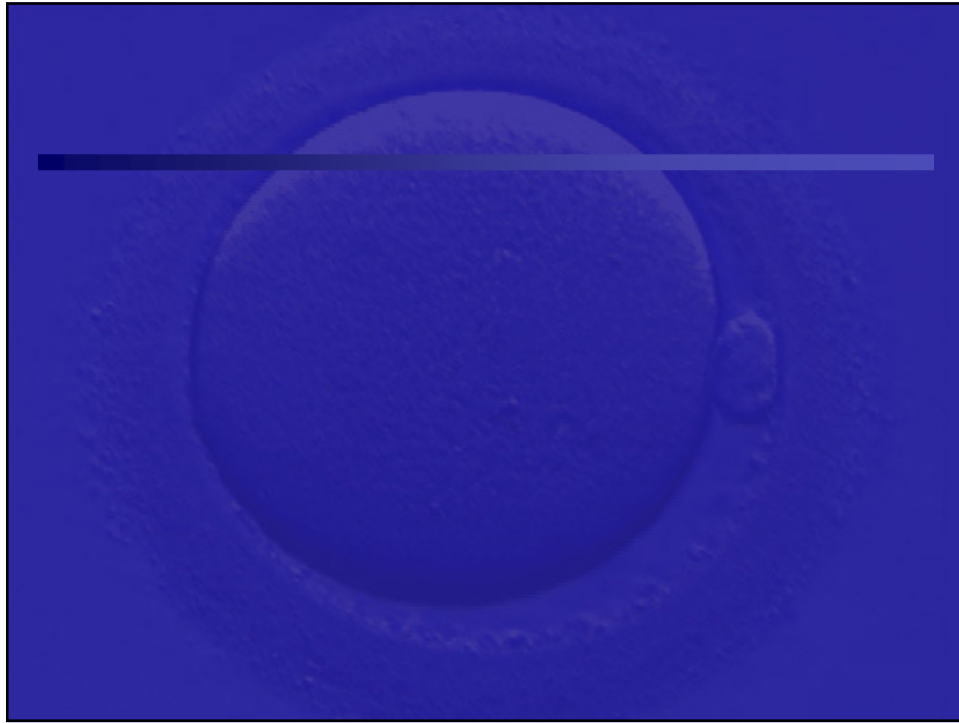
Use of cryo-banked oocytes in an ovum donation programme: a prospective, randomized, controlled, clinical trial



Cobo et al Hum Reprod 2010; 25(9):2239-46

- Live birth rate per thawed egg 6.4%
- Mean of 15 eggs required to achieve live birth

Cobo et al. F&S 2015;104:426-34

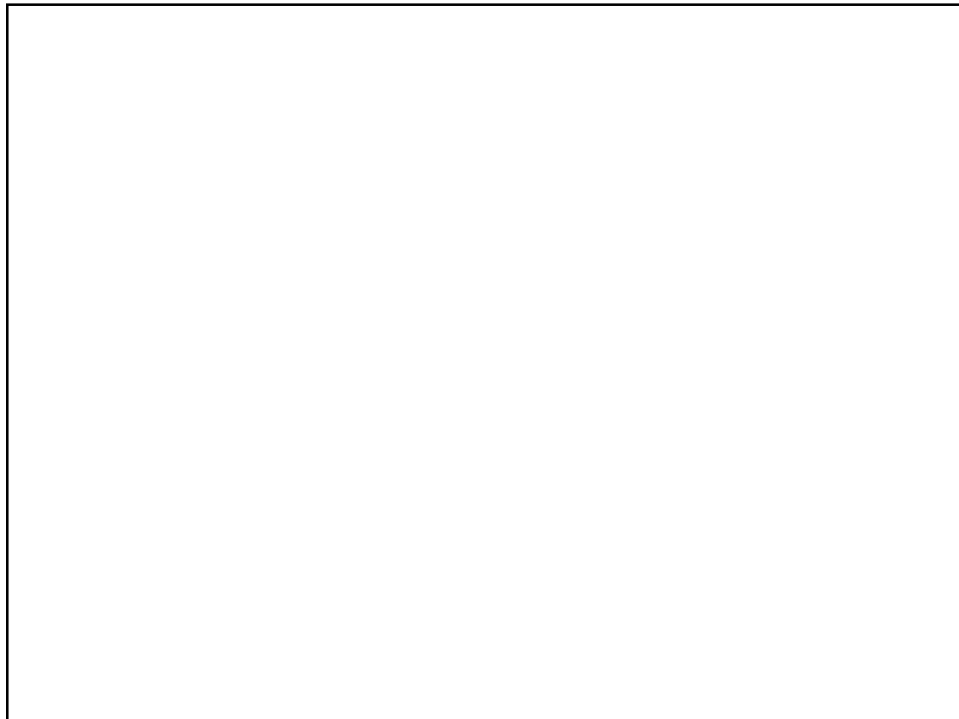


Fertility. Freedom. Finally.

"As women, we lead rich and demanding lives - obtaining advanced degrees, pursuing successful careers, and taking better care of ourselves....."

"But in waiting longer to have children, many women face the real challenge of having successful, healthy pregnancies later in life. While we have made great strides in other areas, our fertility is still limited by basic biology.....Our opportunities are endless, but our egg supply and quality are not."

Christy Jones, Extend Fertility



Egg Calculators

Probability of live birth with social egg freezing according to number of eggs consumed

N = 137 patients returned to use eggs (9%)

Cobo et al. F&S 2016;105:755-64

How many autologous oocytes to bank if trying to preserve fertility?

32 elective egg cryo
52 sperm unavailable
44 limit fertilization

N = 128 thaw cycles (15%) from original 875 patients

LBR per egg = 7.0%

Doyle et al. F&S 2016;105:459-66

How many autologous oocytes to bank if trying to preserve fertility?

32 elective egg cryo
52 sperm unavailable
44 limit fertilization

N = 128 thaw cycles (15%) from original 875 patients

LBR per egg = 6.5%

Doyle et al. F&S 2016;105:459-66

How many autologous oocytes to bank if trying to preserve fertility?

32 elective egg cryo
52 sperm unavailable
44 limit fertilization

N = 128 thaw cycles (15%) from original 875 patients

LBR per egg = 5.2%

Doyle et al. F&S 2016;105:459-66

How many autologous oocytes to bank if doing social banking?

	All ages	<35yo	35-37yo	38-40yo	>40yo
Thaw cycles	89	10	30	32	17
# eggs thawed (total)	1281	126	435	479	241
# eggs thawed (average)	11.0	8.8	11.2	11.6	10.7
Postthaw survival	83.6%	73.0%	84.5%	84.8%	85.1%
Fertilization rate	69.5%	71.6%	69.4%	69.7%	68.3%
# of Fresh ETs	56	6	16	23	11
Ongoing/thaw*	30.3%	40.0%	26.7%	25.0%	41.2%
Cumulative ongoing per thaw*	41.6%	60.0%	40.0%	31.3%	52.9%
% cycles with cryo	57.3%	70.0%	66.7%	50.0%	47.1%
Average # cryo	2.8	2.9	2.7	3.4	2.0
Egg efficiency	5.7%	10.3%	6.6%	4.3%	4.8%

Doyle et al. personal communication

Counseling tool for predicting likelihood of live birth for elective egg freezing

Achieving a 75% LBR

Age 34 - 10 eggs

Age 37 - 20 eggs

Age 42 - 61 eggs

N = 520

Goldman et al. Hum Reprod 2017;32:389-9

Outcomes with frozen eggs from cancer patients



Safety of Egg Freezing

- 804 pregnancies from vitrified oocytes
 - 12.4% own oocytes, 85% donation
- No difference in perinatal outcomes
 - Gestational age at delivery
 - Preterm birth
 - APGAR scores
 - Birth defects
 - NICU admission
 - Perinatal mortality
- Only significant differences:
 - Fewer UTIs
 - More invasive procedures (CVS or Amnio)

Cobo et al (2014);102:1006

Take Home Message

- Cancer patients need to be referred early
- Patients should be advised that there is very limited data on live birth rates after elective egg freezing
- Age at which patients freeze impact the probability of pregnancy - highest probability of live birth when done before age 36, most cost-effective < age 30.
- To achieve a 75% live birth rate with egg freezing:
 - Age 34 - 10 eggs
 - Age 37 - 20 eggs
 - Age 42 - 61 eggs

Fertility Preservation is Expensive

- Provincial programs
 - Medical service contracts (Ontario)
 - Public funding (Quebec)
 - Tax credit (Manitoba)
- Charities - Fertile Future (max \$2500 female \$350 male)
- Clinic discounts
- Pharmaceutical support (compassionate medications)
- Funding initiatives
 - The Walking Egg (2010) www.thewalkingegg.com (Collaboration with ESHRE and WHO)
 - Friends of Lo-Cost IVF (2011) www.freindsoflcivf.org