



5th world Congress of ISFP, Vienna, Austria

Are there any methods to improve transplantation outcomes?

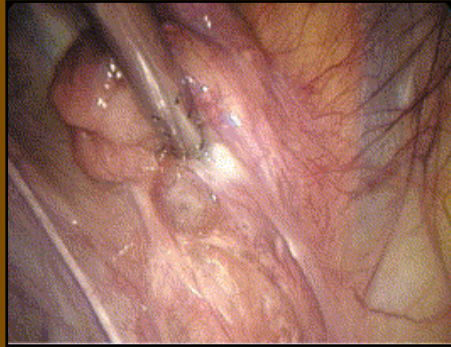
S. Samuel Kim, MD, FACOG
Center for Fertility and Reproduction
American-Sino Women's and Children's Hospital



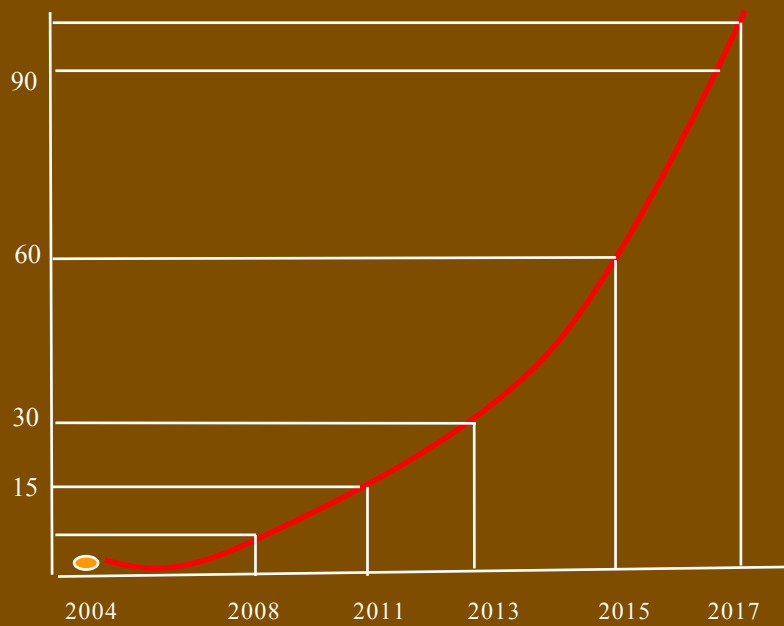
S. Samuel Kim

Disclosure information:
Nothing to declare

The first live birth after orthotopic autotransplantation of cryobanked human ovarian tissue



Donez et al., Lancet 2004



CUMULATIVE NUMBER OF LIVE BIRTHS AFTER AUTOTRANSPLANTATION OF OVARIAN TISSUE

Is ovarian transplantation an efficient procedure?

J Assist Reprod Genet (2017) 34:325–336
DOI 10.1007/s10815-016-0843-9

FERTILITY PRESERVATION

86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children

Annette Klüver Jensen¹ · Kirsten Tryde Macklon² · Jens Fedder³ · Erik Ernst⁴ · Peter Humaldan⁵ · Claus Yding Andersen¹

Human Reproduction, Vol.32, No.3, pp. 1046–1054, 2017
Advance Access publication on March 1, 2017. doi:10.1093/hurrep/daw040

human reproduction ORIGINAL ARTICLE *Infertility*

Efficacy of ovarian tissue cryopreservation for fertility preservation: lessons learned from 545 cases

P. Jadoul⁶, A. Guilmain, J. Squifflet, M. Luyckx, R. Votino, C. Wynaes, and M.M. Dolmans

What is the success rates?

Hum. Reprod. Advance Access published online first
Human Reproduction, Vol.32, No.3, pp. 1–11, 2017
doi:10.1093/hurrep/daw040

human reproduction ORIGINAL ARTICLE *Infertility*

Ninety-five orthotopic transplantations in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network: tissue activity, pregnancy and delivery rates

H. Van der Ven^{1,2}, J. Liebenthron^{1,2}, M. Beckmann³, B. Toth⁴, M. Korell⁵, J. Krüssel⁶, T. Frambach⁶, M. Kupka⁷, M.K. Hohl⁸, K. Winkler-Crepaz⁹, S. Seitz¹⁰, A. Dogan¹¹, G. Griesinger¹², F. Häberlin¹³, M. Henes¹⁴, R. Schwab¹⁵, M. Sütterlin¹⁶, M. von Wolff^{17,18}, and R. Ditzrich^{1,2} on behalf of the FertiPROTEKT network

**1997-2013: 2015
Delivery: 7/21(33%)**

**Pregnancy: n=21
(33%)
Delivery: n=17
(25%)**

What do we know ?

- To date, roughly 100 babies were born after autotransplantation of frozen-thawed ovarian tissue but **the exact number of pregnancies and live births worldwide is unknown.**
- In the literature, pregnancy rates after ovarian tissue transplantation is **20-30%** in some centers.
- However, these rates may not reflect actual pregnancy rates of all centers worldwide due to the **absence of reports of non-pregnancies after attempted transplantations** (unknown denominator).

What do we know ?

- Currently, the number of human ovarian transplantation in the literature is around 455.
- **Utilization rate** of cryopreserved ovarian tissue is between **3-5%**.
- Difficult to assess true POF rates after cancer treatment in patients who stored ovarian tissue (it appears that approximately 70% remains ovarian function).

What do we know ?

- Most of success (live births) came **from Europe** (**82/95**: according to 2017 published data).
- Higher pregnancy rates with women under 35 years old.
- To date, the **slow freezing method** was applied in all (but three) successful cases.
- Very little data on perinatal outcomes.

Challenging issues that can affect the outcomes of ovarian transplantation

- Patient selection criteria:
age, ovarian reserve, prognosis
- Cryoinjury
- Effective graft sites & methods
- Ischemic-reperfusion injuries
- Premature follicle activation
- Quality of oocytes matured in a graft
- Safety issues: especially, cancer cell transmission

To improve the outcomes:

Do we need patient selection criteria?

Age, Ovarian reserve, Prognosis, Risk of POF

Age group	49 patients (68 transplantations)
<30 years	
Number of patients (n)	22
Number of transplantations (n) ^a	32/22
Radiotherapy of the pelvis n/total (%)	2/22 (9.1)
Active tissue 1 year after transplantation n/total (%)	15/22 (68.2)
Pregnancies n/total (%)	9/22 (40.9)
Deliveries n/total (%)	6/22 (27.3)
30 - 34 years	
Number of patients (n)	14
Number of transplantations (n) ^a	18/14
Radiotherapy of the pelvis n/total (%)	2/14 (14.3)
Active tissue 1 year after transplantation n/total (%)	11/14 (78.6)
Pregnancies n/total (%)	5/15 (33.3)
Deliveries n/total (%)	4/14 (28.6)
35 - 39 years	
Number of patients (n)	11
Number of transplantations (n) ^a	13/11
Radiotherapy of the pelvis n/total (%)	0/11 (0)
Active tissue 1 year after transplantation n/total (%)	6/11 (54.5)
Pregnancies n/total (%)	2/11 (18.2)
Deliveries n/total (%)	2/11 (18.2)
≥40 (40 and 44 years)	
Number of patients (n)	2
Number of transplantations (n) ^a	4/2
Radiotherapy of the pelvis n/total (%)	0/2 (0)
Active tissue 1 year after transplantation n/total (%)	1/2 (50.0)
Pregnancies n/total (%)	0/2 (0)
Deliveries n/total (%)	0/2 (0)

^aSome women were transplanted twice.

Age matters?

Higher pregnancy rates with women under 35 years old (28.6 % vs 18.2 %)

No reported pregnancy after 38 years old (age at the time of cryo).

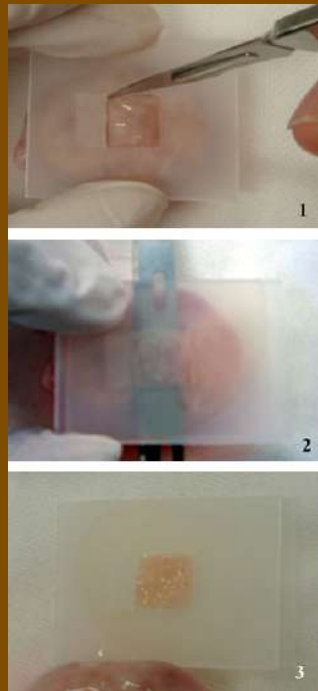
Van der Ven et al.,
Hum Reprod, 2016

To improve the outcomes:

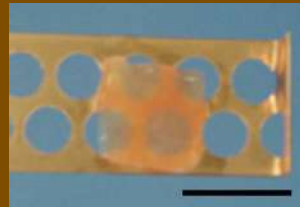
**How to prepare
and cryopreserve
ovarian tissue**

**Cortical thickness matters?
How thin?**





Tissue slicer for vitrification

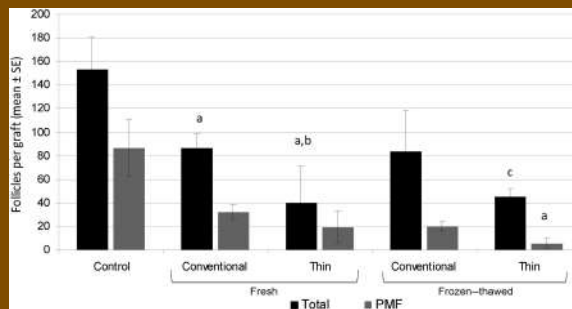
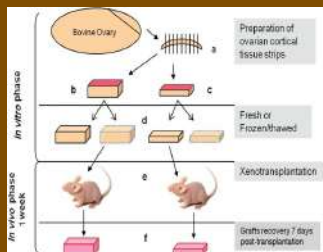


10x10x1 mm

Kagawa et al., RBM Online, 2009

The effect of graft thickness

- 1) Conventional thickness strips 1-2 mm
- 2) Thin strips 0.5-0.9 mm



Gavish et al., Hum Reprod, 2014

How to cryopreserve ovarian tissue?

Slow freezing vs. vitrification

Slow freezing

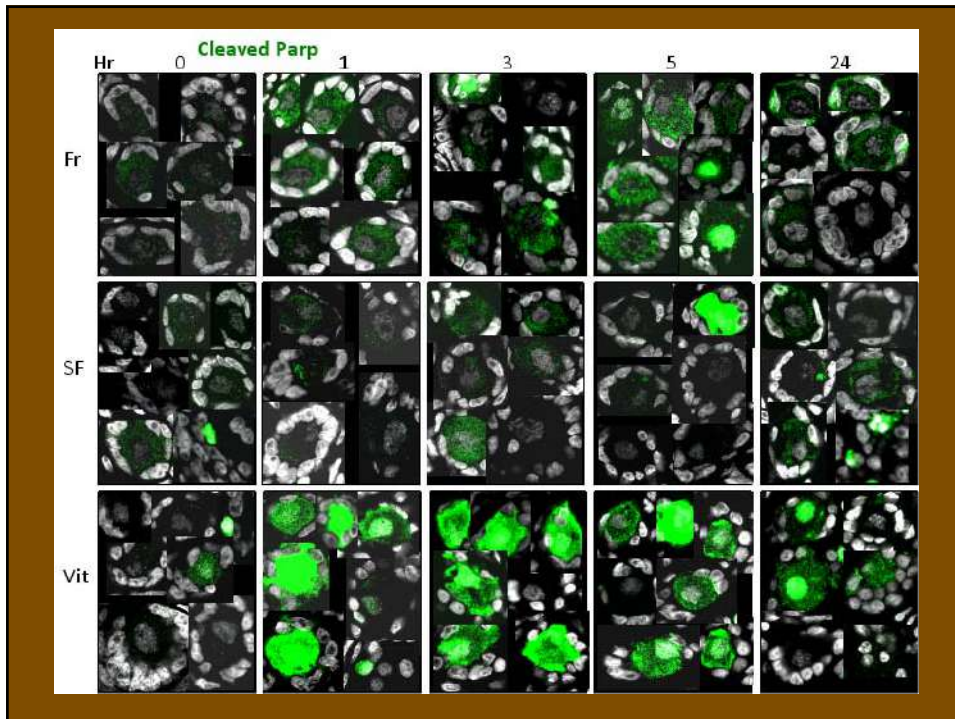
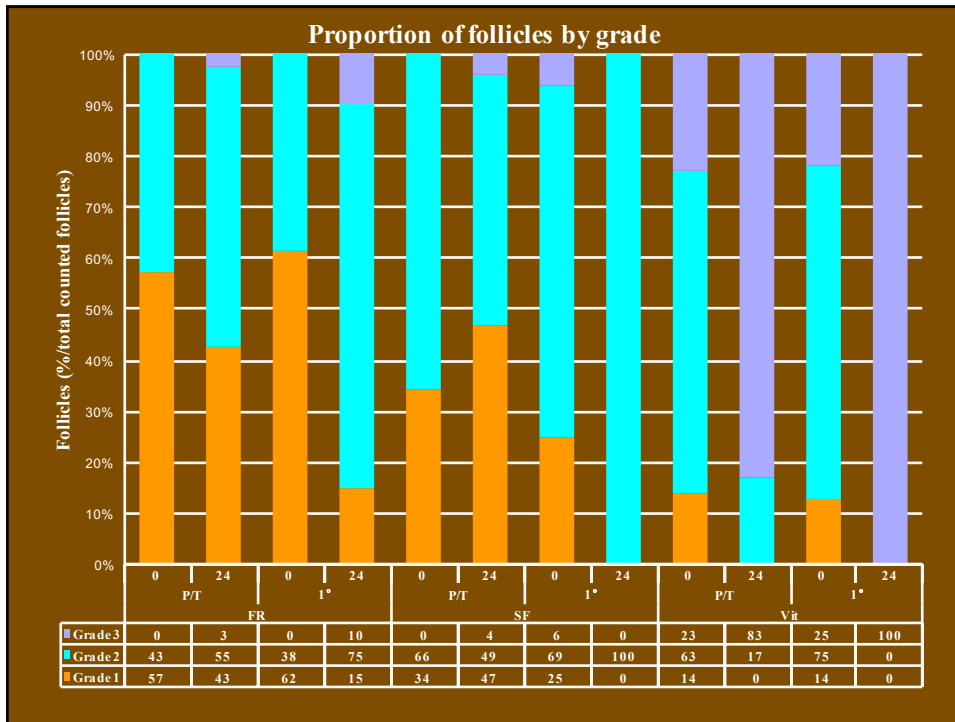
- **Currently, slow freezing is the standard method.** To date, almost all pregnancies after transplantation were from ovarian tissue cryopreserved using a slow freezing method.

70-80% of primordial follicles survive after slow freezing and thawing. Nevertheless, ultrastructural damage can be detected by TEM.

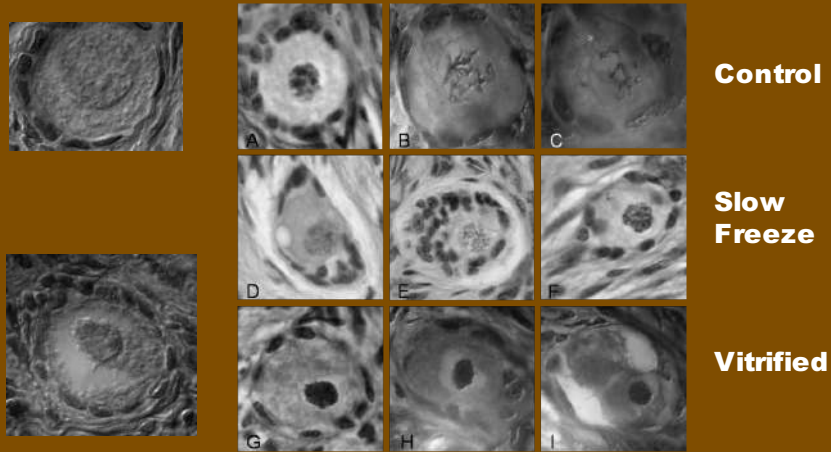
vitrification

- **Improved success with vitrification has been reported** (Ketros et al., Hum Reprod. 2009; 24:1670-83)
- **2 live births after in vitro activation of vitrified ovarian tissue** (Suzuki et al., Hum Reprod. 2015)
- **However, vitrification of ovarian tissue can induce more DNA damage** (Kim SS, et al., Fertil Steril, 2010)

Effects of vitrification on follicles in ovarian tissue

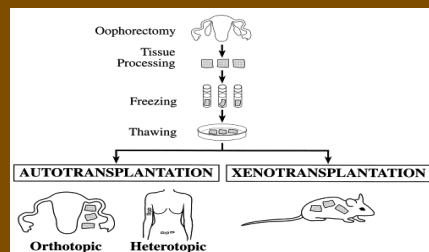


Cryopreservation (both slow freezing and vitrification) leads to oocyte chromatin condensation.



To improve the outcomes:

How and where to transplant?



Surgical techniques and sites of autotransplantation ovarian tissue

Orthotopic:

- onto the remaining ovary
- into the peritoneal pocket

Hetrotopic:

subcutaneous, intramuscular, anterior peritoneum etc.

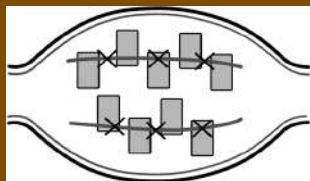
Orthotopic



Meirow et al., NEJM, 2005



Donnez J et al. Hum Reprod Update 2006



Andersen et al., Hum Reprod, 2008

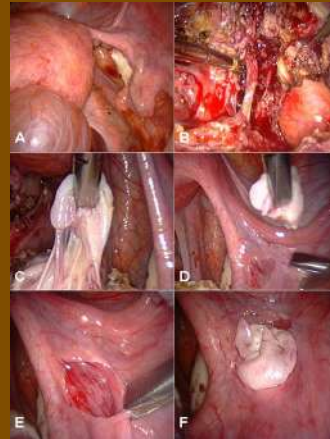
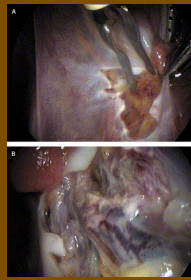


Sherman Silber

Orthotopic



Ralf Dittrich



Jacque Donnez



Kim et al, Fertil Steril, 2009



Heterotopic



Oktay et al., JAMA. 2001;286



Stern CJ et al., Hum Reprod, 2013

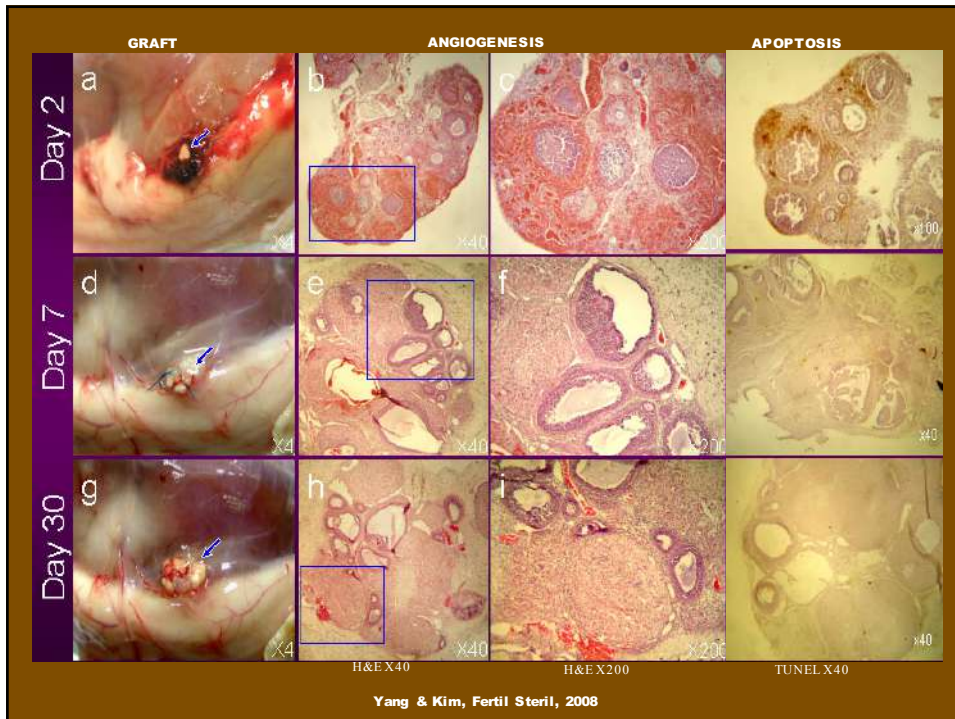
**For fertility restoration,
orthotopic transplantation should
be the method of choice.**

**There is no prospective
randomized study comparing the
efficacy of different surgical
techniques.**

To improve the outcomes:

**Do we need to use
angiogenic agents?**

**Ischemic Injury after transplantation
is the most detrimental to follicles, since
angiogenesis takes more than 48 hours
after transplantation**



How to minimize ischemic injury?

- **Facilitate angiogenesis**: stimulate with angiogenic factors , manipulation of VEGF gene expression
- **Protect oxidative damage and apoptosis caused by hypoxia**: antioxidants, anti-apoptotic agents

Angiogenic agents

Agents that may enhance angiogenesis after transplantation

1. Gonadotropin
2. VEGF, Angiopoietin
3. G-CSF (granulocyte colony stimulating factor)
4. Simvastatin, methylprednisolone
5. Mesenchymal stem cells
6. Extracellular matrix/endothelial cells

Currently, no specific agent for angiogenesis has been clinically applied for ovarian transplantation in most of centers, but it may be in the future

Summary

- **Human ovarian transplantation has been very successful, but its efficacy and safety need to be improved for routine clinical applications.**
- **Currently, slow freezing is the standard cryopreservation method for ovarian tissue.**
- **Orthotopic transplantation of ovarian tissue (either onto the ovary or peritoneal pocket) is recommended for fertility restoration.**
- **It is crucial to minimize ischemic damage after transplantation to improve outcomes.**

Thank you for
your attention!

