



**Karolinska
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Fertility preservation in patients with gynecological cancer

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Fertility preservation

PubMed search on cancer and fertility preservation:

- 1993-1994: 3 articles
- 1990-2000: 50
- 2003-2004: 87
- 2005: 176
- 2006: 250 (12 regarding children)
- 2007: 168 (39 regarding children)
- 2008 (August): 125 articles, 17 regarding children

Cancer in Sweden

- The annual number of cancer cases has increased constantly over the last two decades
 - Ageing of the population +improvement in screening, diagnosis
- The average annual increase is 1.7 % for men and 1.1 for women
- In the age 25-29 to 55-59 years the incidence is higher among females, mostly because of the dominance of breast and genital cancer.

Cancer incidence in Sweden 2006, The National Board of Health and Welfare Centre for Epidemiology, Stockholm 2007

- Delaying childbearing results in more female cancer survivors interested in fertility preservation

Why fertility preservation ?

- Improved long-term survival in young and children cancer patients
- Improved long-term survival in patients treated with cytotoxic agents for non-malignant diseases
- Infertility resulting from cancer treatment is associated with psychosocial distress

High priority to improve quality of life for cancer patients

Current methods for fertility preservation

- Ovarian transposition
- Assisted reproduction techniques:
 - Embryo cryopreservation
 - Oocyte cryopreservation
- Ovarian tissue cryopreservation:
 - Ovarian transplantation
 - In vitro folliculogenesis and in vitro maturation

Sexually mature women

- Embryo cryopreservation (partner or donor sperm)
- Well-established technique
- 2-6 weeks needed to perform the IVF treatment

Cryopreservation of mature oocytes

- single women without a partner, religious or ethical objections to embryo freezing
- Problems:
 - Metaphase II oocytes are large
 - Damage of the cell spindle and zona pellucida are frequent
 - Survival rates 25-95% Al-Hasani 1987, Gook 1995, Kuleshova 1999, Yoon 2000, Porcu 1997, Katayama 2003
 - Fertilization rates 13.5-71% Imoedemhe and Sigue 1992, Kazem 1995, Porcu 1997, Fabri 2001, Chen 2002

Cryopreservation of mature oocytes

- 1986: first pregnancies reported
- 1986-1997: 5 live births
- 1997: ICSI was first used
- 120 deliveries reported by 2005 (>300 by today)

- Low pregnancy rates (<3%) Porcu 1997, Oktay 1998
- Approximately 2% live birth per thawed oocyte (3-4 times lower than standard IVF)
- Pooled data from 21 studies, survival 47%, fertilization 52.5 and pregnancy rate per thawed oocytes 1.52% Sonmezer and Oktay, 2004

A new vitrification method for cryopreservation of human oocytes

- Kuwayama M, Vajta G, Kato O, Leibo SP
Reprod Biomed Online Sept 2005
- 64 vitrified oocytes
- 58 (91%) had normal morphology after warming
- 52 became fertilized after ICSI and 32 (50%) developed to the blastocyst stage in vitro
 - - 5 blastocysts were normal diploid embryos
- 29 ET (2.2 embryos per transfer) resulted in 12 pregnancies, 7 healthy babies and 3 ongoing pregnancies

A new vitrification method for cryopreservation of human oocytes

- Kuwayama M
Gynecol Endocrinol Jun 2006
111 frozen oocytes, 94.5% successfully thawed
Pregnancy rate 41.9% after IVF compared to the 42.5% rate with fresh oocytes
- 50 children born by Jan 2007 (*Theriogenology*) using the cryotop technique.
- Similar results reported by other authors

Experimental studies of ovarian tissue cryopreservation and transplantation

- Studies started in 1950-60
- More effective protectants since 1970
propanediol, ethylene glycol, DMSO
- Gosden, 1994: sheep ovaries (more similar to human in follicle density and stromal fibrosity)
 - transplantation into the infudibulopelvic ligament (fresh and frozen), 6 cases
 - arterial blood supply after 1 week
 - ovulation after 4 months
 - two pregnancies

Cryopreservation of ovarian tissue

- Primordial follicles: immature oocytes may be less susceptible to cryodamage
 - lower cell volume
 - low metabolic rate
 - absence of zona pellucida
 - lack of metaphase spindle
- The ovarian biopsy may be performed by laparoscopy
- Vitrification techniques have improved the survival of the tissue (2008)

Human ovarian transplantation trials

- Pelvic transplantation (orthotopic):
May allow natural pregnancy
Requires abdominal surgery and general anaesthesia
- First case: 27 year old woman (Oktay, 2001)
Slow-freeze protocol
Laparoscopic transplant
Aspirin and FSH for a week
15 weeks: ovulation after FSH treatment
9 months: no ovarian function left

Human ovarian transplantation trials

- Transplantation at the forearm (heterotopic)
(Wagner, 1976)
- Whole ovary: vascular anastomosis (Leporrier, 1987)
- Accidental transplantation at the subcutaneous tissue at the abdominal wall (Marconi, 1997)

Human ovarian transplantation trials

- First report of ovulation in a woman Oktay, 2000
- Ovulation and oocyte aspiration Oktay, 2001
- Oocyte aspiration and embryo generation Oktay, 2004
- Livebirth (Donnez, 2004)
- By 2008 few pregnancies reported and six children born

Ovarian auto-transplantation

- Possibility of reintroducing malignant tumor cells ??
- High risk: Leukemias
- Moderate risk: Neuroblastoma, breast cancer
- Low: Wilm's tumor, lymphomas (exception Burkitt's), osteosarcomas, Ewing's sarcoma and extragenital rhabdomyosarcomas, squamous cell cervical cancers

In-vitro folliculogenesis and maturation

- Still experimental

Edinburgh criteria for cryopreservation of ovarian cortical tissue

- Age < 30 years
- No previous chemotherapy (patient <15 y with previous low-risk chemotherapy)
- Realistic chance of long-term survival
- High risk of treatment-induced immediate ovarian failure (estimated >50%)
- Informed consent from patient or parents
- Negative HIV and hepatitis serology
- No existing children

- Criteria are based on multidisciplinary discussion and the working group report of the Royal College of Obstetricians and Gynaecologists, 2000.

A 3D architectural rendering of a Gothic cathedral. The main structure is made of red brick with dark, pointed spires. A large, metallic globe is mounted on a tall, dark spire. In the foreground, a modern building with a dark, multi-tiered, rounded roof and many windows is visible. The scene is set against a clear blue sky.

Thanks for your attention