



UNIVERSITY *of* MARYLAND
MEDICAL CENTER

Cancer and Fertility

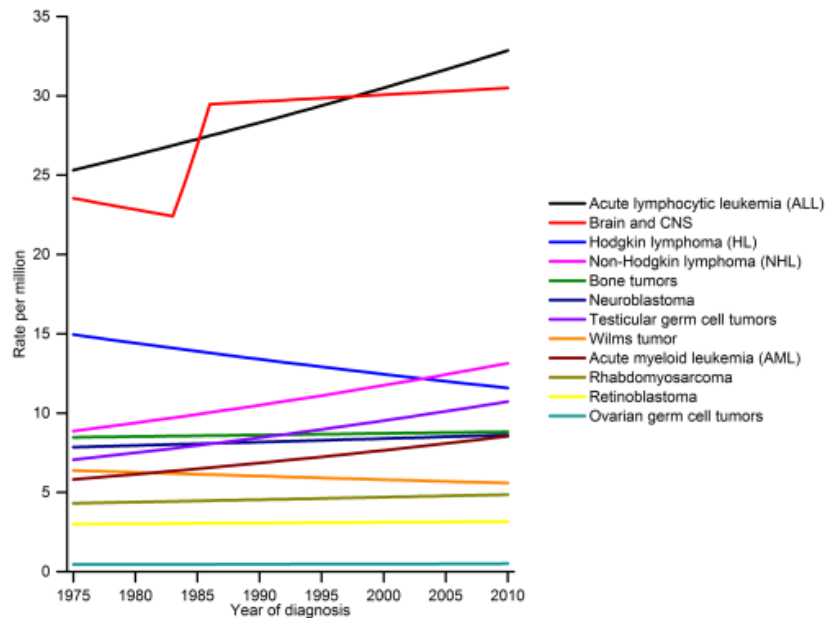
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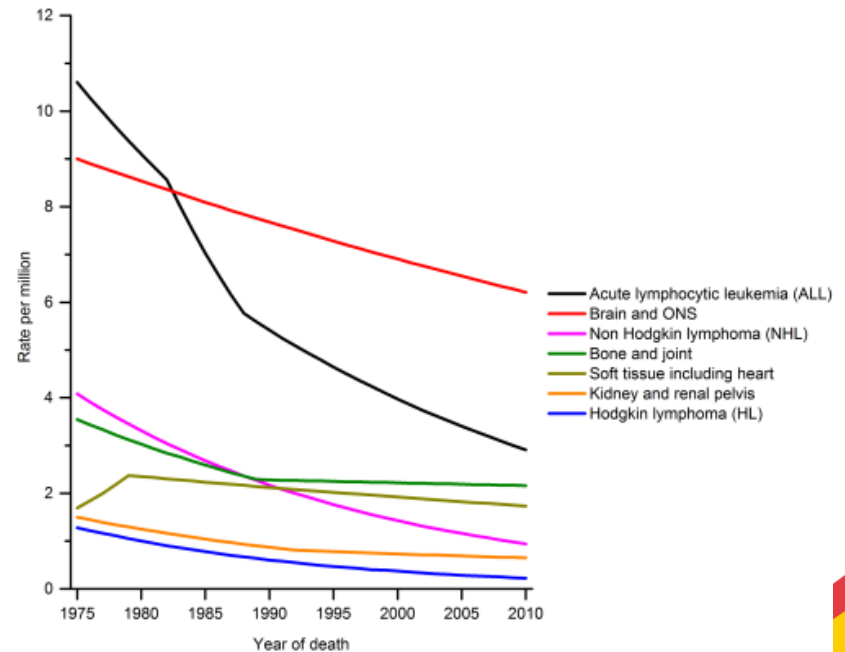
University of Maryland Medical Center

Trends in Pediatric Cancer

Incidence Rates by Site, Ages Birth to 19 Years, 1975 to 2010.



Mortality Rates by Site, Ages Birth to 19 Years, 1975 to 2010.





Rates of infertility among cancer survivors

Impossible to determine rates/risk of infertility in cancer survivors

- People only realize if they are infertile if they try to have a baby
- No definitive test to prove someone is infertile
- Infertility is common in people with no history of cancer
 - *10.9% of US women report having difficulty getting pregnant*
 - *6% of US women report being infertile (defined as not conceiving a child after 12 months of unprotected sex with a male partner)*
 - *12% of US men report difficulty conceiving a child*
- Almost all pediatric cancers are treated with multiple drugs so it is difficult to know the culprit

Childhood Cancer Survivor Study (CCSS)

- Survey of children treated for cancer from 1970-1986 and a sibling control group (14,358 survivors and 4,023 sibling controls)
- Participants in the fertility survey
 - *3,531 female survivors and 1,366 same-sex sibling controls*
 - *938 male survivors and 174 same-sex sibling controls*
 - *Survivors defined as*
 - Lived 5 years from diagnosis from ANY childhood malignancies
 - If patient survived 5 years but then died, next-of-kin could answer the questions
 - *If multiple siblings, the closest age sibling was asked to participate*

Definition of infertility for females

- 1. Clinical infertility- If there was ever a period in your life when you and your partner tried for one year or more to become pregnant without success?*
- 2. Total infertility- Women with clinical infertility AND ovarian failure regardless of ever having tried to get pregnant. Ovarian failure was defined as*
 - Never having a menstrual cycle OR Menstrual period stopping five years or more from time of questionnaire

Definition of infertility for males

- 1. Has your female partner ever had difficulty (it took longer than a year) becoming pregnant by you?*

CCSS Fertility Study Results-Female

- Total infertility 16% in survivors and 10.8% in sibling controls
- Clinical infertility 12.9% in survivors and 10% in sibling controls
 - *2/3 of survivors who met definition of clinical infertility had a child*
- Cancer specific risk of factors
 - *Diagnosis of lymphoma*
 - *Radiation to abdomen or pelvis or total body*
 - *Higher doses of alkylators (cyclophosphamide, busulfan, ifosfamide, melphalan)*
 - *Pituitary radiation*

CCSS Fertility Study Results- Male

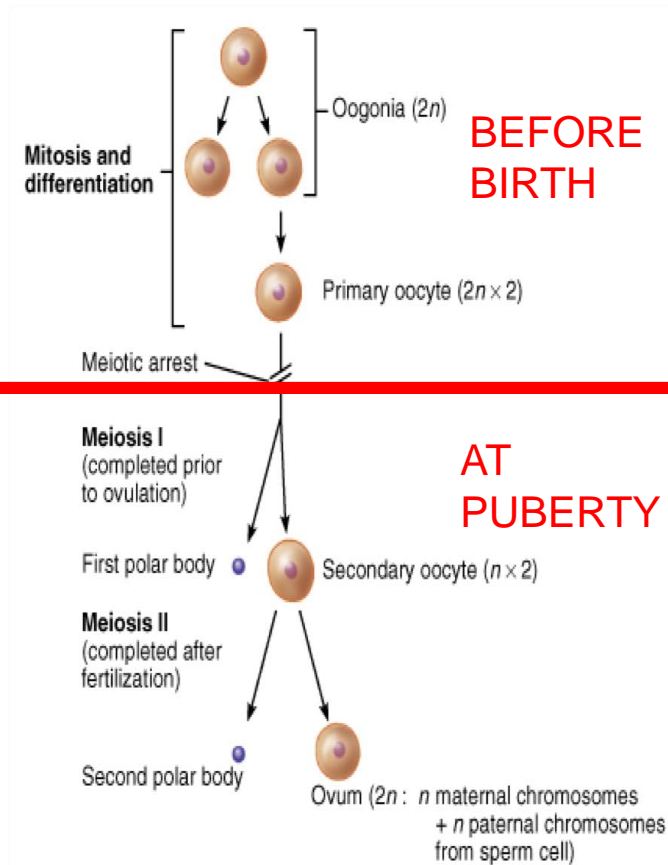
- 46% of survivors vs 17.5% sibling controls met definition of infertility
 - 37% of survivors who met definition of infertile went on to have at least one child
 - 8% reported pregnancy but no live birth
- Of those who sought medical evaluation for infertility 96% survivors and 89% controls identified male problem (low sperm count, motility)
- Cancers-specific risk factors
 - *Hodgkin, osteosarcoma and soft tissue sarcomas*
 - *Increased dose of alkylators*
 - *> 4 Gy radiation to testicles*
 - *Orchiectomy*

Fertility and Bone Marrow Transplantation

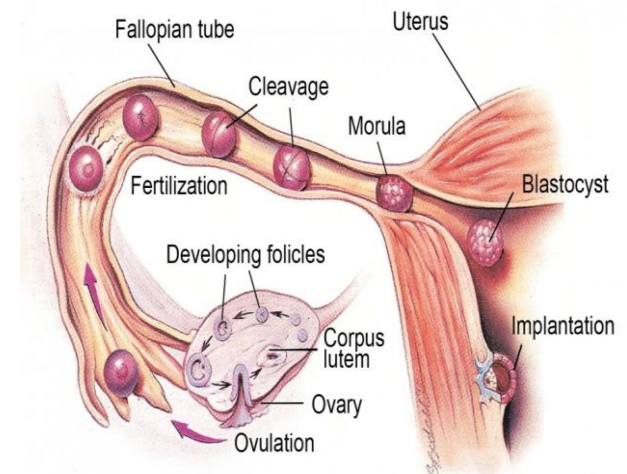
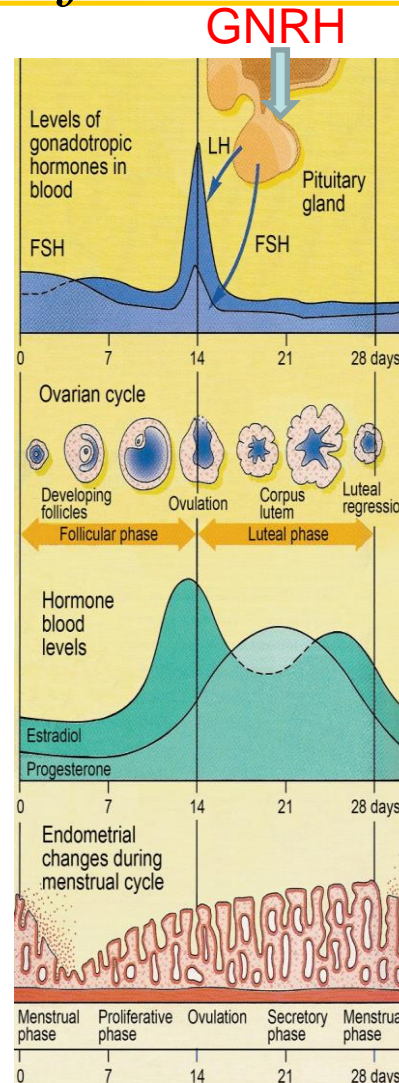
- Highest risk of infertility in pediatric population
- Conditioning regimens are high doses of alkylators +/- total body irradiation
- 4.5% of female BMT recipients had children in long-term follow-up
 - *This did not take in account desire or attempt at becoming pregnant*
- 56% of male BMT recipients under the age of 25 at the time of transplant had sperm in semen analysis
 - *Took up to 12 years in some patients.*

Female Fertility

Oogenesis, ovulation, fertilization and implantation



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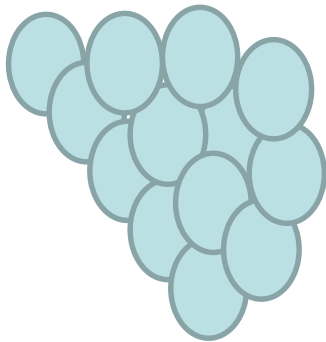
Cause of infertility

- Ovarian failure
 - *Direct injury to ovary or oocytes*
 - *Hypothalamic/Pituitary failure disrupting hormonal regulation of ovulation*
- Uterine/cervical incompetence

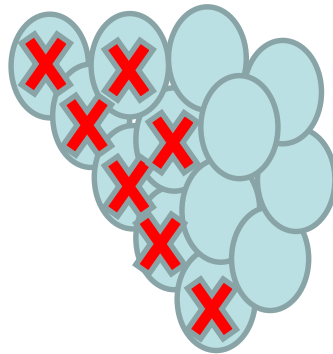
Ovarian Failure

Ovarian Failure

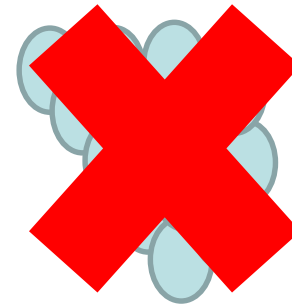
- Premature ovarian failure: retain function after cancer treatment but experience menopause prior to age of 40
- Acute ovarian failure: during or shortly after cancer treatment



Normal
ovary



Premature
ovarian
failure



Acute
ovarian
failure

Uterine or Cervical Incompetence

Uterine/cervical Incompetence

- Successful ovulation and fertilization but functional problem with uterus and/or cervix
- Miscarriages, preterm births, placental insufficiency and still birth
- Causes
 - *Hysterectomy*
 - *Abdominal or pelvic XRT > 5Gy*
 - *Craniospinal XRT*

Female Fertility Preservation Options

Fertility Preservation Options

- Hormonal suppression during therapy
- Embryo cryopreservation
- Oocyte cryopresevation
- Ovarian tissue cryopreservation

Hormonal Ovarian Suppression

- Oral contraceptive pills or GnRH agonists
- To date there is no evidence that this preserves fertility long term
- Can decrease menstruation during treatment which is potentially beneficial for preventing menorrhagia

Embryo/oocyte cryopreservation

- Egg retrieval- minimum of 3 weeks
 - *Ovarian suppression: 2-4 weeks*
 - *Ovarian stimulation: 8-12 days*
 - *Egg retrieval: 30 minutes*
- Post retrieval
 - *Oocyte cryopreservation- eggs are immediately frozen*
 - *Embryo cryopreservation- undergo fertilization in vitro and then frozen*

Embryo/oocyte cryopreservation

- Embryo cryopreservation
 - *First successful pregnancy in 1983*
 - *Live birth rate based on age at time of transfer of thawed embryos*
 - 44% if < 35yo
 - 21% if > 42yo
- Oocyte cryopreservation
 - *First successful pregnancy in 1986*
 - *Clinical pregnancy rate 4-12%*
 - *About 900 reported live births in US in 30 years*

Embryo/oocyte cryopreservation limitations

- Patient must be post-pubertal
- Time to retrieval is often not feasible
- Cost
 - *Harvest and first year of storage \$5000-\$6000*
 - *Yearly storage fee of \$350-\$500*
 - *Cost of reimplantation*
- Embryo- must have a father
- Ethical considerations of these procedures in minors
- May be a better option to offer cancer survivors in long term follow-up

Ovarian Cortical Tissue Cryopreservation

- Laparoscopic surgical removal of ovarian cortical tissue and then reimplanted after treatment
 - *Orthotopic- near or within remaining ovarian tissue*
 - *Heterotopic- tissue implanted in forearm, chest wall or abdominal wall*
- Outcomes
 - *Resumption of normal menses in 4-9 months*
 - *Longest reported graft survival was 7 years*
 - *Pregnancy*
 - Orthotopic: 24 live births worldwide in 10 years of experience
 - Heterotopic: Successful retrieval of oocytes but no successful pregnancies
- Risks
 - *Reintroducing cancer cells*
 - *Multiple surgical procedures*

Whole Ovary Cryopreservation

- Entire ovary is removed intact and frozen. Then thawed and surgically reattached to the blood vessels after treatment
- Outcomes
 - *No successful births*
 - *No documentation of resuming normal menses*
- Risks
 - *Reintroducing the cancer*
 - 6/8 ovaries contained malignant cells
 - *Multiple surgical procedures*

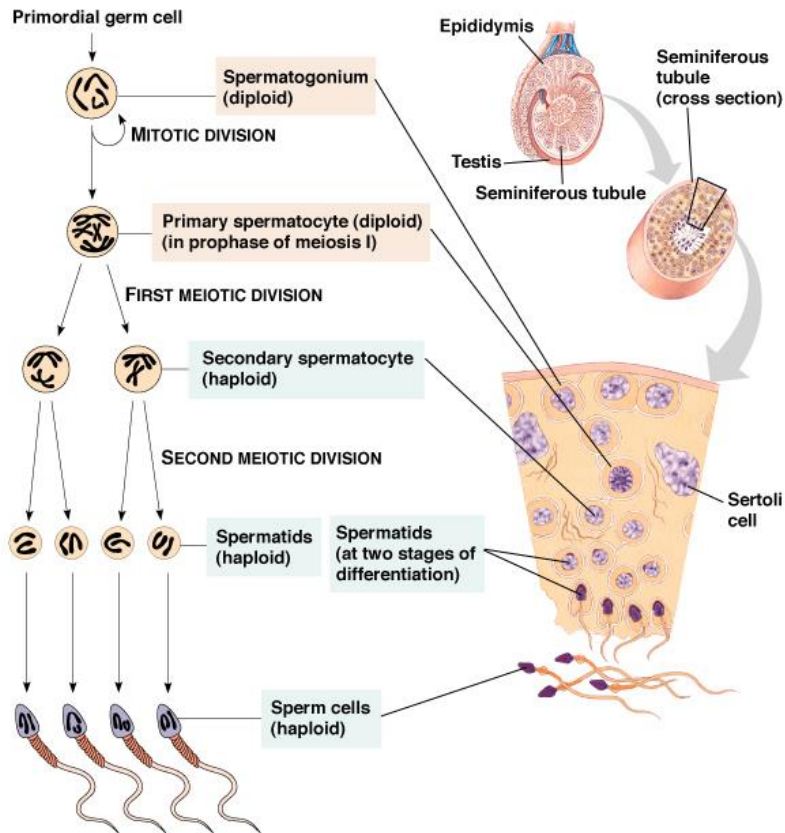
Problems of ovarian failure beyond infertility

Other problems of ovarian failure

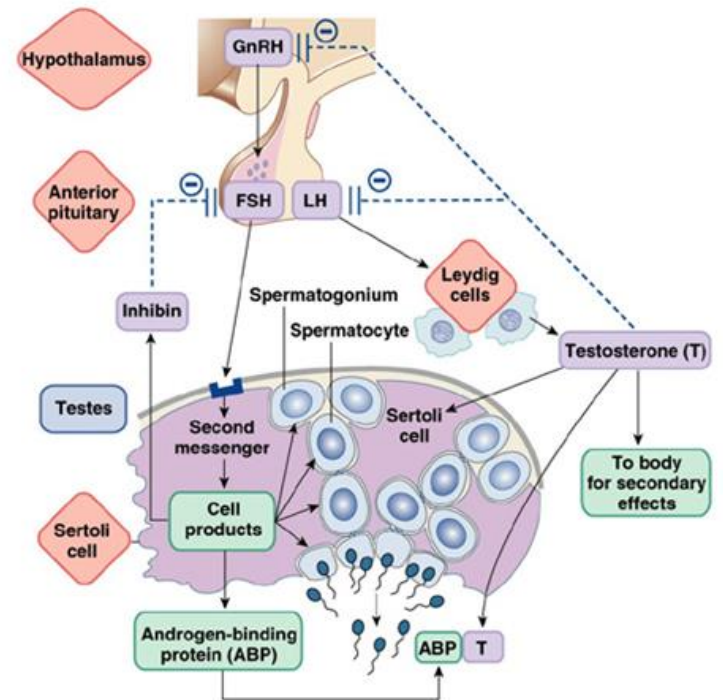
- Increased risk of osteoporosis, cardiovascular disease, dementia, depression/anxiety
 - *Hormone replacement is recommended in women with POF until the age of 50*
- Increased rates of non-marriage or divorce

Male Infertility

Spermatogenesis



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Causes of male infertility

- Pretesticular: Disruption of FSH/LH production or release
- Testicular:
 - *Destruction of the germ cells*
 - *Destruction of Leydig cells->decreased testosterone production. Leydig cells highly resistant to chemo but not radiation*
- Post-testicular/obstructive: Make sperm cells but cannot ejaculate due to obstruction of the vas deference or urethra

Male Fertility Preservation Options

Sperm banking

- Collection and cryopreservation of sperm
 - *Masturbation and collection of the ejaculate*
 - *Surgical sperm extraction*
- In vitro fertilization with female partner
 - *Samples can be frozen for 20-30 years*
- Ideally done prior to initiation of therapy but can be attempted after therapy has been started
 - *Effect on offspring after chemotherapy has started is unknown*
 - *One cycle of chemo can cause (temporary) azoospermia*

Sperm banking limitations

- Psychological/logistical concerns with collection
- Surgical collection can have low yields and surgical complications
- Cost (Not usually covered by insurance)
 - *Initial processing fee of \$300-\$500/ sample*
 - *Yearly fee \$200-\$400/sample per year*

Cryopreservation of testicular tissue

- Surgical procedure in which a small portion or the entire testicle is removed and frozen
- No documented births resulting from cryopreserved testicular tissue
- Some argue that we should offer this because in 20-30 years when current children want to have children the technology may be in a place where that is possible

Children's Oncology Group Surveillance Recommendations

Highest Risk Factors for Male Gonadal Dysfunction

- Busulfan $\geq 600\text{mg/m}^2$
- Cyclophosphamide $\geq 7.5\text{mg/m}^2$
- Ifosfamide $\geq 60\text{g/m}^2$
- Any alkylator combined with testicular, pelvic, total body or neuroaxis radiation
- $\geq 30\text{Gy}$ radiation to cranial, infratemporal, nasopharyngeal, orbital
- $\geq 6\text{Gy}$ radiation to testes

Highest Risk Factors for Female Gonadal Dysfunction

- ≥ 10 Gy (pubertal) or ≥ 15 Gy (prepubertal) radiation to abdomen or pelvis
- Any alkylator combined with abdominal, pelvic, total body or neuroaxis radiation
- ≥ 30 Gy radiation to cranial, infratemporal, nasopharyngeal, orbital
- ≥ 30 Gy to uterus (uterine insufficiency)

Annual evaluation for normal pubertal development

- **Females**

- *Normal onset is 8yo-13yo*
- *Breast development is first sign of puberty*
- *Delayed puberty: Absence of breast development by 13yo, pubic hair by 14yo or menarche by 16yo*

- **Males**

- *Normal onset is 9yo-14yo*
- *Testicular enlargement is first sign of puberty*
- *Delayed puberty: No testicular enlargement by 14yo or pubic hair by 15yo*

Laboratory screening

- **Females**

- *FSH, LH and estradiol baseline at age 13yo and then repeated as clinically indicated*
- *Anti-Muellerian Hormone*
 - Marker of ovarian reserve
 - AMH concentrations slowly decrease with increasing age until becoming undetectable ~5 years before menopause when the stock of primordial follicles is exhausted
 - Has been shown to be helpful to be in adult cancer survivors but not well studied pediatrics

- **Males**

- *FSH, LH and testosterone baseline at 14 yo and then repeated as clinically indicated*
- *Semen analysis*
 - Should be repeated periodically because resumption of spermatogenesis has been documented up to 10 years after completion of chemo

Hormone levels are inaccurate predictors of fertility

- Many females with abnormal FSH levels get pregnant and vice versa
- Males often still produce testosterone because Leydig cells are resistant to chemo

Summary

- Difficult to predict individual risks of infertility
- Most pediatric cancer survivors are capable of having children
- No data that there is increased risk of chromosomal abnormalities in offspring
- Presentation of infertility in cancer survivors differs between males and females
 - *Females tend to have a period of fertility after cancer therapy but go through menopause early*
 - *Males tend to be acutely infertile but may resume spermatogenesis up to years later*
- Best options for fertility preservation
 - *Female cancer survivors should be counseled on oocyte or embryo cryopreservation as part of long-term follow care*
 - *All post-pubertal males should be offered chance to sperm bank prior to treatment*
- No good options for fertility preservation in pre-pubertal patients
 - *However they likely have less risk of infertility because there is not active division of the cells*
- Gonadal dysfunction leads to osteoporosis, cardiovascular disease, dementia and patients should be counseled and screened accordingly

Questions