# The Effects of Cancer Treatment on Future Fertility: Clinical Aspects

ISFP Vienna

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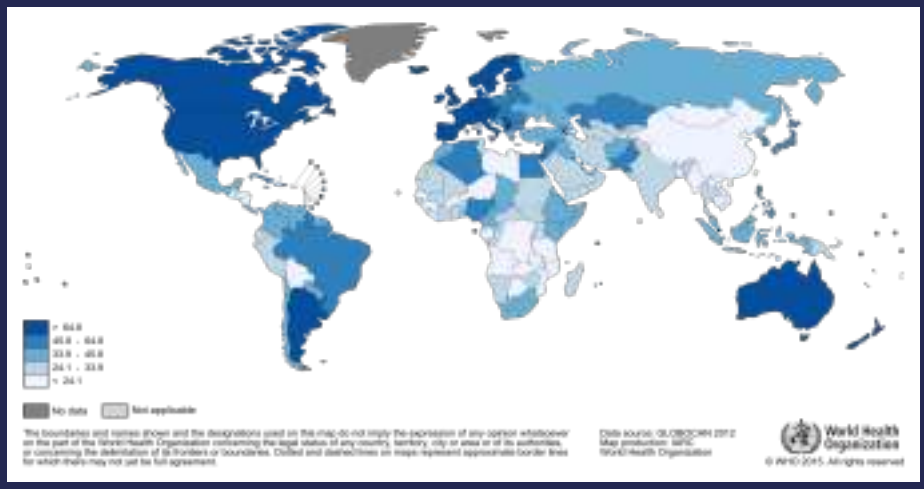
## Disclosures

- none

# Cancer Incidence Worldwide

over 14 million cancer cases
expected to be over 24 million by 2035



# Common Cancers (USA)

> 150,000 new diagnosis in reproductive age patients

**Estimated New Cases**

| | Males | | | Females | |
|---|---|---|---|---|---|
| Prostate | 180,890 | 21% | | Breast | 246,660 | 29% |
| Lung & bronchus | 117,920 | 14% | | Lung & bronchus | 106,470 | 13% |
| Colon & rectum | 70,820 | 8% | | Colon & rectum | 63,670 | 8% |
| Urinary bladder | 58,950 | 7% | | Uterine corpus | 60,050 | 7% |
| Melanoma of the skin | 46,870 | 6% | | Thyroid | 49,350 | 6% |
| Non-Hodgkin lymphoma | 40,170 | 5% | | Non-Hodgkin lymphoma | 32,410 | 4% |
| Kidney & renal pelvis | 39,650 | 5% | | Melanoma of the skin | 29,510 | 3% |
| Oral cavity & pharynx | 34,780 | 4% | | Leukemia | 26,050 | 3% |
| Leukemia | 34,090 | 4% | | Pancreas | 25,400 | 3% |
| Liver & intrahepatic bile duct | 28,410 | 3% | | Kidney & renal pelvis | 23,050 | 3% |
| **All Sites** | **841,390** | **100%** | | **All Sites** | **843,820** | **100%** |

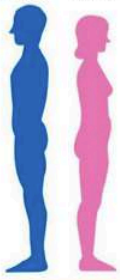
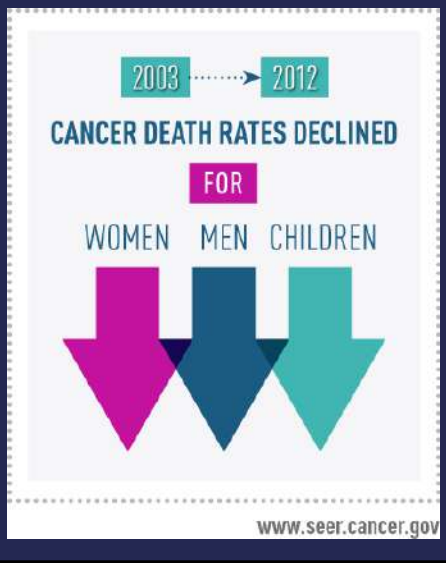


FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2016.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

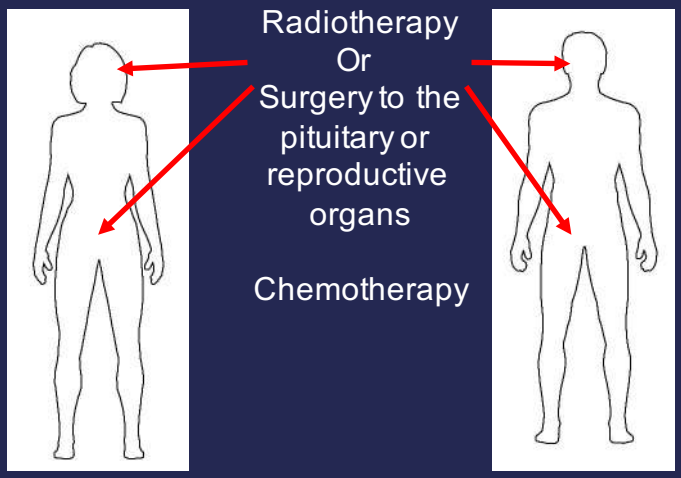
Common Cancers in Children: CNS, hematologic, sarcomas, bone, renal

# Improved Therapies have Increased Survival

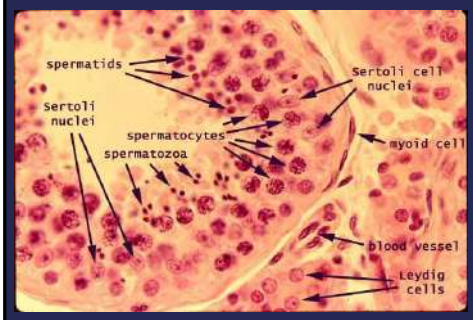



>80% survival for childhood cancers

# Therapies Pose Reproductive Risks



# Male Gonadotoxicity



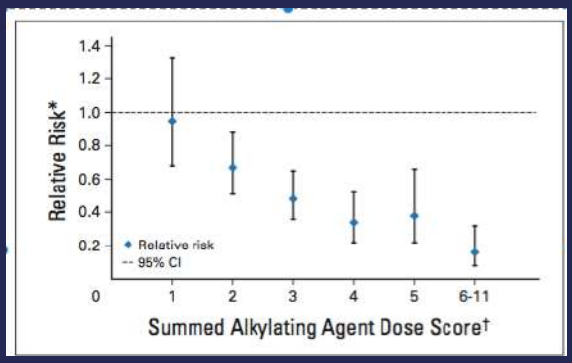

- Testes is composed of spermatogonia (germ cells), sertoli cells (support cells), and leydig cells (testosterone production)
- Differentiating spermatogonia and spermatogonial stem cells are most susceptible to injury from chemotherapy and radiation
- For most survivors, sexual function and pubertal development are preserved, but fertility may be affected

# Fertility of Male Survivors: Data from CCSS

- 6,224 survivors; 1,390 sibling comparison
- Self-reported fathering a pregnancy
- HR 0.56 (95% CI 0.49-0.63)
- Risk factors for impaired fertility:
  - Testicular RT (≥ 750 cGy)
  - Exposure to alkylators
    - high doses of cyclophosphamide or procarbazine
  - Age at dx >4

**Green et al, J Clin Oncol;28:332 2010**

# Likelihood of Pregnancy by Alkylating Agent Exposure




Dose dependent relationship was confirmed with Cyclophosphamide Equivalent Dose in CCSS analysis

**Green et al, J Clin Oncol 2010**
**Chow et al. Lancet Oncol 2016**

# Impaired sperm production

- Radiation is very damaging
  - >250 cGy in men
  - >600 cGy in boys
- Because treatment is multimodal, it can be difficult to isolate the effect of individual treatments

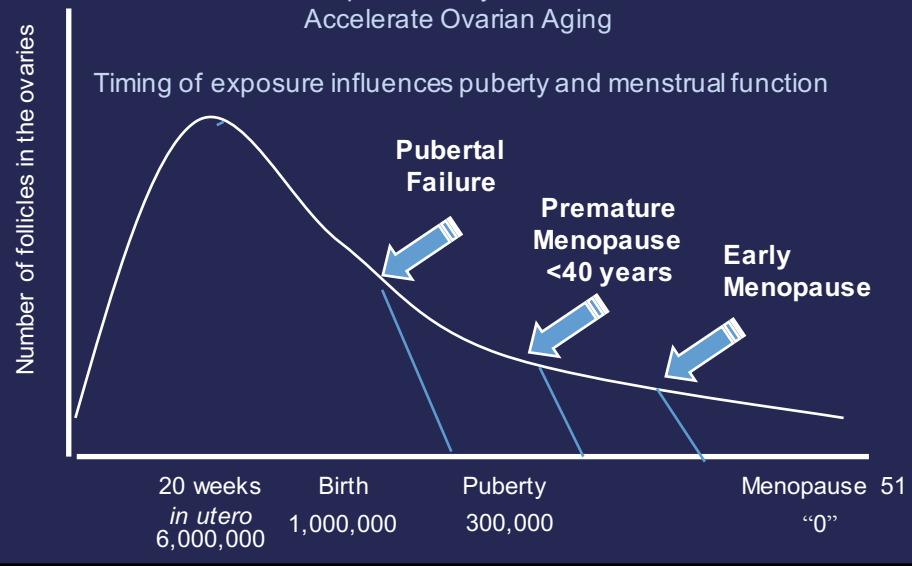
| Testicular dose (cGy) | Effect on spermatogenesis |
|---|---|
| < 10 | No effect |
| 10-30 | Temporary oligospermia |
| 30-50 | Temporary azoospermia at 4-12 mo. after radiation. 100% recovery by 48 mo. |
| 50-100 | 100% temporary azoospermia for 3-17 mo. after radiation. Recovery begins at 8-26mo. |
| 100-200 | 100% azoospermia from 2 months to at least 9 mo. Recovery begins at 11-20 mo. |
| 200-300 | 100% azoospermia beginning at 1-2 mo. May lead to permanent azoospermia. If recovery takes place, it may take years. |
| 1200 | Permanent azoospermia |
| 2400 | Permanent azoospermia |

Loren JCO 2013

# Reproductive Risks: Females

Cancer Therapies destroy ovarian follicles and Accelerate Ovarian Aging

Timing of exposure influences puberty and menstrual function



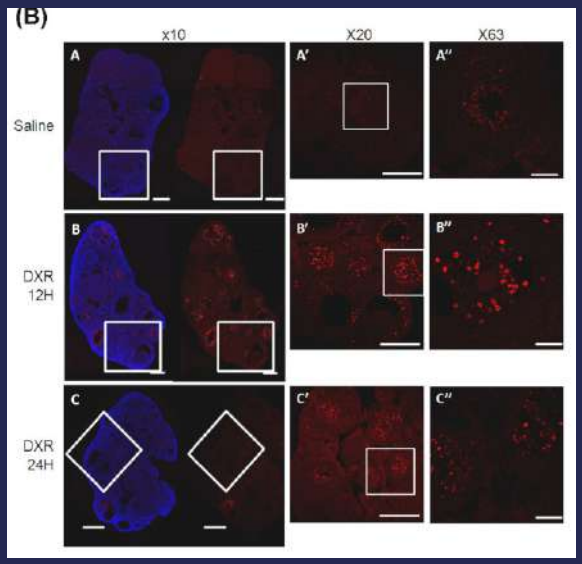

# Acute follicular destruction: Doxorubicin-Induced Ovarian Toxicity

Confocal micrographs of ovaries excised from saline vs. doxorubicin-treated mice at 12 and 24 hours post treatment

Caspase-3 (red) staining for detection of apoptosis.

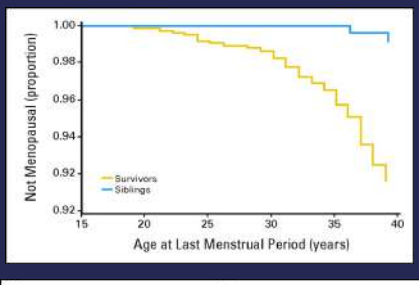
Clearly manifested in 2º, pre-antral and antral follicles both 12 and 24 h post-treatment

Note: Heochst 32242 (blue) staining for DNA




Ben-Aharon etal. Reproductive Biology and Endocriology 2010;8:20

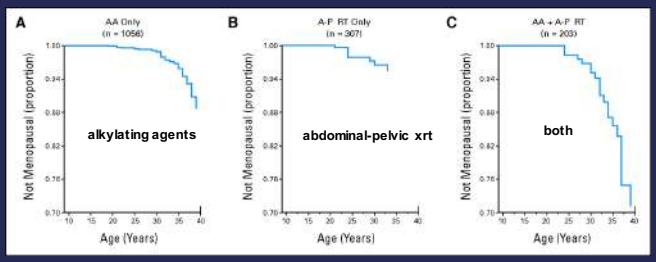
# Cumulative incidence of premature menopause in the CCSS




Acute ovarian failure = 6.3%
Premature menopause = 8%

Risk substantially higher for survivors than for siblings RR=13.21; 95%CI, 3.2-53; P<.001

Risk depends on exposure to AA and Pelvic RT




**For survivors treated with both, the cumulative incidence approached 30%.**

Green et al. J Clin Oncol; 27:2374-2381 2009

# Breast Cancer

## Age at treatment is associated with return of menses

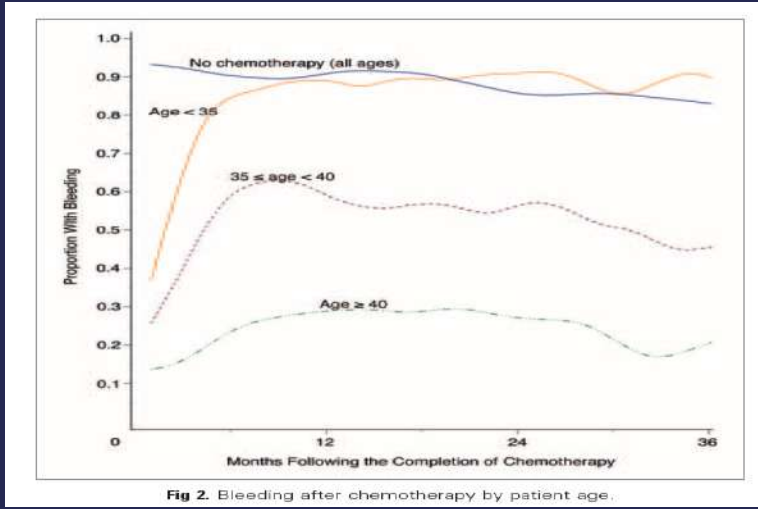
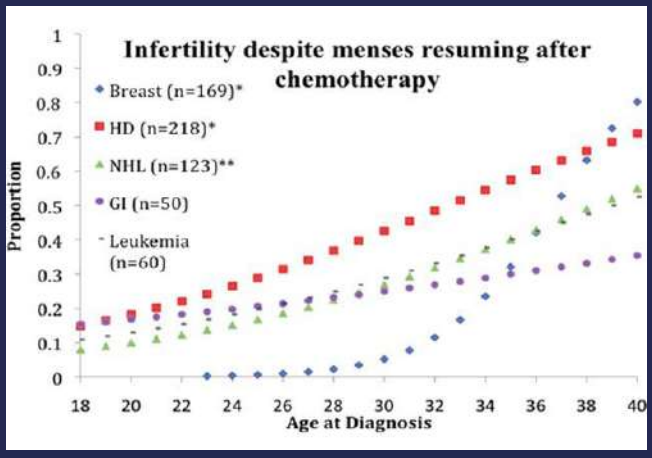



**Fig 2.** Bleeding after chemotherapy by patient age.

Menstrual calendars 595 women age 20-45 Petrek et al. J Clin Oncol 2006:1045.

## Menstrual Function ≠ Fertility




Letourneau, et al. Cancer 2011

## Fertility of Female Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

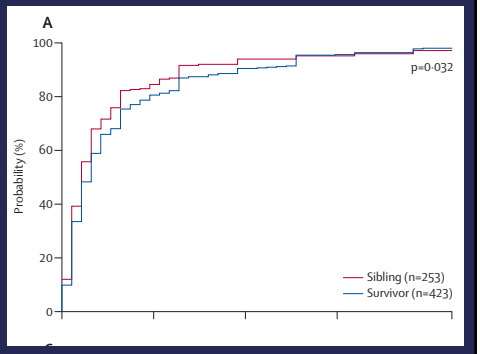
*Daniel M. Green, Toana Kawashima, Marilyn Stovall, Wendy Leisenring, Charles A. Sklar, Ann C. Mertens, Sarah S. Donaldson, Julianne Byrne, and Leslie L. Robison*

- 5,149 CCSS survivors, 1,441 sibling controls 15-44 years
- Survivors less likely to report a pregnancy RR 0.81 (95%CI 0.73-0.90)
- Chemotherapy:
  - Alkylating Agent Dose Score = 3-4 (RR 0.7)
- XRT:
  - Hypothalamic/pituitary XRT ≥ 30 Gy (RR 0.61)
  - Ovarian/uterine XRT 5 - 10 Gy (RR 0.56)
  - Ovarian/uterine XRT >10 Gy (RR 0.18)

JCO 2009

# Assessing Fertility in Survivors

- Self reported pregnancy may not truly reflect fertility
- Follow up CCSS study
  - Increased risk of infertility (RR 1.48)
  - Longer time to pregnancy
- Finnish birth registry study
  - Survivors more likely to use fertility treatments (OR 1.8)




Barton, Lancet Oncol 2013
Melin, Acta Oncol 2017

# Survivors have Diminished Ovarian Reserve

| | Exposed (*n* =71) | Unexposed (*n* =67) | P-value* |
|---|---|---|---|
| **Age** | 25.67 | 27.26 | 0.10 |
| **FSH** | **11.12** | **7.25** | **0.001** |
| **AMH** | **0.81** | **2.85** | **<0.001** |
| **AFC** | **14.55** | **27.20** | **<0.001** |

Early follicular phase
*Adjusted for age, race, BMI

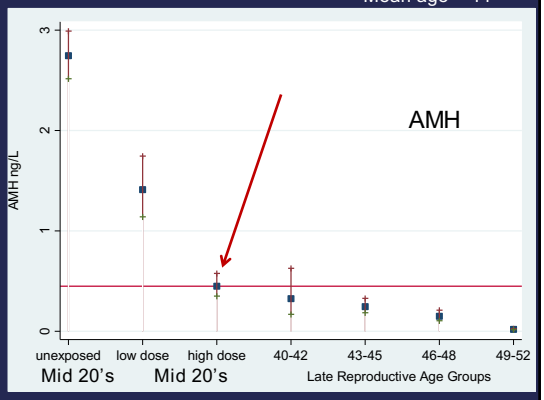
Gracia 2012
Nielsen 2013
Charpenter 2014
Thoma-Teinturier 2015

- Still, epidemiologic studies may be biased and risk is unpredictable
- Can we quantify impact?
- Several studies show decreased AMH and AFC in survivors compared to similar age controls
- Alkylators and pelvic radiation consistently associated with DOR

## Ovarian reserve in survivors compared to naturally aging women

79 Late Reproductive Women
Mean age = 44

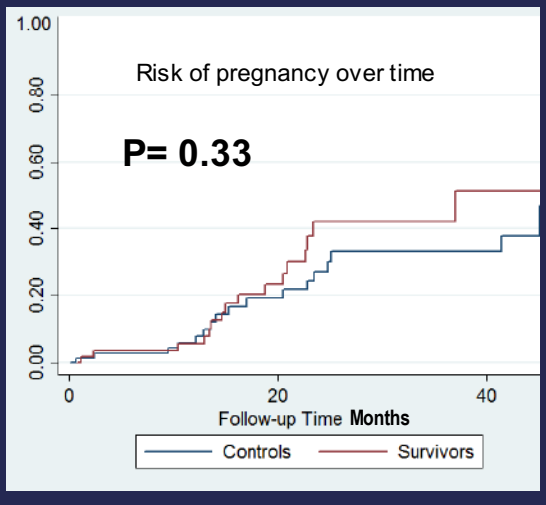
- Impaired in a dose dependent manner
- High risk survivors in Mid-20's have AMH levels similar to naturally aging women in early 40's




High Dose – AAD≥3 or pelvic XRT

Gracia et al. Fertil Steril. 2012;97:134-140

## Measures do not appear to predict fertility in survivors

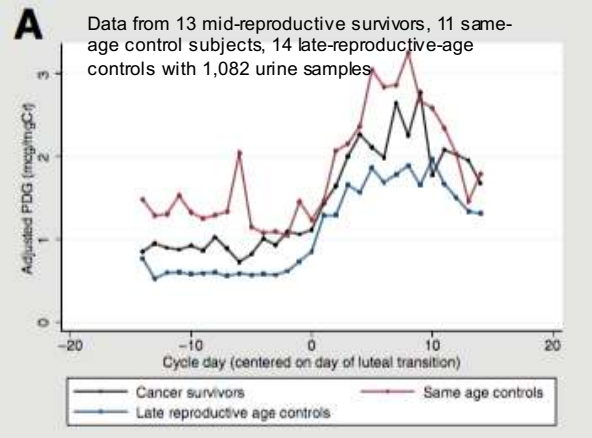



- 85 survivors and 98 controls were at risk for pregnancy during the study
- Pregnancy rates over the study were no different between groups despite DOR in survivors
- Suggests good quality of follicles

Average follow-up time: 17.5 months
Longest follow-up time – 5 years

Pediatr Blood Cancer. 2013

# Urinary Hormone PDG: normal despite impaired ovarian reserve

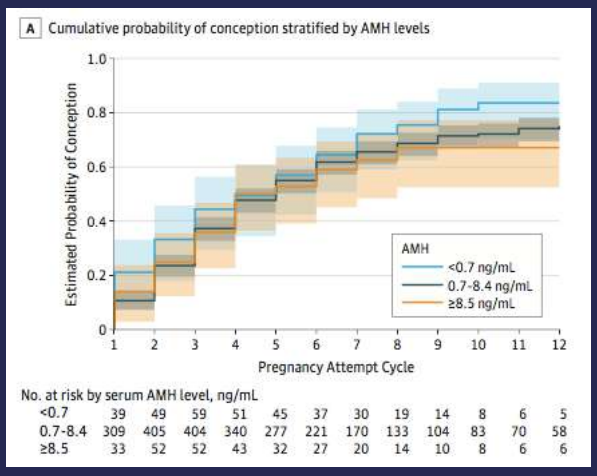



Despite lower ovarian reserve, survivors have similar urinary PDG as similar age controls but higher than late reproductive age controls

PDG = pregnanediole glucoronide

Johnson et al. Fert Steril 2016

# Measures of ovarian reserve do not predict unassisted conception




Prospective time to pregnancy over 12 months in 981 couples without infertility
Women age 30-44 years

Steiner JAMA 2017

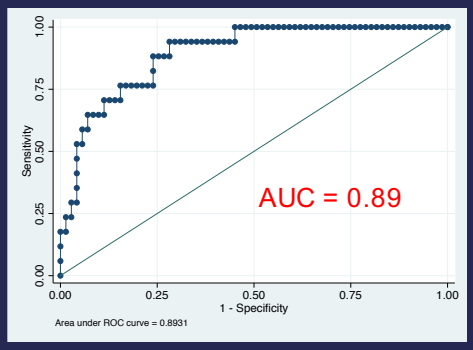
# Implications of Post Treatment Diminished Ovarian Reserve

- Survivors are less likely to respond to infertility treatments if they cannot conceive without assistance
- Live birth rates with IVF are LOWER among survivors using autologous oocytes (47.7% without cancer versus 24.7% with cancer, P =0.0001)
- May be helpful in predicting time to menopause as in non-cancer populations– anticipate long term health issues and HRT

Luke Hum Reprod 2015
Freeman et al. JCEM 2012
Anderson Eur J Cancer 2017

# Predicting Risk to Target FP

- Several studies suggest that AMH before treatment may predict long term amenorrhea
- We believe a simple clinical prediction tool can be developed to predict DOR



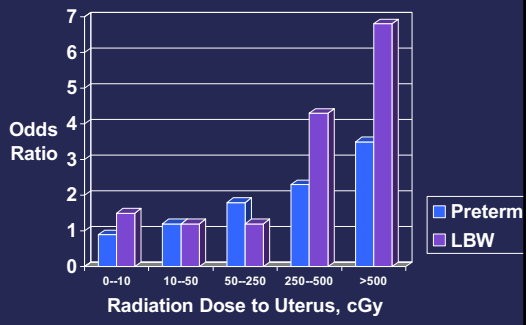

Age, Cancer Type, AMH, Alkylator Exposure predicts AMH <1 12-24 months post treatment

Data from ongoing cohort study

Anderson 2013, Su 2015, Henry 2014, Gracia unpublished

# Uterine Radiation

- Impact on fertility is not clear
- Increased risk of miscarriage, pre-term birth and low birth weight
- Uterine volumes smaller with radiation at a younger ages




Signorello et al. J Natl Cancer Inst 2006;98:1453.

# Conclusions

- Cancer therapies increase the risk of gonadal failure, infertility and diminished ovarian reserve
- Currently, strategies to predict the risk of infertility after cancer therapies are limited
  - Alkylating agent exposure, Pelvic radiation
  - Age, Pretreatment ovarian reserve
  - A validated risk calculator would be helpful
- Therefore fertility preservation options should be discussed with ALL patients

# THANK YOU!

- Katherine Cameron, MD
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- NIH
- ASRM
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