FERTILITY PRESERVATION

DR. J. HOLLETT-CAINES M.D. FRCSC, G.R.E.I. (AWC)

ASSOCIATE PROFESSOR

DEPT. OBSTETRICS AND GYNECOLOGY

DIVISION OF REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

WESTERN UNIVERSITY

FERTILITY THREATENING THERAPIES

- OVER 100,000 INDIVIDUALS < 45 YEARS OF AGE ARE DIAGNOSED WITH CANCER ANNUALLY IN USA
- ADVANCEMENTS IN CHEMOTHERAPEUTICS HAVE LED TO DRAMATIC IMPROVEMENTS IN SURVIVAL
- REPRODUCTIVE RISKS OF CANCER THERAPIES AND IMPROVED LONG-TERM SURVIVAL HAVE LED TO EXPANDING INTEREST IN FERTILITY PRESERVATION FOR CANCER PATIENTS

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

- 2006 – PUBLISHED RECOMMENDATIONS ON FERTILITY PRESERVATION STATING THAT
  - " AS PART OF EDUCATION AND INFORMED CONSENT BEFORE CHEMOTHERAPY, ONCOLOGISTS SHOULD ADDRESS THE POSSIBILITY OF INFERTILITY WITH PATIENTS TREATED DURING THEIR REPRODUCTIVE YEARS AND BE PREPARED TO DISCUSS POSSIBLE FERTILITY PRESERVATION OPTIONS OR REFER PATIENTS TO REPRODUCTIVE SPECIALISTS."

FERTILITY PRESERVATION SERVICES ARE UNDERUTILIZED

- IN ORDER TO EXPAND REPRODUCTIVE OPTIONS OF PATIENTS, NEED:

- IMPROVED MULTIDISCIPLINARY COLLABORATION BETWEEN ONCOLOGISTS AND REPRODUCTIVE SPECIALISTS

- WIDESPREAD AVAILABILITY OF FERTILITY PRESERVATION SERVICES

REQUIREMENTS FOR A FERTILITY PRESERVATION PROGRAM

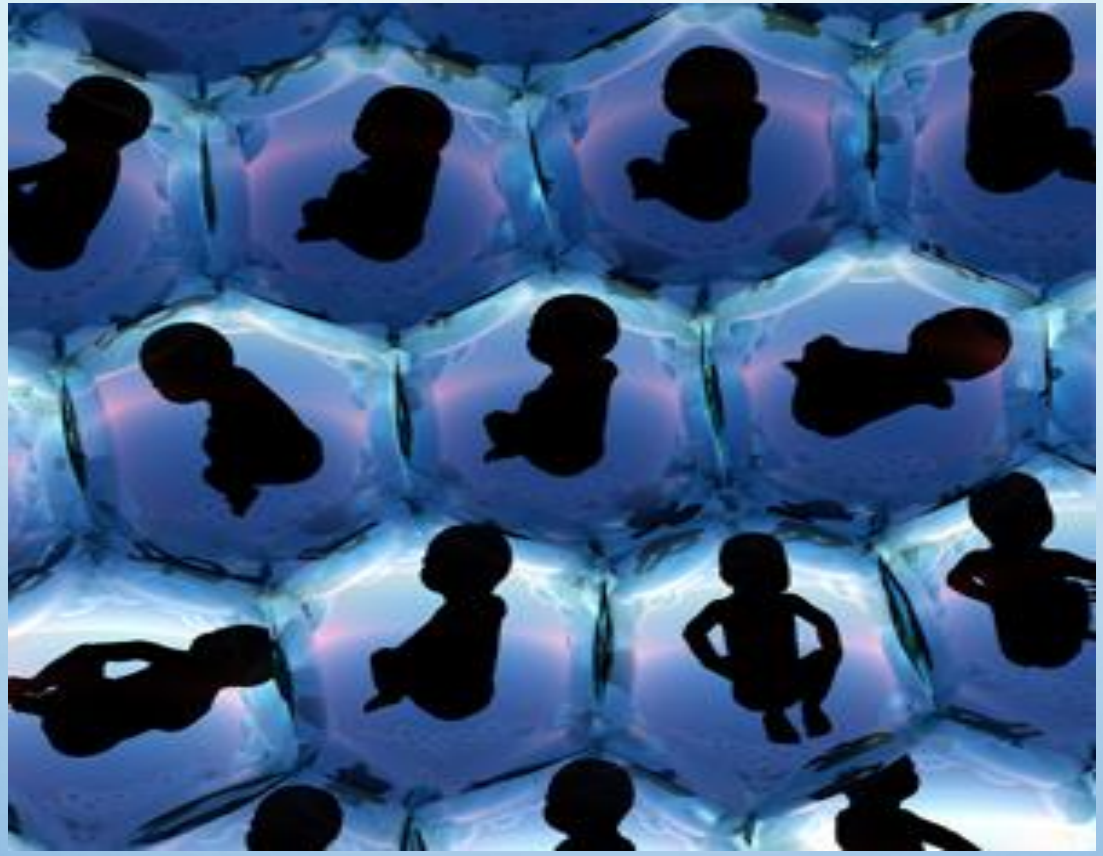
- RAPID ACCESS
- INTERDISCIPLINARY MEDICAL TEAM
- EXPERIENCED ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAM
- COUNSELORS: MENTAL HEALTH, GENETIC, FINANCIAL
- INTERDISCIPLINARY COLLABORATION

CURRENTLY AVAILABLE STRATEGIES - FEMALE

- EMBRYO CRYOPRESERVATION
- MATURE OOCYTE CRYOPRESERVATION
- OVARIAN TRANSPOSITION
- OVARIAN TISSUE CRYOPRESERVATION
- IN VITRO MATURATION
- GNRH/LHRH AGONISTS

CURRENTLY AVAILABLE STRATEGIES - MALE

- EJACULATED SPERM CRYOPRESERVATION
- EXTRACTED SPERM CRYOPRESERVATION
- CRYOPRESERVATION OF TESTICULAR TISSUE IN PREPUBERTAL BOYS

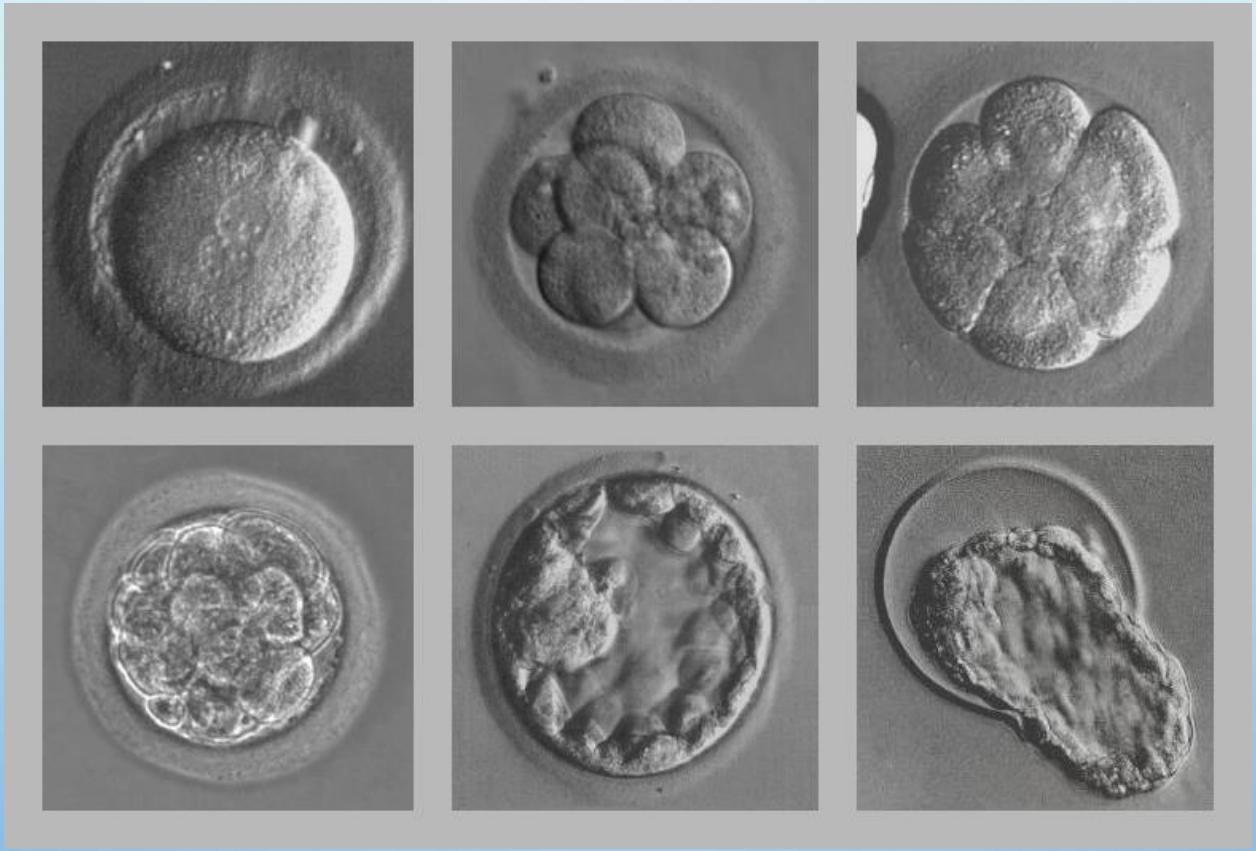


EMBRYO CRYOPRESERVATION

- FOR POST-PUBERTAL FEMALES
- HAVE A COMMITTED PARTNER OR WISH TO USE DONOR SPERM
- UNDERGO OVARIAN STIMULATION WITH GONADOTROPINS FOR IN VITRO FERTILIZATION (+/- ICSI)
- GOAL OF RETRIEVING 8-10 OOCYTES
- FREEZE EMBRYOS – BEST SUCCESS RATE FOR PREGNANCY

MATURE OOCYTE CRYOPRESERVATION

- FOR POST PUBERTAL FEMALES
- WITHOUT A COMMITTED PARTNER OR WHO DO NOT WISH TO USE DONOR SPERM
- UNDERGO OVARIAN STIMULATION WITH GONADOTROPINS FOR IN VITRO FERTILIZATION
- GOAL OF RETRIEVING 8-10 OOCYTES
- FREEZE OOCYTES (CURRENT SUCCESS RATES 8-20%)



J CLIN ONCOL. 2008] JUN 1;26(16): 2630-5.

- AZIM AA[1], COSTANTINI-FERRANDO M, OKTAY K.

- GOAL WAS TO DETERMINE THE EFFECT OF CONTROLLED OVARIAN STIMULATION (COS) USING A COMBINATION OF LETROZOLE WITH STANDARD FERTILITY MEDICATIONS ON DISEASE-FREE SURVIVAL IN WOMEN UNDERGOING EMBRYO OR OOCYTE CRYOPRESERVATION BEFORE ADJUVANT CHEMOTHERAPY

J CLIN ONCOL. 2008] JUN 1;26(16): 2630-5.

- OF 215 WOMEN WITH BREAST CANCER WERE PROSPECTIVELY EVALUATED FOR FERTILITY PRESERVATION BEFORE ADJUVANT CHEMOTHERAPY.
- N = 79 ELECTED TO UNDERGO COS WITH LETROZOLE AND GONADOTROPINS FOR EMBRYO OR OOCYTE CRYOPRESERVATION.
- N = 136 PATIENTS UNDERWENT NO FERTILITY-PRESERVING PROCEDURE AND SERVED AS CONTROLS.

J CLIN ONCOL. 2008] JUN 1;26(16): 2630-5.

- TIME BETWEEN SURGERY AND CHEMOTHERAPY WAS LONGER FOR IVF PATIENTS (45.08 VS 33.46 DAYS; $P < .01$).
- PEAK ESTRADIOL LEVELS : 1,486.76 +/- 942.13 PMOL/L IN COS PATIENTS.
- THE MEDIAN FOLLOW-UP AFTER CHEMOTHERAPY WAS 23.4 MONTHS (RANGE, 7.5 TO 63.6 MONTHS) IN THE COS GROUP AND 33.05 MONTHS (RANGE, 4.5 TO 63.6) IN THE CONTROL GROUP.
- THE HAZARD RATIO FOR RECURRENCE AFTER IVF WAS 0.56 (95% CI, 0.17 TO 1.9), HOWEVER, THE SURVIVAL WAS NOT COMPROMISED COMPARED WITH CONTROLS.

FERTIL STERIL 2012 OCT;98(4):957-60.

- ALMOG B[1], AZEM F, GORDON D, PAUZNER D, AMIT A, BARKAN G, LEVIN I.
- EVALUATE THE EFFECTS OF CANCER ON OVARIAN RESPONSE IN CONTROLLED OVARIAN HYPERSTIMULATION (COH).
- COMPARED 81 CANCER PATIENTS UNDERGOING COH CYCLES FOR FERTILITY PRESERVATION WITH AGE- AND DATE-MATCHED CONTROLS UNDERGOING COH FOR IN VITRO FERTILIZATION (IVF) FOR MALE FACTOR INFERTILITY.

FERTIL STERIL 2012 OCT;98(4):957-60.

- NUMBER OF DOMINANT FOLLICLES AND OOCYTES ASPIRATED OF THE STUDY GROUP AND CONTROL WERE COMPARABLE
  - 8.8 ± 5.3 VS. 9.7 ± 4.9, AND 11.93 ± 8.3 VS. 12.3 ± 7.9, RESPECTIVELY.
- TOTAL DOSE OF GONADOTROPINS USED (2,250 IU) AND NUMBER OF STIMULATION DAYS (9.5) OF THE STUDY GROUP WERE ALSO SIMILAR TO THE CONTROLS (2,100 IU AND 10 DAYS).
- COMPARISON BETWEEN FOUR SUBGROUPS OF CANCER: BREAST CANCER, SOFT TISSUE SARCOMA, HEMATOLOGIC MALIGNANCIES, AND GASTROINTESTINAL TRACT CANCERS
  - SHOWED NO DIFFERENCE IN THEIR OVARIAN RESPONSE INDEXES.

FERTIL STERIL 2010 FEB;93(3):865-8.

- QUINTERO RB[1], HELMER A, HUANG JQ, WESTPHAL LM.
- EVALUATE CONTROLLED OVARIAN HYPERSTIMULATION (COH) IN WOMEN WITH CANCER COMPARED WITH HEALTHY WOMEN
- FIFTY WOMEN UNDERGOING OOCYTE RETRIEVAL BEFORE CANCER TREATMENT AND 50 AGE-MATCHED CONTROLS

FERTIL STERIL 2010 FEB;93(3):865-8.

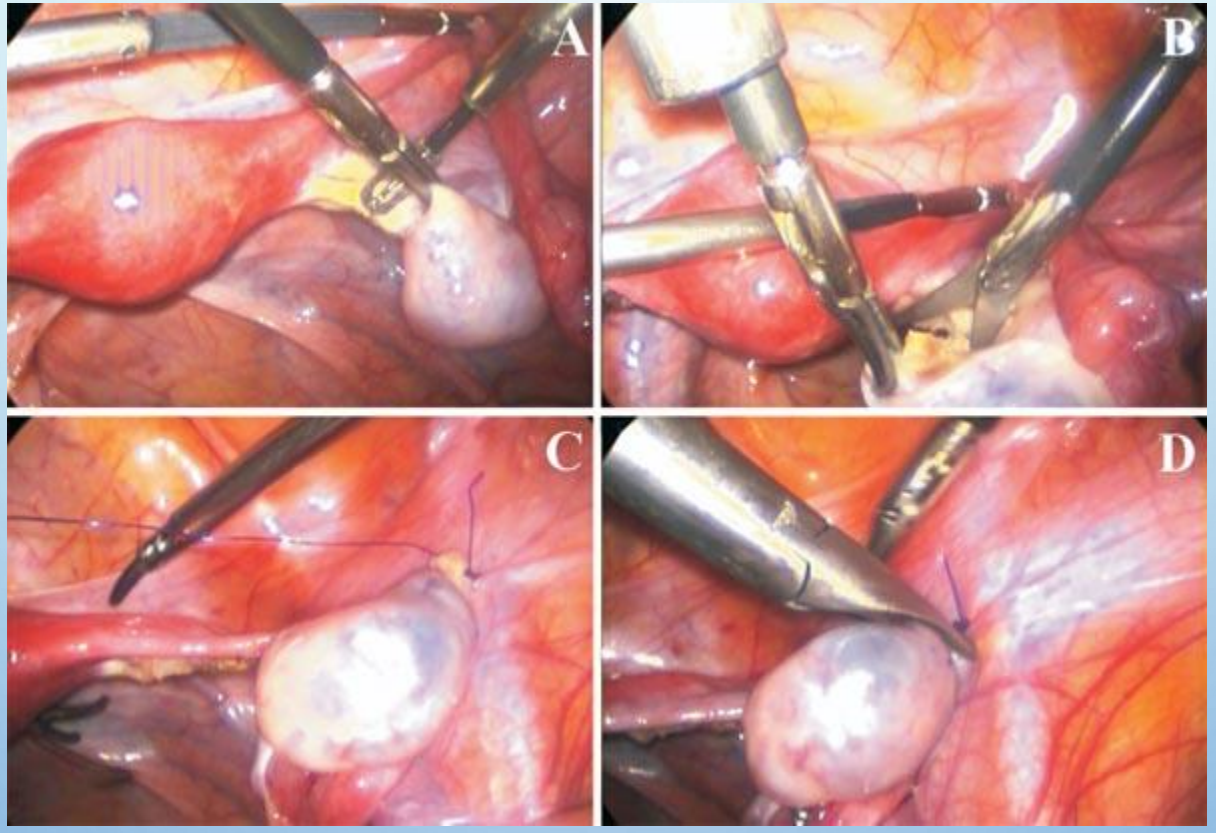
- THERE WERE NO SIGNIFICANT DIFFERENCES IN
  - NUMBER OF OOCYTES RETRIEVED (13 VS. 11.5)
  - NUMBER OF MATURED OOCYTES RETRIEVED (9.7 VS. 9.6)
  - NUMBER OF OOCYTES FERTILIZED (7.4 VS. 6.8).

HOWEVER, THE PATIENTS WITH CANCER HAD A LONGER DURATION OF STIMULATION (10.5 VS. 9.0 DAYS) AND HIGHER TOTAL DOSE OF GONADOTROPINS (4,174 IU VS. 3,416 IU).


From:
God

OVARIAN TRANSPOSITION

- FOR PATIENTS REQUIRING LOCAL PELVIC RADIATION THERAPY
- TRANSPOSE THE OVARIES TO SITES AWAY FROM MAXIMAL RADIATION EXPOSURE
- MAY PREVENT FUTURE TRANSVAGINAL OOCYTE RETRIEVAL IF IVF IS REQUIRED


A
B
C
D

OVARIAN TISSUE CRYOPRESERVATION

- STILL CONSIDERED EXPERIMENTAL
  - THEORETICALLY COULD PRESERVE THOUSANDS OF OVARIAN FOLLICLES AT ONE TIME
- ESPECIALLY IMPORTANT FOR PREPUBERTAL GIRLS OR FOR THOSE WHO CANNOT DELAY CANCER TREATMENT IN ORDER TO UNDERGO COH AND OOCYTE RETRIEVAL
- TO DATE NO LIVE BIRTHS HAVE BEEN REPORTED IN FEMALES WHO CRYOPRESERVED TISSUE BEFORE PUBERTY

OVARIAN TISSUE CRYOPRESERVATION

- INVOLVES OBTAINING OVARIAN CORTICAL TISSUE BY LAPAROSCOPY OR LAPAROTOMY
  - 1) DISSECT THIS TISSUE INTO SMALL FRAGMENTS AND CRYOPRESERVE IT OR
  - 2) WHOLE OVARY CRYOPRESERVATION
    - CHALLENGES OF CRYOPRESERVING THE ENTIRE OVARY

OVARIAN TISSUE CRYOPRESERVATION

- MAY POSSIBLY REINTRODUCE CANCER CELLS THAT REMAIN IN THE OVARIAN MEDULLARY TISSUE (LYMPHOMA) OR BLOOD VESSELS (LEUKEMIA)
- SYSTEMATIC REVIEW OF AUTO TRANSPLANTATION OF OVARIAN TISSUE FROM 289 PATIENTS WITH LEUKEMIA, LYMPHOMA, EWING SARCOMA, COLORECTAL, BREAST, GASTRIC, ENDOMETRIAL AND CERVICAL CANCER
  - METASTASES WERE COMMON IN PATIENTS WITH LEUKEMIA, LESS COMMON IN OTHER CANCERS, AND NOT SEEN WITH LYMPHOMA OR BREAST CANCER PATIENTS

SAFETY CONCERNS

- GIVEN THE UNCERTAINTIES REGARDING TRANSMISSION OF DISEASE, OVARIAN TISSUE TRANSPLANTATION IS NOT RECOMMENDED FOR PATIENTS WITH
- BLOOD-BORNE CANCERS
- MALIGNANCIES THAT METASTASIZE TO THE OVARY
- AN INHERENT PREDISPOSITION TO OVARIAN CANCER

OVARIAN TISSUE TRANSPLANTATION AND OUTCOMES

- AUTOLOGOUS OVARIAN TISSUE TRANSPLANTATION HAS BEEN APPLIED SUCCESSFULLY
- DEMONSTRATE RESTORATION OF OVARIAN FUNCTION BY
  - ENDOGENOUS HORMONE PRODUCTION
  - ACHIEVEMENT OF PREGNANCY
- INVOLVES ATTACHING VIABLE CORTICAL OVARIAN TISSUE TO
  - PELVIC SITE (ORTHOTOPIC)
  - EXTRA-PELVIC SITE (HETEROTOPIC) – FOREARM/ABDOMINAL WALL

ORTHOTOPIC TRANSPLANTATION OF CORTICAL TISSUE

- ATTACH TO MEDULLARY PORTION OF REMAINING OVARY OR TO PERITONEUM OF THE OVARIAN FOSSA
  - ADVANTAGE: POSSIBILITY OF NATURAL CONCEPTION
  - DISADVANTAGE: INVASIVE PROCEDURE AND LIMIT TO # OF FRAGMENTS THAT CAN BE TRANSPLANTED
- RESUMPTION OF MENSES OCCURS 4-9 MONTHS AFTER TRANSPLANTATION
- VARIABILITY IN GRAFT SURVIVAL AND OVARIAN FUNCTION
  - SEVERAL MONTHS TO 7 YEARS

PREGNANCY OUTCOME AFTER ORTHOTOPIC TRANSPLANTATION

- 24 BIRTHS WORLD WIDE AFTER 10 YEARS
- CONFOUNDER
  - MOST SURGERIES DID NOT INVOLVE THE REMOVAL OF BOTH OVARIES
  - THUS SITE OF OVULATION NOT CONFIRMED (NATIVE REMAINING OVARY OR THE TRANSPLANTED TISSUE)
  - PREGNANCY COULD HAVE BEEN THE RESULT OF OVULATION FROM THE NATIVE OVARY AND NOT FROM THE TRANSPLANTED TISSUE

HETEROTOPIC TRANSPLANTATION OF CORTICAL TISSUE

- REPORTS OF RESTORATION OF OVARIAN FUNCTION AND FOLLICULAR DEVELOPMENT
- PREGNANCY CAN ONLY BE ACHIEVED THROUGH IVF
- DISADVANTAGE:
  - NO LIVE BIRTHS YET RECORDED
- ADVANTAGE:
  - EASIER SURGERY
  - EASIER FOLLICULAR MONITORING AND RETRIEVAL

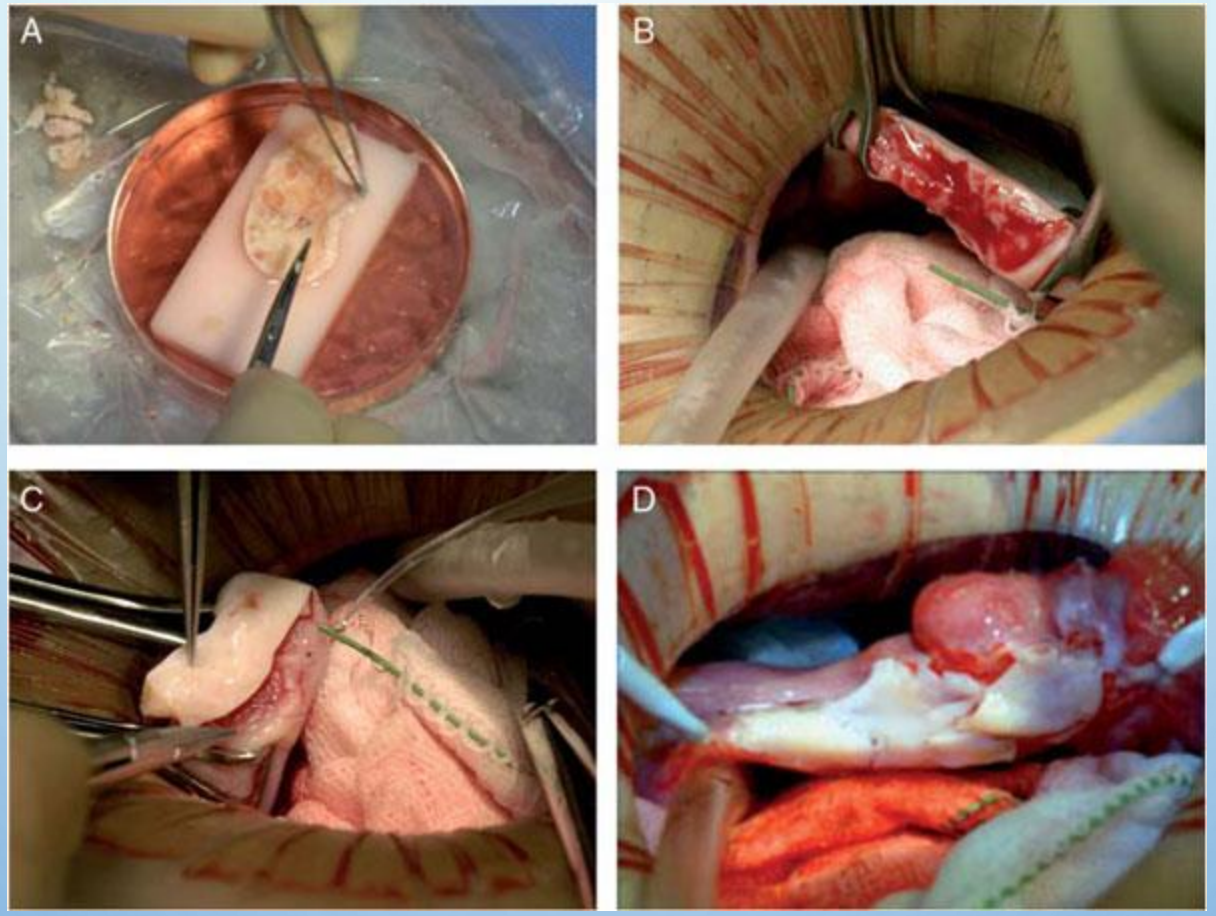
WHOLE OVARY TRANSPLANTATION

- DECREASES RISK OF TISSUE ISCHEMIA
- DECREASES RISK OF LIMITED SURVIVAL OF THE GRAFT
- NO REPORT OF A SUCCESSFUL TRANSPLANTATION OF A PREVIOUSLY CRYOPRESERVED WHOLE OVARY IN HUMANS
- FRESH WHOLE OVARY TRANSPLANTATION BETWEEN A LIVE DONOR TO A RECIPIENT HAS BEEN SUCCESSFUL IN HUMANS
  - ONE STUDY SHOWED A LIVE BIRTH

CRYOPRESERVATION OF OVARIAN TISSUE

- METHODS TO CRYOPRESERVE OVARIAN TISSUE
  - SLOW FREEZING
  - VITRIFICATION (NO PREGNANCIES RECORDED WITH THIS PROCESS YET)

- OVARIAN TISSUE CRYOPRESERVATION IS STILL CONSIDERED EXPERIMENTAL


A
B
C
D

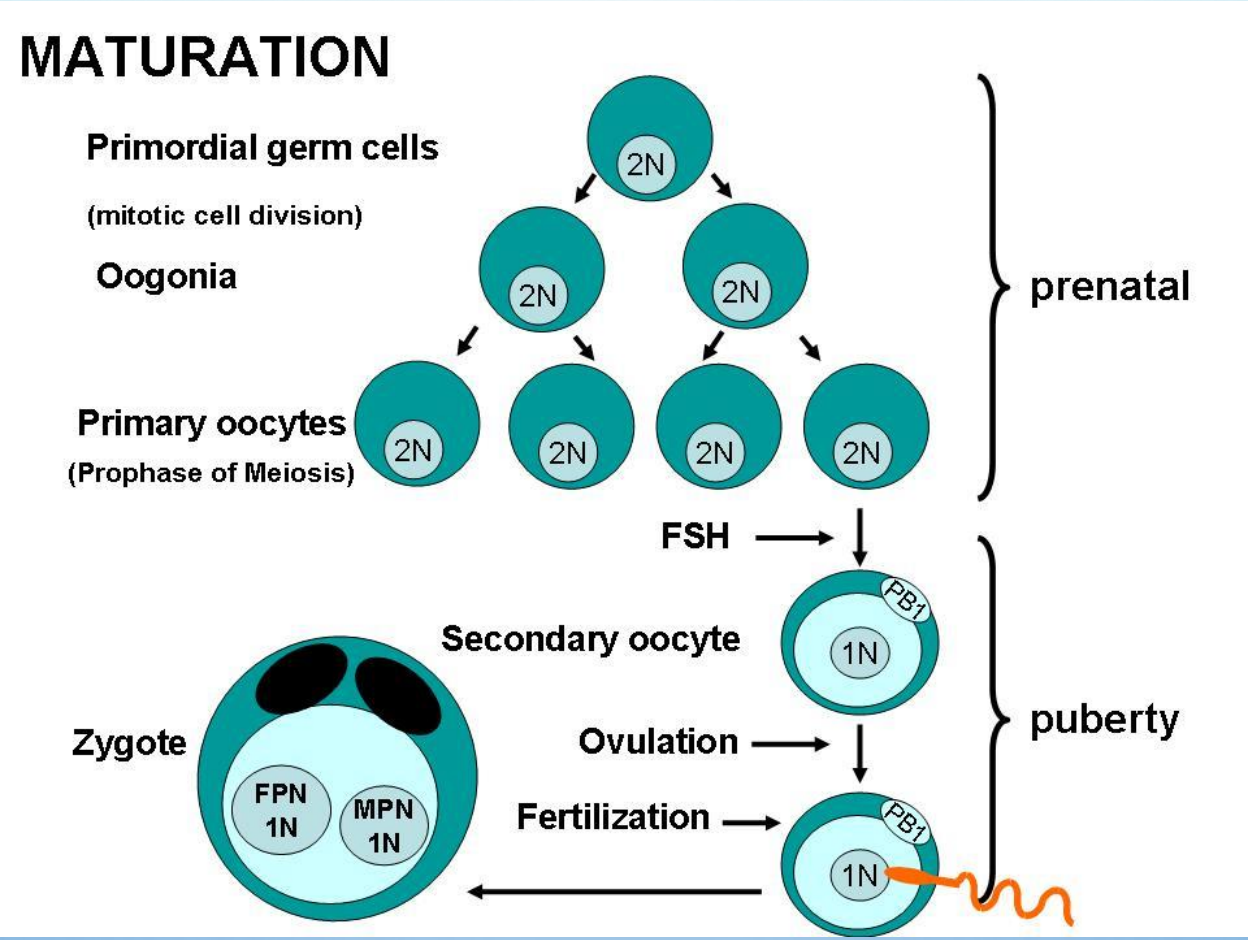
IN VITRO MATURATION

- ALTERNATIVE TO TRANSPLANTATION OF THE HARVESTED OVARIAN TISSUE
- MATURATION IN CULTURE OF IMMATURE OOCYTES
- IMMATURE OOCYTES PROGRESS FROM PROPHASE I STAGE THROUGH MEIOSIS I TO REACH METAPHASE II
- CRYOPRESERVE MATURE OOCYTES OR EMBRYOS

IN VITRO MATURATION

- PATIENTS NEED TO BE AWARE THAT IMPLANTATION AND PREGNANCY RATES ARE SIGNIFICANTLY LOWER THAN WITH STANDARD IVF
  - PREGNANCY RATES 5.5 – 21%

- STILL CONSIDERED AN EXPERIMENTAL PROCEDURE


MATURATION
Primordial germ cells
(mitotic cell division)
Oogonia
Primary oocytes
(Prophase of Meiosis)
2N
prenatal
FSH
Secondary oocyte
PB1
1N
puberty
Ovulation
Fertilization
Zygote
FPN
1N
MPN
1N

GNRH/LHRH AGONISTS

- STILL CONTROVERSIAL

- "THE EFFICACY OF GNRH AGONISTS IN REDUCING THE RISK OF OVARIAN FAILURE, ASSOCIATED WITH THE USE OF CHEMOTHERAPY, IN PREMENOPAUSAL WOMEN IS STILL CONSIDERED UNCERTAIN AND ITS USE IS NOT CONSIDERED AS STANDARD OF CARE TO PRESERVE FERTILITY"
  - GYNE: ASRM, CFAS, ESHRE
  - ONC: ASCO, ESMO

WHY IS THERE CONTROVERSY?

- CONFLICTING RESULTS OF PREVIOUSLY PUBLISHED TRIALS AND METHODOLOGY OF PREVIOUS SYSTEMATIC REVIEWS WITH META-ANALYSES

- 2 RECENT META-ANALYSES MAY PUT THIS CONTROVERSY TO REST

LUCIA DEL MAESTRO ET AL, CANCER TREATMENT REVIEWS 2014 JUN; 40(5):675-683

- ITALIAN STUDY RELEASED 2014

- SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS EVALUATING THE EFFICACY OF GNRH AGONISTS GIVEN BEFORE AND DURING CHEMOTHERAPY FOR THE PREVENTION OF PREMATURE OVARIAN FAILURE (POF) IN PREMENOPAUSAL WOMEN

LUCIA DEL MAESTRO ET AL, CANCER TREATMENT REVIEWS 2014 JUN; 40(5):675-683

- 501 STUDIES IDENTIFIED
- ONLY 9 INCLUDED
- SELECTION CRITERIA:
  - ENGLISH LANGUAGE
  - RANDOMIZED TRIAL DESIGNED TO COMPARE GNRH AGONISTS AND CHEMOTHERAPY WITH CHEMOTHERAPY ALONE IN TERMS OF
    - RESUMPTION OF MENSTRUAL ACTIVITY OR
    - OCCURRENCE OF POF IN PREMENOPAUSAL CANCER PATIENTS
  - ODDS RATIO FOR POF HAD TO BE REPORTED OR COULD BE COMPUTED FROM THE DATA PRESENTED

LUCIA DEL MAESTRO ET AL, CANCER TREATMENT REVIEWS 2014 JUN; 40(5):675-683

- THE EFFECT OF TREATMENT WAS EVALUATED IN TERMS OF AN ODDS RATIO (OR) COMPUTED AS THE ODDS OF POF IN THE GNRH A PLUS CHEMO ARM DIVIDED BY THE ODDS OF POF IN THE STANDARD CHEMO ALONE ARM

- ODDS RATIO < 1 FAVOURS THE GNRH A PLUS CHEMO TREATMENT ARM

LUCIA DEL MAESTRO ET AL, CANCER TREATMENT REVIEWS 2014 JUN; 40(5):675-683

- TYPES OF CANCER INCLUDED IN THE STUDIES
  - OVARIAN – 1
  - BREAST – 6
  - HODGKIN'S/NON HODGKIN'S LYMPHOMA – 2
- DURATION OF FOLLOW UP: 6-36 MONTHS
- MEDIAN AGE
  - CHEMO PLUS GNRH A: 21-45 YEARS
  - CHEMO ALONE: 22-45 YEARS

RESULTS

- OVERALL 225 EVENTS OF POF WERE RECORDED IN 765 PATIENTS
  - 89 IN 401 PATIENTS TREATED WITH GNRH A (22%)
  - 136 IN 364 CONTROLS (37%)
- OVERALL POOLED ODDS RATIO FOUND A HIGHLY SIGNIFICANT REDUCTION IN THE RISK OF POF IN PTS RECEIVING GNRH A IN ADDITION TO CHEMO
  - OR = 0.43
  - 95% CI: 0.22 – 0.84
  - P = 0.013

RESULTS OF SUBGROUP ANALYSIS

- SIGNIFICANT INTERACTION SEEN BETWEEN THE TREATMENT ARM AND THE TYPE OF CANCER (P = 0.028)
- EFFECT OF GNRH A IN THE 3 TUMOUR TYPES WAS HETEROGENEOUS
  - NO PROTECTIVE EFFECT OBSERVED IN LYMPHOMA PATIENTS (2 STUDIES)
    - OR = 1.02, 95% CI: 0.39 – 2.6
  - PROTECTIVE EFFECT FOR BREAST CANCER (8 STUDIES)
    - OR = 0.39, 95% CI: 0.19 – 0.84)
  - PROTECTIVE EFFECT FOR OVARIAN CANCER (1 STUDY)
    - OR = 0.06, 95% CI: 0.00 – 1.24

RESULTS OF SUBGROUP ANALYSIS

- NO SIGNIFICANT INTERACTION BETWEEN THE TREATMENT ARM WAS SEEN WHEN COMPARE
  - PATIENTS AGE (</ 35 AND >35)
  - TIMING OF POF ASSESSMENT (</ 12 MONTHS AND > 12 MONTHS)

M. LAMBERTINI ET AL, ANNALS OF ONCOLOGY 2015 DEC; 26(12): 2408 - 2419

- ITALIAN STUDY (2015) META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS
  - INCLUDED BREAST CANCER PATIENTS ONLY (PREMENOPAUSAL)
- INVESTIGATE WHETHER TEMPORARY OVARIAN SUPPRESSION WITH LHRH AGONIST DURING CHEMO, IN PREMENOPAUSAL BREAST CANCER PATIENTS, AFFECTS
  - RATE OF TREATMENT RELATED POF
  - PREGNANCY RATE
  - DISEASE FREE SURVIVAL (DFS)

M. LAMBERTINI ET AL, ANNALS OF ONCOLOGY 2015 DEC; 26(12): 2408 - 2419

- SELECTION CRITERIA FOR ARTICLES
  - RANDOMIZED TRIALS
  - CONDUCTED IN EARLY STAGE PREMENOPAUSAL BREAST CANCER PATIENTS WHO WERE CANDIDATES FOR NEO-ADJUVANT AND/OR ADJUVANT CHEMO
  - THE ODDS RATIO (OR) FOR POF AND/OR PREGNANCY HAD TO BE REPORTED OR COULD BE COMPUTED FROM THE DATA PRESENTED IN THE SELECTED STUDIES
- NO LANGUAGE RESTRICTIONS

M. LAMBERTINI ET AL, ANNALS OF ONCOLOGY 2015 DEC; 26(12): 2408 - 2419

- 676 STUDIES IDENTIFIED
- ONLY 12 PAPERS INCLUDED
- 2 STUDIES PATIENTS RECEIVED OTHER FORMS OF ENDOCRINE AGENTS IN ADDITION TO CHEMO WITH OR WITHOUT CONCURRENT LHRH A
  - TAMOXIFEN OR LHRH ANTAGONIST
- OCCURRENCE OF POF WAS DIAGNOSED BY EITHER
  - NO RESUMPTION OF MENSES AND/OR
  - MENOPAUSAL LEVELS OF FSH AND ESTRADIOL

M. LAMBERTINI ET AL, ANNALS OF ONCOLOGY 2015 DEC; 26(12): 2408 - 2419

- PATIENT AGE IN 12 STUDIES
  - LHRH A PLUS CHEMO: 29 – 45
  - CHEMO ALONE: 30 – 46

- TIMING OF ASSESSMENT OF POF
  - RANGE OF 6 – 36 MONTHS

M. LAMBERTINI ET AL, ANNALS OF ONCOLOGY 2015 DEC; 26(12): 2408 - 2419

- ODDS RATIO (OR) FOR PREGNANCY WAS CALCULATED AS THE ODDS OF PATIENTS WITH PREGNANCY IN THE LHRH A AND CHEMO GROUP DIVIDED BY THE ODDS OF PATIENTS PREGNANT IN THE CONTROL GROUP (CHEMO ALONE)
  - AN OR > 1 INDICATES THAT THE USE OF LHRH A INCREASED THE PROBABILITY OF SUBSEQUENT PREGNANCIES
- HAZARD RATIO (HR) WAS CALCULATED FOR THE EFFECT OF LHRH A VERSUS CHEMO ALONE FOR DFS
  - A HR < 1 INDICATES THE USE OF LHRH A REDUCED THE PROBABILITY OF DEVELOPING DFS

RESULTS

- 320 POF EVENTS RECORDED IN 1231 PATIENTS
  - 114 OF 616 PATIENTS TREATED WITH LHRH A DURING CHEMO (18.5%)
  - 206 OF 615 PATIENTS UNDERGOING CHEMO ALONE (33.5%)

- SIGNIFICANT RISK REDUCTION OF POF IN PATIENTS RECEIVING LHRH A DURING CHEMO
  - OR = 0.36
  - 95% CI: 0.23 – 0.57
  - P , 0.001

RESULTS

- THERE WAS SIGNIFICANT HETEROGENEITY BETWEEN STUDIES
- THE ESTIMATED ODDS RATIO COMPUTED EXCLUDING EACH STUDY AT A TIME, RANGED FROM 0.33 TO 0.41, WITH ALL RESULTS SHOWING STATISTICAL SIGNIFICANCE

AMENORRHEA (POF) 1 YEAR AFTER THE COMPLETION OF CHEMO

- 8 STUDIES
- 326 EVENTS RECORDED IN 882 PATIENTS
  - 136 OF 439 PATIENTS TREATED WITH LHRH A DURING CHEMO (31%)
  - 190 OF 443 UNDERGOING CHEMO ALONE (42.9%)
- SIGNIFICANT REDUCTION IN THE RISK OF AMENORRHEA 1 YEAR AFTER THE END OF CHEMO WITH USE OF LHRH A
  - OR = 0.55
  - 95% CI: 0.41 – 0.75
  - $P < 0.001$

PREGNANCY

- 5 STUDIES
- OF 359 PATIENTS TREATED WITH LHRH A DURING CHEMO, 33 WERE PREGNANT (9.2%)
- 19 OF 347 WOMEN PREGNANT WHO HAD CHEMO ALONE (5.5%)
- HIGHER CHANCE OF BECOMING PREGNANT IF PATIENT TREATED WITH LHRH A DURING CHEMO
  - OR = 1.83
  - 95% CI: 1.02 – 3.28
  - P = 0.041

DISEASE FREE SURVIVAL (DFS)

- 3 STUDIES
  - 1 STUDY (LI ET AL) - ALL PATIENTS HAD HORMONE RECEPTOR POSITIVE DISEASE
  - POEMS-SWOG SO230 – ALL PATIENTS HAD HORMONE RECEPTOR NEGATIVE DISEASE
  - PROMISE – 80.4% OF PATIENTS HAD HORMONE RECEPTOR POSITIVE DISEASE
- FOLLOW UP RANGED FROM 35.6 MONTHS TO 7.3 YEARS

DFS

- PATIENTS TREATED WITH LHRH A AND CHEMO:
  - 60 DFS EVENTS IN 307 PATIENTS (19.5%)
- PATIENTS TREATED WITH CHEMO ONLY:
  - 60 DFS EVENTS IN 319 PATIENTS (18.8%)
- THUS NO DIFFERENCE AND USE OF LHRH A DOES NOT WORSEN DFS
  - HAZARD RATIO (HR) = 1.00
  - 95% CI: 0.49 – 2.04
  - P = 0.939

SPECIAL CLINICAL CONSIDERATIONS - FEMALE PATIENTS

- BREAST CANCER
- BRCA MUTATIONS
- HEMATOLOGIC MALIGNANCIES
- CHILDREN AND ADOLESCENTS

SPECIAL CLINICAL CONSIDERATIONS FEMALE PATIENTS – BREAST CANCER

- POTENTIAL IMPACT OF COH RELATED HYPERESTROGENEMIA
- USE CO-ADMINISTRATION OF AROMATASE INHIBITORS TO MINIMIZE CIRCULATING ESTROGEN LEVELS

SPECIAL CLINICAL CONSIDERATIONS FEMALE PATIENTS – BRCA MUTATIONS

- MAY BE OFFERED BILATERAL SALPINGO-OOPHORECTOMY AS A RISK REDUCTION STRATEGY
- USUALLY PERFORMED AFTER CHILDBEARING COMPLETED
- MAY WISH TO INSTEAD CRYOPRESERVE EMBRYOS OR OOCYTES WITH PRE-IMPLANTATION GENETIC DIAGNOSIS (PGD) OF BRCA MUTATIONS PRIOR TO EMBRYO TRANSFER OR IVM OF HARVESTED TISSUE FROM BSO

SPECIAL CLINICAL CONSIDERATIONS FEMALE PATIENTS: HEMATOLOGIC CANCERS

- USUALLY TOO ILL AT DIAGNOSIS TO BE ELIGIBLE FOR A DELAY IN TREATMENT REQUIRED FOR FERTILITY SPARING THERAPY
- ALSO, RISK WITH TISSUE CRYOPRESERVATION AND AUTOLOGOUS TRANSPLANTATION RESEEDING MALIGNANT CELLS
- ABNORMAL HEMATOLOGIC PARAMETERS MAY BE AT RISK FOR SURGICAL COMPLICATIONS

CHILDREN AND ADOLESCENTS

- SEVERAL FACTORS IMPAIR FERTILITY PRESERVATION
  - LACK OF AVAILABLE FERTILITY-PRESERVATION PROGRAMS AT PEDIATRIC HEALTH CARE FACILITIES
  - LACK OF KNOWLEDGE OF THE VULNERABILITY OF THESE PATIENTS TO CANCER THERAPIES
  - DISCOMFORT IN DISCUSSING REPRODUCTIVE HEALTH ISSUES WITH THESE PATIENTS AND THEIR PARENTS

MALE – EJACULATED SPERM CRYOPRESERVATION

- SEMEN COLLECTED BY MASTURBATION PRIOR TO ADMINISTRATION OF CHEMO/RADIATION THERAPY
- FOR USE IN POST PUBERTAL MALES
- IDEALLY 2 – 3 EJACULATED SAMPLES SHOULD BE OBTAINED

MALE – CRYOPRESERVATION OF SURGICALLY EXTRACTED SPERM

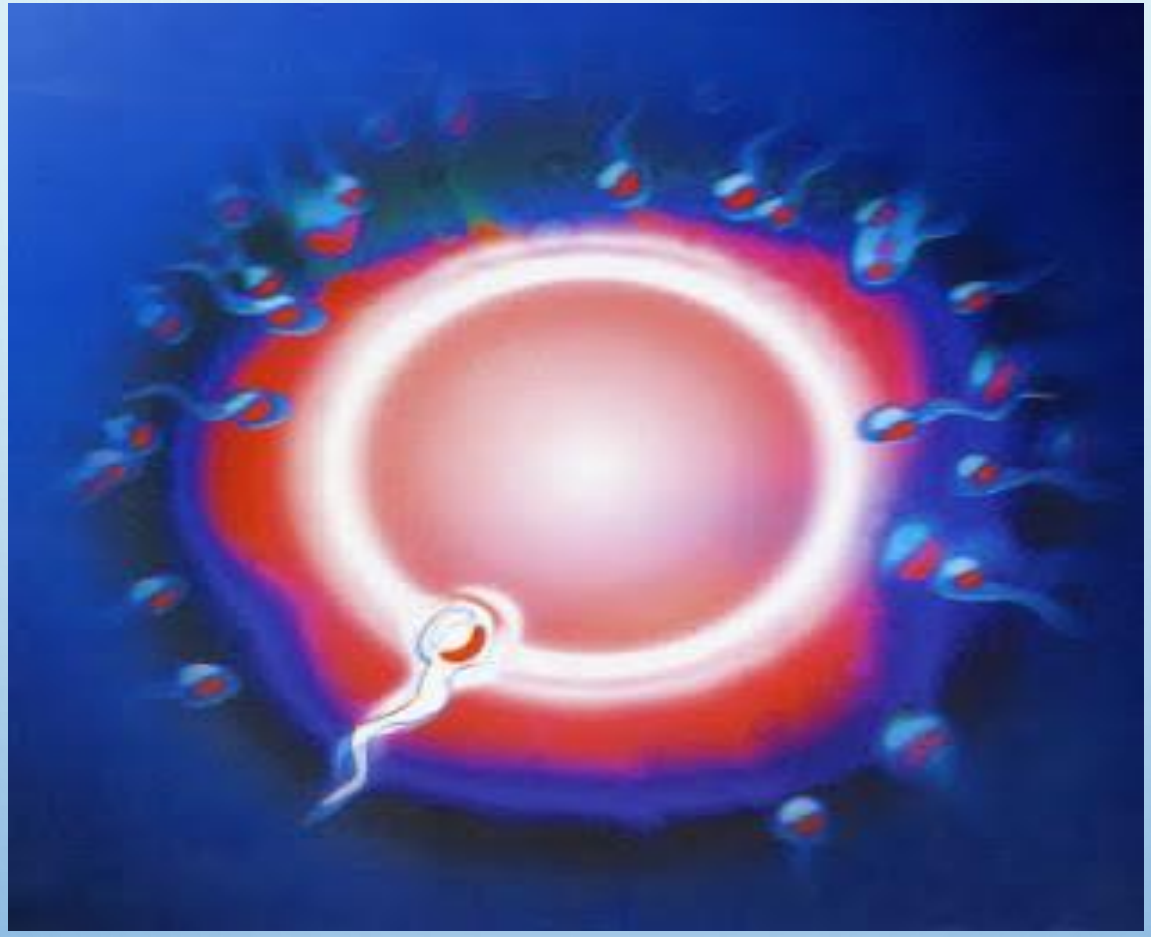
- ALTERNATIVE STRATEGY FOR MALES WHO
  - CANNOT EJACULATE
  - HAVE NO VIABLE SPERM IN EJACULATE
  - HAVE SEVERE OLIGOSPERMIA IN EJACULATE
- CAN BE OBTAINED VIA
  - PERCUTANEOUS EPIDYDIMAL SPERM ASPIRATION (PESA)
  - TESTICULAR SPERM EXTRACTION (TESE)
  - TESTICULAR SPERM ASPIRATION (TESA)
  - MICROSURGICAL EPIDYDIMAL SPERM ASPIRATION (MESA)

TESTICULAR TISSUE CRYOPRESERVATION

- IN PREPUBERTAL BOYS
- INVESTIGATIONAL – GERMINAL EPITHELIAL STEM CELLS ISOLATED AND CRYOPRESERVED
- TO DATE HAS NOT DEMONSTRATED EFFICACY IN HUMANS

GNRH AGONISTS

- EXPERIMENTAL
- ADMINISTER DURING CHEMOTHERAPY
- SOME ANIMAL STUDIES REVEALED PROMISING RESULTS
- TO DATE HUMAN STUDIES HAVE FAILED TO DEMONSTRATE FERTILITY PRESERVATION OR MORE RAPID RETURN OF SPERMATOGENESIS AFTER CHEMOTHERAPY



SPECIAL CLINICAL CONSIDERATIONS - MALE PATIENTS

- TESTICULAR CANCER
- CHILDREN AND ADOLESCENTS

SPECIAL CLINICAL CONSIDERATIONS - MALE PATIENTS

- TESTICULAR CANCER
  - SOME OF THESE MEN WILL HAVE AZOOSPERMIA OR SEVERELY IMPAIRED SEMEN PARAMETERS
  - MAY HAVE SPERM EXTRACTION (PESA OR TESE) PRIOR TO ORCHIECTOMY OR AT TIME OF ORCHIECTOMY (ONCO-TESE)

SPECIAL CLINICAL CONSIDERATIONS - MALE PATIENTS

- CHILDREN AND ADOLESCENTS
  - SEVERAL FACTORS HAMPER FERTILITY PRESERVATION:
    - LACK OF FERTILITY PRESERVATION PROGRAMS AT PEDIATRIC HEALTH CARE FACILITIES
    - LACK OF KNOWLEDGE OF THE VULNERABILITY OF THESE INDIVIDUALS TO CANCER THERAPIES
    - DISCOMFORT IN DISCUSSING REPRODUCTIVE HEALTH ISSUES WITH THESE PATIENTS AND THEIR PARENTS