Pregnancy and Fertility Issues

Turner Syndrome

Turner Syndrome Statistics
Hook EB. 2014
- 1:2000 Live Female Births
- Over 90% of 45,X conceptions are aborted
- **Karyotypes**: Pure vs partial X monosomy
  - 45,X (cryptic mosaics?)
  - 45,X/46,XX
  - 45,X/46,XX with structural abnormality of 2nd X (or Y)
  - 46,XX with structural abnormality of 2nd X

Turner Syndrome Phenotypes
- Variable but **Gonadal Dysgenesis** and **Short Stature** are most consistent features
- Ovaries develop normally but almost complete **follicle depletion** by birth and early childhood
- Up to 30% have spontaneous puberty and 2-5% have regular menstrual periods prior to premature menopause (Visser et al, 2013)

Overview
- Case Study
  - How much of a concern is fertility for Turner syndrome?
  - Spontaneous pregnancy
  - Assisted reproduction
  - Risks to fetus
  - Risks to mother

Turner Syndrome Case Presentation
- Presented at age 12 years with short stature and irregular periods
- Had mild TS features and T IV development at age 12
- Karyotype: 45, X (7)/46,XX (47)
- Normal ECHO, Renal U/S
- Normal Pelvic U/S

Turner Syndrome Case Study
- Normal gonadotropins and other screening labs
- Bone age 13 ½ years
- Received short term GH treatment
**Turner Syndrome Case Study**
- Recent follow up visit at age 23 years revealed concerns about fertility and pregnancy.
- Regular Periods
- Normal blood pressure, short stature
- Normal gonadotropins
- Normal thyroid studies, biochem profile, celiac screen and abnormal lipid profile

**Are Turner Syndrome girls/women concerned about fertility?**
*Sutton et al, 2005*
- 97 girls and women + 21 parents
- Patients divided into 4 age groups: 7-13, 14-19, 20-39, 20-59 years old
- Infertility was the primary concern in all age groups, regardless of Karyotype
- Cited more frequently than other most common concerns: short stature, sexual development and overall health concerns

**Pregnancy Outcomes in Turner Syndrome**
*Hadnott et al, 2011*
- 276 TS patients from NICHD natural history study of TS (2001-2010)
- Phenotypic females from 21-67 years of age with 50 cell karyotype with 70% of cells showing loss of all or part of second X

**Pregnancy in Turner Syndrome**
*Ackerman, 2014*
- 2012: American Society of Reproductive Endocrinologists identified TS as a relative contraindication to pregnancy.
- TS with known cardiac anomalies – absolute contraindication to pregnancy.
- Increased cardiovascular mortality, even in those with normal cardiac evaluations
- Adoption or Surrogacy should be considered

**Pregnancy Outcomes in TS**
*Hadnott et al, 2011*
- [Figure showing pregnancy outcomes]
Pregnancy Outcomes
Hadnott et al, 2011

Spontaneous Pregnancies:
- 5 women had seven live births
- 4/5 had a 45,X in over 49% of cells
- 1/5 had 45,X in 90% of cells with distal Xp - deletion in the remaining 10%
- Major features of TS: Height was 139.9 cm +/- 7.1 cm, common cardiac anomalies, history of OM, hyperlipidemia, thyroid dysfunction, skeletal anomalies

Pregnancy Outcomes
Hadnott, 2011

- All women with spontaneous pregnancy had spontaneous pubertal development and menarche
- Average age at delivery was 25.6 years +/- 2.1 years
- Average age at menopause was 38 years +/- 5.8 years

Pregnancy Outcomes
Hadnott et al, 2011

- 3 of 7 pregnancies were unexpected and unintentional
- No obstetric complications
- No cardiovascular events
- C/sections in 4/7
- One offspring with CP, no low birth weight or preterm infants

Pregnancy Outcomes
Hadnott et al, 2011

- Spontaneous pregnancy is possible even in 45, X0 and “Classic TS” women
- No reports of Down Syndrome in offspring which may be more related to maternal age
- No chromosomal anomalies

Assisted Reproduction Techniques
Turner Syndrome
Hewitt et al, 2013

- Oocytes received from a healthy donor, followed by in vitro-fertilization and fresh or frozen-thawed embryo transfer
- Established technique in adult women with TS with pregnancy rate (visualization of gestational sac) of 17-40% per transfer as opposed to 73% in women undergoing oocyte donation for other reasons

Ovum Donation and IVF- Embryo Transfer
Hewitt et al, 2013

- Oocyte donation and IVF, embryo transfer
- Homologous oocyte collection, IVF, embryo transfer
- Oocyte donation and cryopreservation
- Oocyte cryopreservation
- Ovarian tissue cryopreservation
Ovum Donation
Kamm et al, 2003
- Surveyed CDC’s 1997 Fertility Clinic Reports
- 146 TS women treated with oocyte donation
- Only 49.3% had cardiac screening prior to treatment; 6.3% had CV anomalies
- Live birth rate of 64% was consistent with oocyte-donation pregnancies for other indications

Ovum Donation
Belgium study of 23 TS women showed clinical pregnancy rate of 24.4% per embryo transfer/ 11 births resulted from 55 embryo transfers (Mercadal et al, 2011)
- Swedish study of 30 women following ovum donation showed miscarriage rate of 26% vs 45% using patient’s own gametes (Bryman et al, 2011)

Ovum donation and Cryopreservation
Hewitt et al, 2013
- Ovum can be donated for a child and cryopreserved until appropriate time for IVF and embryo transfer
- Mother to daughter oocyte donation and preservation is being performed but there are no reported pregnancies in TS

Oocyte Cryopreservation
- Involves ovarian stimulation, collection of mature oocytes, transvaginal collection and vitrification or slow freezing of oocytes
- Requires physical and psychological maturity and not appropriate for pre pubertal children
- Over 1000 births in general adult population
- Case reports in adolescents and women with TS but no pregnancies yet reported

Ovarian Tissue Cryopreservation
Hewitt et al, 2013
- Laparoscopic collection of ovarian tissue containing immature ovarian follicles which is then cryopreserved
- Can be done in children as no preoperative ovarian stimulation is necessary
- Ovarian tissue cryopreservation has a poorer success rate than oocyte preservation due to difficulties with in vitro maturation of primordial follicles for oocyte retrieval
- Whole ovarian tissue transplantation with in situ maturation has had a high success rate
- Tissue can be transplanted into orthotopic site (ovarian fossa or preexisting ovary) or a heterotopic site (ie abdominal wall)
Ovarian Tissue Cryopreservation

- Precedent for using this technique in children has been established in cancer patients about to undergo gonadotoxic treatments.
- Over 30 live births have been reported in adult women but none yet from tissue taken from adolescents or girls and none from 45,X women.
- Procedure in children and adolescents is recommended only in specialized centers with institutionally approved protocols and informed consent.

Candidates for Ovarian Tissue Cryopreservation

- Borgstrom et al, 2009 studied 57 girls with TS, aged 8-19.8 yrs.
- Offered laparoscopy, ovarian biopsy and cryopreservation.
- Karyotypes: 45,X in 28, Mosaicism in 7 (45,X/46,XX/47XXX) and structural anomalies in one of the X chromosomes in 22.
- Did not deny participation to girls based on pubertal development, gonadotropin levels or treatment.
- No Imaging was done.

Assisted Reproduction

New Program Makes Fertility Preservation Standard of Care

Lynda Koen Beaupri, MD (https://www.roswellpark.org/lynda-koen-beaupri)
Director of IVF Cancer Program

Prior to treatment, all patients will have access to in-house fertility counseling thanks to a new insolvency program established by Roswell Park’s IVF Department.

Candidates for Ovarian Tissue Preservation in Turner Syndrome

- Laparoscopy was done to obtain ovarian cortical tissue.
- In 10 girls, insufficient tissue for biopsy or identification.
- In 47 girls, 25-50% of ovarian tissue from one ovary was obtained.
- Small amt. of tissue saved for histological analysis and the rest cryopreserved.
- Follicles were identified in 15 cases.

Candidates for Ovarian Tissue Preservation in Turner Syndrome

- In summary: the following categories of girls would have the highest chances of having follicles:
  1. Girls with mosaicism (45,X/46XX/47XXX).
  2. Girls with spontaneous onset of puberty and 45,X or 45,X/46,X+SAs.
  3. Girls with normal serum FSH and/or normal AMH levels with or without spontaneous puberty.

Recommended Criteria for Consideration of Ovarian Tissue Cryopreservation

- Age of 14 years or above.
- Spontaneous pubertal commencement.
- FSH < 40 IU/L.
- AMH measurable.
- Normal Cardiac Status.
- Informed consent from child and family.
- Institutional clinical or research ethics approval.
Risks to Mother

- No deaths during or after pregnancy. One woman died of aortic dissection while awaiting treatment.
- Reviewed literature of ART and TS pregnancy from US and calculated from lit review and calculated 2% death rate from aortic dissection.

Risks to Mother

- Bondy and Hadnott, 2011: reviewed case reports of spontaneous and ART pregnancies in women with TS; 145 pregnancies of 76 TS women.
- Aortic dissection rate – 4.8%.
- ART pregnancies more complicated by life-threatening maternal complications – 37% vs 5.9% of spontaneous pregnancies.
- ART pregnancies confounded by higher maternal age and more frequent multiple births.

Risks to Mother

- ART pregnancies for all women with infertility have higher risk of complications: abortions, prematurity, preeclampsia, diabetes etc.
- Higher risk of hypertensive disorder in oocyte donation.
- Risk to TS may be exacerbated by high estrogen exposure to abnormal cardiovascular system.

Risks to Mother

- 100% of catastrophic cardiovascular events (7 of 7) had underlying CV disease—often not recognized prior to pregnancy (hypertension, BAV, coarctation).
- 2/3 of patients with preexisting CV conditions suffer life-threatening events.

Risks to Mother

- All methods of conception:
  - 5 deaths.
  - 7 aortic dissections - only 1 non-fatal aortic dissection reported in spontaneous pregnancy (Bondy, 2014).
  - 6 cases of severe hypertensive disorders.
  - Overall risk of severe complications = 111% and overall risk of pregnancy related death = 3.5%.

Risks to Mother

- Mothers of twins experienced aortic dissections five times more frequently than the average pregnant TS woman.
- Hemodynamic changes of pregnancy are exaggerated in twin gestation.
**Risks to Fetus**
*Bondy, 2011*
- Increased risk of spontaneous abortion and chromosomal abnormalities
- Spontaneous pregnancy were more likely to end in fetal death vs assisted pregnancies (40.4% vs 17.2%)
- Spontaneous pregnancies more likely to result in offspring with abnormal karyotype than assisted pregnancies (16.5% vs 0%)
- 22-55% of offspring have IUGR, low birth weight or prematurity

**Contraindications to Pregnancy in Turner Syndrome**
*Hewitt, 2013*
- History of Aortic Surgery of Aortic Dissection
- Coarctation of the Aorta
- Aortic size index > 2.5 cm/m² or max aortic diameter ≥ 3-5 cm
- Uncontrolled hypertension despite treatment
- Portal Hypertension with esophageal varices
- Other major cardiac anomalies

**Counseling Recommendations**
*Bondy, 2011*
- Pregnancy is associated with high risk for life-threatening CV complications
- Spontaneous pregnancy is rare but may occur, even in 45, X0 women
- Contraception
- Advise against pregnancy in girls with know congenital heart disease
- Alternatives such as adoption or surrogacy

**Counseling Recommendations**
*If considering pregnancy, a comprehensive CV eval should be done prior to attempting conception: MRI needed/baseline and serial during pregnancy*
- Determination of aortic dilatation needs to take into account their small body size
- Ambulatory blood pressure monitoring should be part of pre-screening

**Turner Syndrome Case Study**
- Can our patient have spontaneous pregnancy?
- Should she be advised to attempt this?
- Risks to fetus
- Risks to herself
- Type of care before and during pregnancy
- Fertility preservation options

- Only one embryo should be transferred in ART with Turner Syndrome
- Even in cases where screening CV eval is normal, Turner syndrome families should be counseled that there is a greater risk for CV and metabolic complications (e.g. thyroid, diabetes)