



State of Fertility in X and Y Chromosomes Variations Individuals What You Should Know in 2025

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Disclosures

- Active Patent: 5/294,154 | 9865-185
- METHOD OF PRODUCING IN VITRO
- TESTICULAR CONSTRUCTS AND USES THEREOF

Application AU2019200730A events

Priority claimed from US201161492151P

2019-02-04

Application filed by Inguran LLC

2019-02-04

Priority to AU2019200730A

2019-02-21

Publication of AU2019200730A1

2021-08-12

Application granted

2021-08-12

Publication of AU2019200730B2

Status

Active

2032-06-01

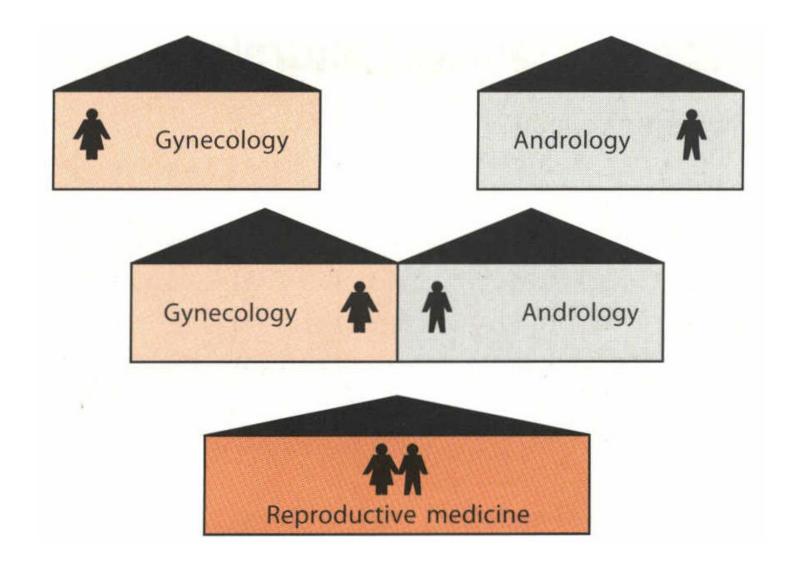
Anticipated expiration





Objectives

- Infertility in general population (Male & Female)
- Fertility in Klinefelter syndrome
- Fertility in Triple X syndrome
- Current clinical options to treat infertility
- Future options to treat infertility





Terminology

Fertility refers to the capability to **conceive or induce a pregnancy**.

Fecundity refers to the probability of producing a **live birth** arising from a given menstrual cycle.

Infertility is the term used when a couple **fails** to induce a pregnancy within **one year** of regular unprotected intercourse.

Primary infertility defines the condition when **no pregnancy at all** has been Achieved.

Secondary infertility means **no further** pregnancies have occurred. The term infertile can be applied to both men and women.

ke Forest® School of Medicine



Infertility Prevalence







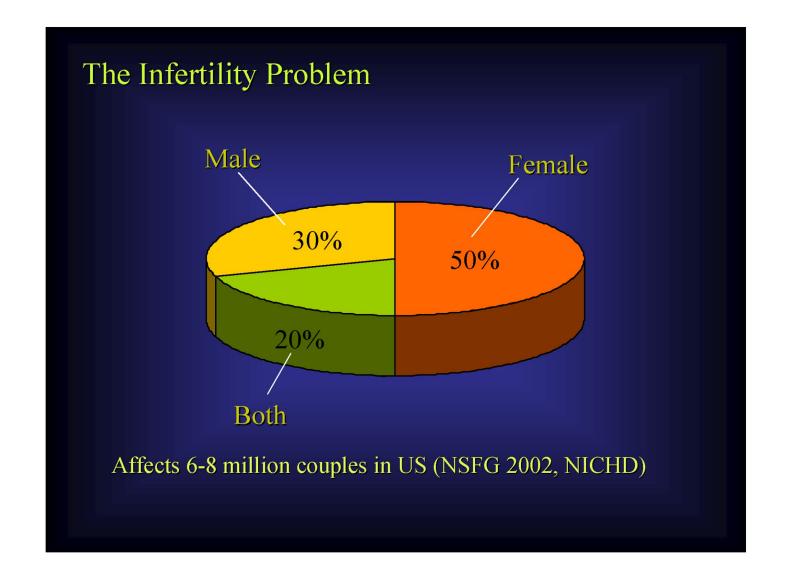
One out of every six couples experiences infertility.





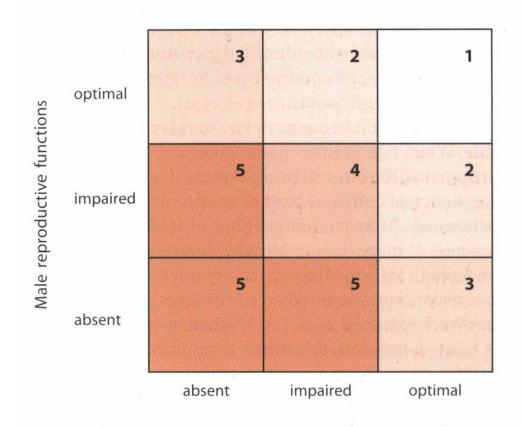








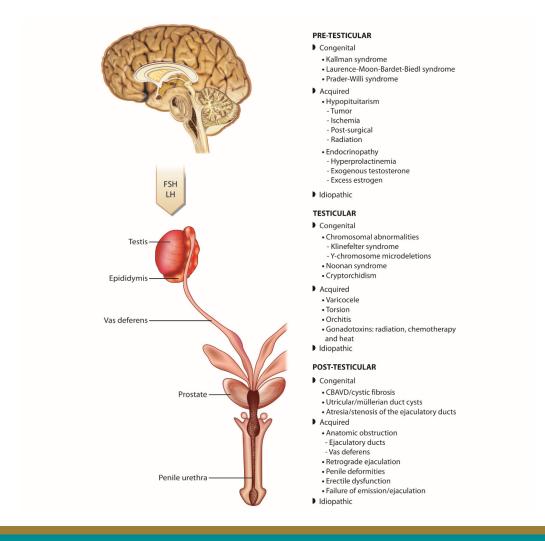
Interdependence of male and female reproductive functions



Female reproductive functions



Classification of causes of the male infertility







Distribution of Diagnostic

Category	N	%
Varicocele	629	26.4
Infectious	72	3.0
Hormonal	54	2.3
Ejaculatory dysfunction	28	1.2
Systemic diseases	11	0.4
Idiopathic	289	12.1
Immunologic	54	2.3
Obstruction	359	15.1
Cancer	11	0.5
Cryptorchidism	342	14.3
Genetic	189	7.9
Testicular failure	345	14.5
TOTAL	2,383	100.0

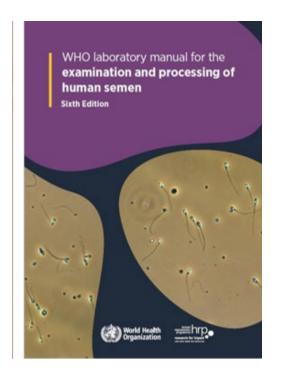




Semen Analysis

- 2-3 days of abstinence
- Collection technique
- Note: SA best performed in andrology lab;
 If abnormal always repeat



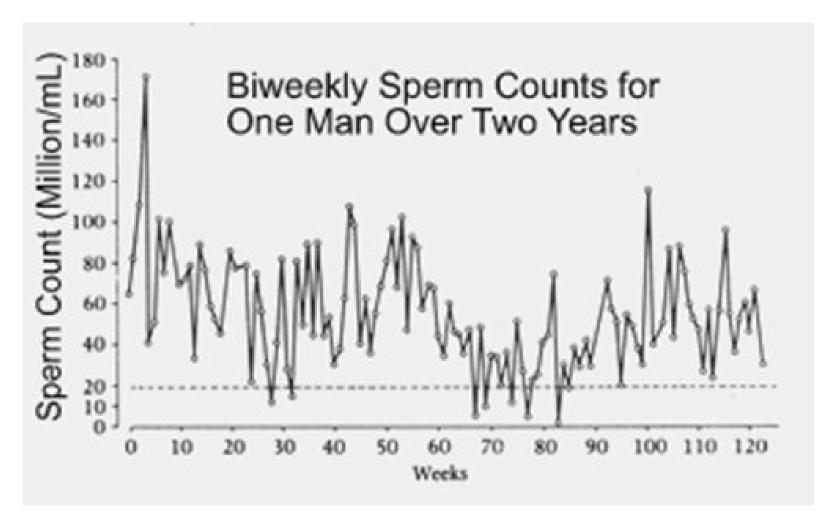


Semen parameter	WHO 1980	WHO 1987	WHO 1992	WHO 1999	WHO 2010 ¹	WHO 2021
Volume (mL)	ND	≥2	≥2	≥2	1.5	1.4
Sperm concentration (x10 ⁶ /mL)	20-200	≥20	≥20	≥20	15	16
Total sperm number (x106)	ND	≥40	≥40	≥40	39	39
Total motility (%)	≥60	≥50	≥50	≥50	40	42
Progressive motility (%)2	≥2 ³	≥25	≥25 (grade a)	≥25 (grade a)	32 (a+b)	30
Vitality (%)	ND	≥50	≥75	≥75	58	54
Normal morphology (%)	80.5	≥50	≥30	(14)	4	4

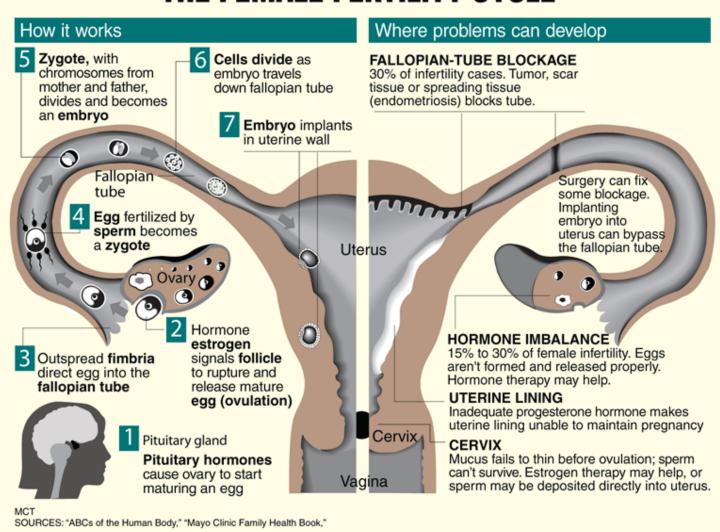




Sperm count vary over time



THE FEMALE FERTILITY CYCLE





Common Causes Female Infertility

Ovulation Disorders Causes:

- Aging
- Diminished ovarian reserve
- Premature ovarian failure
- Endocrine disorders (as PCOS)

Tubal Causes:

- Pelvic inflammatory disease
- Tubal Surgery
- Previous ectopic pregnancy
- Salpingectomy

Uterine/Cervical Causes:

- Congenital uterine anomaly
- Fibroids
- Endometriosis
- Poor cervical mucus quantity/quality
- Infection

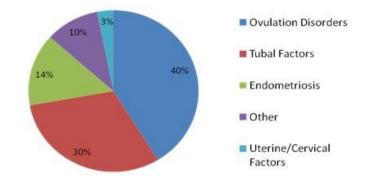
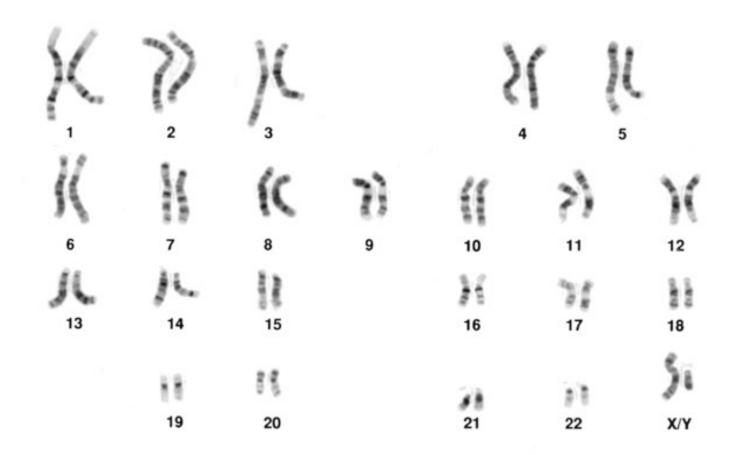


TABLE 4.14 Incidences of Selected Chromosomal Abnormalities in Live-Born Infants

Abnormality	Incidence in Live Births		
Autosomal trisomies Trisomy 21 (Down syndrome)	1:650 to 1:1,000		
Trisomy 13 (Patau syndrome)	1:4,000 to 1:10,000		
Trisomy 18 (Edwards syndrome)	1:3,500 to 1:7,500		
Sex chromosome disorders 45,X (Turner syndrome)	1:2,500 to 1:8,000 females		
47,XXX (triple X)	1:850 to 1:1,250 females		
47,XXY (Klinefelter syndrome)	1:500 to 1:1,000 males		
47,XYY (Jacobs syndrome)	1:840 to 1:1,000 males		
Structural abnormalities			
Rearrangements (e.g., translocations, deletions)	~1:440 live births		

Note: Based on statistics from surveys in different populations and not age adjusted. Data prior to use of prenatal diagnosis and selective termination of pregnancies became widespread.





Normal Karyotype Male





Klinefelter Syndrome (KS)

- First described in 1942 as an "endocrine disorder"
- Extra-X chromosome identified in 1959; reclassified as "chromosomal disorder"



Harry F. Kleinfelter, MD

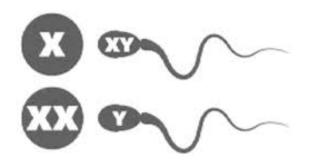
KS Prevalence

• 1 in 500 men

- Most common sex chromosome disorder in men
- Most common genetics cause of male infertility

Error in Cell Division

- Usually, a random error
- Either the egg or the sperm can have an imbalance in number of chromosomes



KS Variability!

- 47,XXY 80-90% of KS patients
- Extra X chromosomes
 (48,XXXY, 49XXXXY etc.)
- Mosaicism (46,XY/47,XXY)
- Structurally abnormal X chromosome

10-20% of KS patients

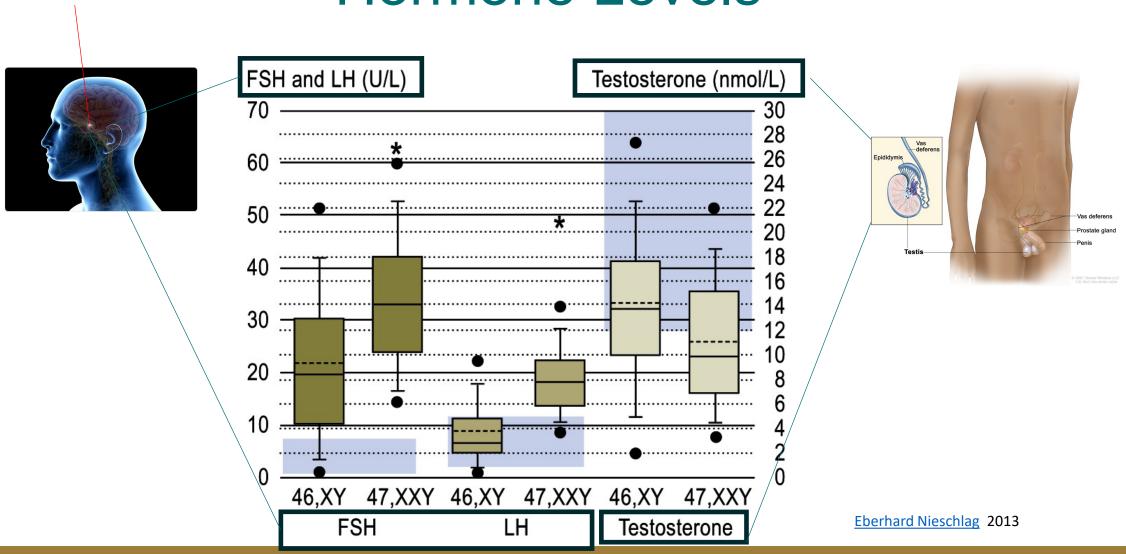
The "classic" KS patient is....not so classic

Testosterone (T) Production

- T levels are normal in infants and pre-pubertal boys
- Most boys initiate puberty normally, but might fail to progress
- T levels rise in early puberty, plateau in the lownormal range in mid-puberty, then decline

Pituitary Gland

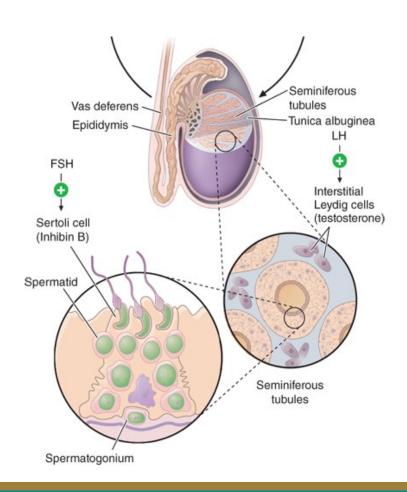
Hormone Levels







Sperm Production

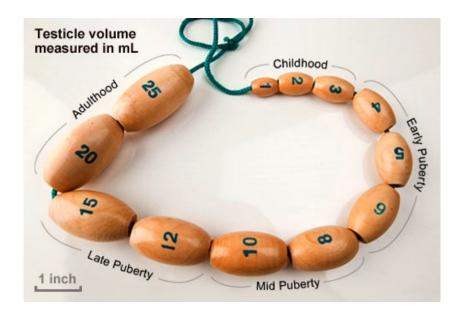


- Klinefelter syndrome
 - Germ cells do not progress normally to produce sperm
 - Seminiferous tubes become scarred
 - Rare areas of sperm production are possible



Testicular Size

- Boys with KS have smaller testes compared to their peers
- Testicular growth briefly increases after the onset of puberty to midpuberty, then declines



Puberty: A Critical Time

- Decline in testicular function begins shortly after entering puberty
- This is the time to consider testosterone therapy
- This is also the time to think about fertility preservation

Testosterone Therapy (TRT)

- Testosterone supplementation is helpful because testosterone plays many important roles:
 - Promotes growth
 - Increases muscle mass
 - Preserves bone density
 - Allows development of secondary sexual characteristics
 - Has positive psychological benefits
 - May increase libido and improve erection function



Testosterone therapy does **not** improve spermatogenesis and should **not** used by men of reproductive age

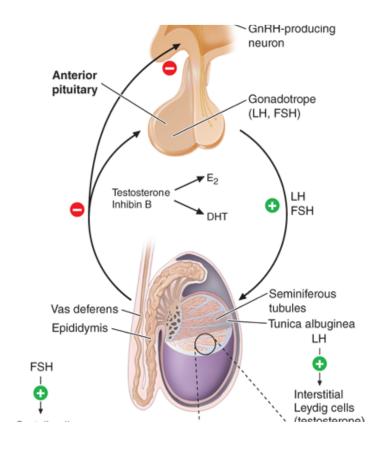






Options

- Use non-testosterone based hormone therapies
 - hCG
 - Clomiphene citrate
 - Anastrazole/Letrozole
- Nasal Testosterone







Nasal Gel Testosterone

One pump (5.5 mg) in each nostril 3 times daily, for a total daily dose of 33 mg

Each dose should be taken 6 to 8 hours apart: once in the morning, once in the afternoon, once in the evening











Natesto appears to increase testosterone while maintaining semen parameters in a majority of men.

Clinical Trial > J Urol. 2020 Sep;204(3):557-563. doi: 10.1097/JU.0000000000001078. Epub 2020 Apr 15.

Effect of Natesto on Reproductive Hormones, Semen Parameters and Hypogonadal Symptoms: A Single Center, Open Label, Single Arm Trial

Ranjith Ramasamy 1 , Thomas A Masterson 1 , Jordan C Best 1 , Joshua Bitran 1 , Emad Ibrahim 1 , Manuel Molina 1 , Ursula B Kaiser 2 , Feng Miao 3 , Isildinha M Reis 3 4

Affiliations + expand

PMID: 32294396 DOI: 10.1097/JU.000000000001078

Received: 16 March 2022 | Revised: 7 April 2022 | Accepted: 18 April 2022

DOI: 10.1111/and.14453

ORIGINAL ARTICLE

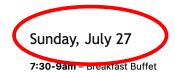
andrologia WILEY

Direct conversion from long-acting testosterone replacement therapy to Natesto allows for spermatogenesis resumption: Proof of concept









8:30-3pm – Childcare

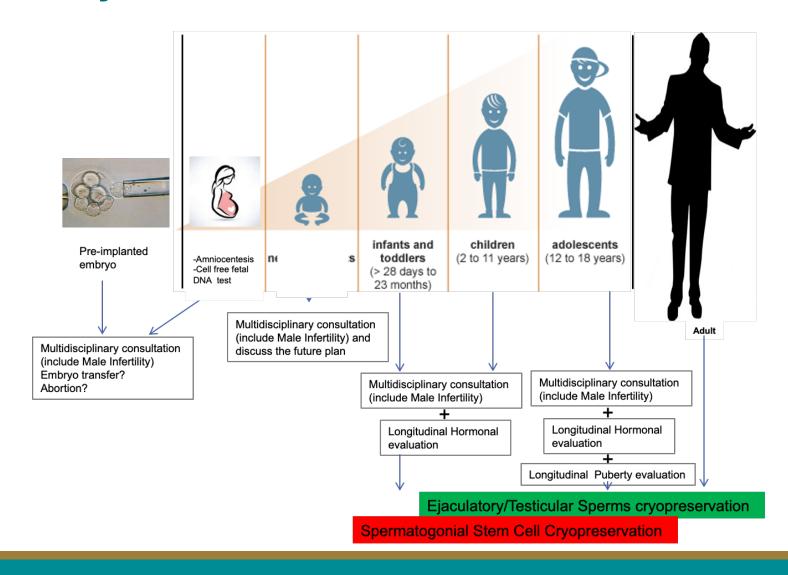
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	Room	9-10am Session 7	10-11am Session 8	11am-12pm Session 9	12-1:30pm Lunch and Poster Session	1:45-3pm Session 10
	Emory Amphitheater (Live Streamed & Recorded) ••	Unpacking Social and Emotional Challenges for Teens/Young Adults with X/Y Variations Caitlin Middleton Kate Deer Rebecca Wilson	Eval and Treatment Of ADHD & Anxiety In Children Caitlin Middleton Ciara Gurley	Understanding X and Y Variations: Genetic Diagnosis, Terminology & Next Steps Planning Susan Howell Kayla Molison		Support Groups by Genetic Signature
	Oak Amphitheater	Supporting Academic and Social-Emotional Education of Students with X&Y Chromosome Variations Amy Talboy Catherine Trapani	Testosterone Treatment Options in Klinefelter Syndrome Hooman Sadri	What Adults with X/Y Variations Want Parents and Others to Know Panel Discussion Mod. by Sharron Close		Support Groups by Genetic Signature
	Azalea	Tips for Staying Healthy for Teens and Adults with X and Y Chromosome Variations Maria Vogiatzi	X/Y Chromosome Variations and Autism: Insights from Large Scale Population Research Matthew Oetjens	Promoting physical activity in Children with XXY T. Zachary Huit		Support Groups by Genetic Signature
	Mt. Laurel	Disclosing the Diagnosis- Panel Discussion Mod. by Susan Howell	Unassigned	Unassigned		Support Groups by Genetic Signature
بن	Hickory	Unassigned	Unassigned	Unassigned		Support Groups by Genetic Signature





Fertility Preservation Consultation & Services

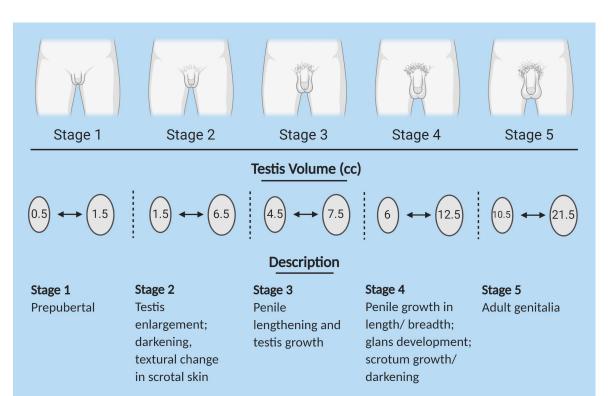


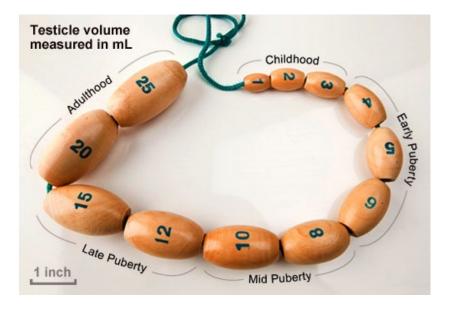




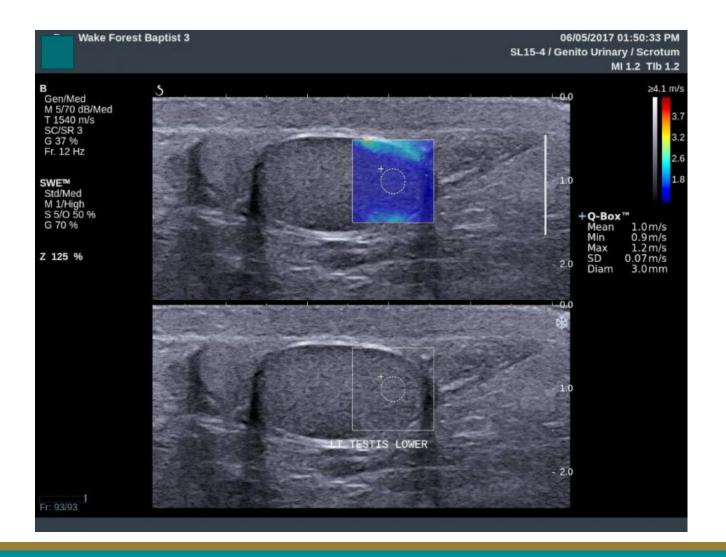
Physical Exam (sexual maturity)

Tanner Staging

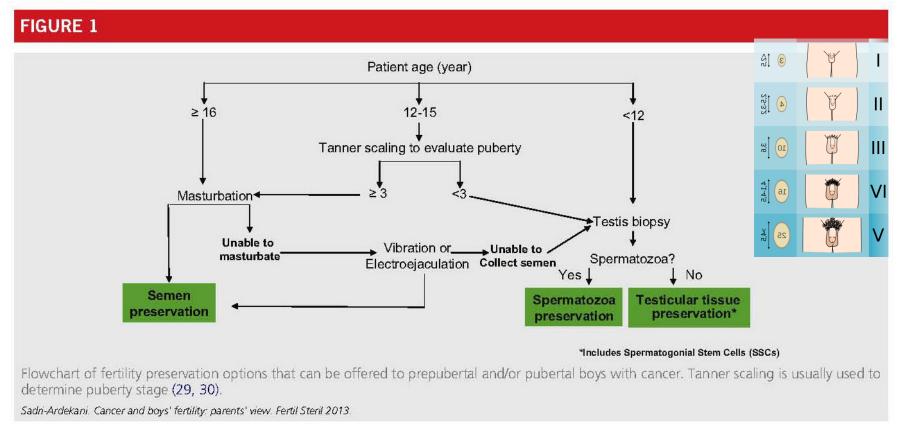




Special Elastography Ultrasound (stiffness; Fibrosis)



One Step Encounter Fertility Preservation







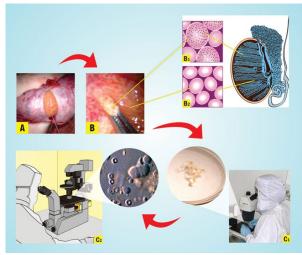
Sadri-Ardekani et al, Fertility and Sterility 2013

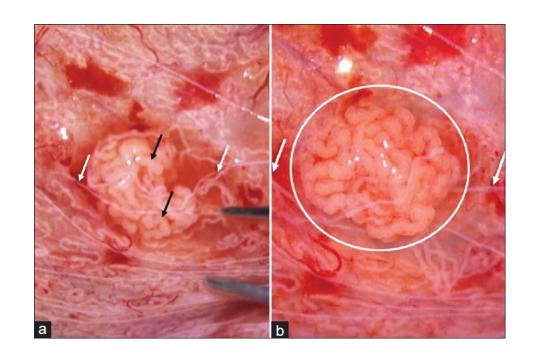




Microscopic Testicular Sperm Extraction (mTESE)







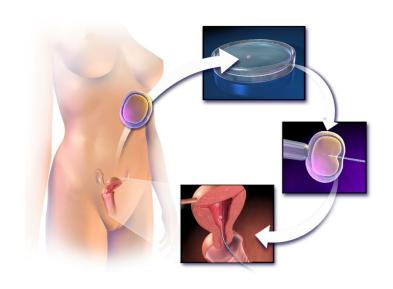
Clinical Andrology 2011, EAU/ESAU Course Guidelines; Edited by L BjÖrndahl, A Giwercman, H Tournaye and W Weidner

Medical and Surgical Management of Male Infertility 2014; Edited by Rizk, Aziz & Agarwal





In Vitro Fertilization (IVF) using stored sperms



Intra-cytoplasmic sperm injection (ICSI)



April 1991- Jan 1992

Overall Sperm Retrieval: 44%
Overall Live Birth Rate per ICSI cycle: 43%

Clinical Andrology 2011, EAU/ESAU Course Guidelines; Edited by L BjÖrndahl, A Giwercman, H Tournaye and W Weidner

Medical and Surgical Management of Male Infertility 2014; Edited by Rizk, Aziz & Agarwal

Corona et al 2017, HRU





Pre-Implantation Genetic Diagnosis (PGD)



(Fresh) mTESE (at least 70% chance of finding sperm)



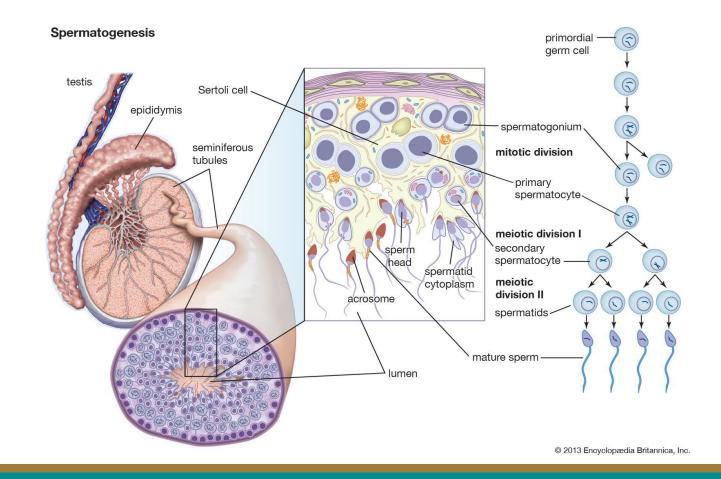
Pregnancy (70% per Embryo Transfer if partner is <35 yr old)







From Spermatogonia Stem Cell to Sperm







Human Reproduction Update, Vol.26, No.1, pp. 58-72, 2020

Advance Access Publication on December 10, 2019 doi:10.1093/humupd/dmz038

human reproduction update

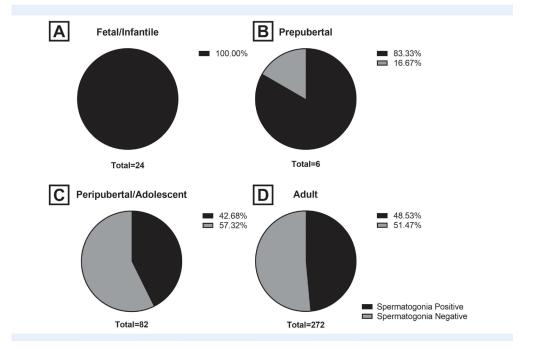
Age-related presence of spermatogonia in patients with Klinefelter syndrome: a systematic review and meta-analysis

Nicholas A. Deebel^{1,2}, Guillermo Galdon², Nima Pourhabibi Zarandi², Kimberly Stogner-Underwood³, Stuart Howards¹, James Lovato⁴, Stanley Kogan^{1,2}, Anthony Atala^{1,2}, Yanhe Lue⁵, and Hooman Sadri-Ardekani 1,2,*

¹Department of Urology, Wake Forest University School of Medicine, Winston-Salem, NC, USA ²Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA ³Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, NC, USA ⁴Department of Biostatistics and Data Science, Wake Forest University School of Medicine, Winston-Salem, NC, USA ⁵Division of Endocrinology, Department of Medicine, Los Angeles Biomedical Research Institute and Harbor-UCLA Medical Center, Torrance, CA, USA

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Submitted on June 4, 2019; resubmitted on September 15, 2019; editorial decision on September 30, 2019





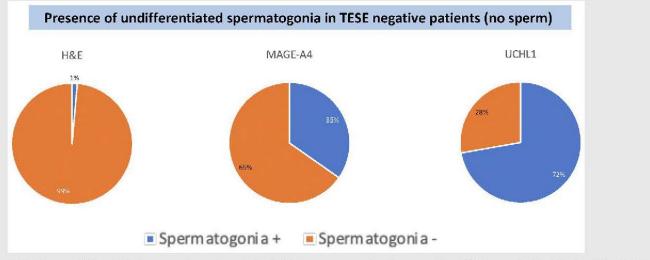




Morphometric and immunohistochemical analysis as a method to identify undifferentiated spermatogonial cells in adult subjects with Klinefelter syndrome: cohort study

Nicholas A. Deebel, M.D., ^{a,b} Haleh Soltanghoraee, M.D., ^{cd} Aaron William Bradshaw, M.D., ^{a,b} Omar Abdelaal, M.D., ^{b,e} Karl Reynolds, B.S., ^b Stuart Howards, M.D., ^a Stanley Kogan, M.D., ^{a,b} Mohammad Reza Sadeghi, Ph.D., ^{cd} Anthony Atala, M.D., ^{a,b} Kimberly Stogner-Underwood, M.D., ^{a,e} and Hooman Sadri-Ardekani, M.D., Ph.D. ^{a,b,†}

Fertil Steril. 2022 Nov;118(5):864-873



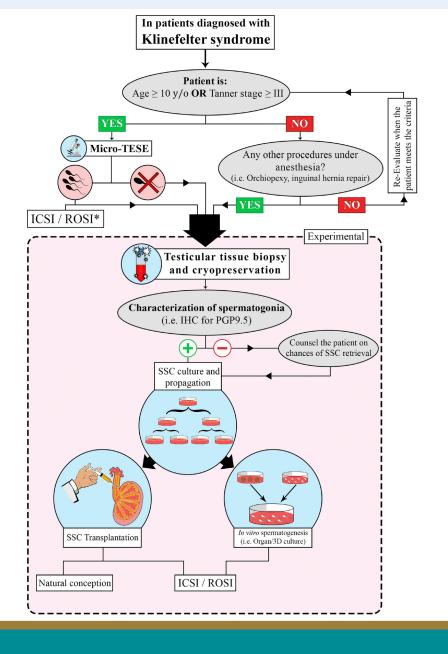
The chance of finding undifferentiated spermatogonia cells in testicular sperm extraction negative (TESE-negative) subjects, detected by hematoxylin and eosin (H & E), UCHL1, or MAGE-A4 staining in histology samples from TESE procedures.

Deebel. Undifferentiated spermatogonia in Klinefelter testes. Fertil Steril 2022.





⁸ Department of Urology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; ^b Wake Forest Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina; ^c Reproductive Biotechnology Research Center, Avicenna Research Institute, Academic Center for Education, Culture and Research, Tehran, Iran; ^d Avicenna Infertility Clinic, Avicenna Research Institute, Avicenna Research Institute, Academic Center for Education, Culture and Research, Tehran, Iran; ^e Department of Urology, Faculty of Medicine, Zagazig University, Zagazig, Egypt; and ^f Department of Pathology, Wake Forest University School of Medicine, Winston-Salem, North Carolina.



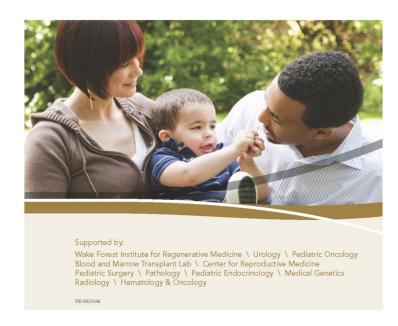




Institute for Regenerative Medicine

Testicular Tissue Banking

for Fertility Preservation in Boys and Men at Risk for Infertility



Cancer Bilateral UDT Klinefelter Registry denied

IRB approval March 2013

EXPERIMENTAL EXPERIMENTAL

Good Tissue Practice (GTP) regulations

FDA registration June/July 2014

First patient recruitment 07/22/2014

221 Patients

Updated July 25, 2025







TYPE Original Research PUBLISHED 28 September 2022 DOI 10.3389/fendo.2022.1002279



OPEN ACCESS

Rick Francis Thorne, The University of Newcastle, Australia

Yi Zheng, Northwest A&F University, China

Peter Schlegel,

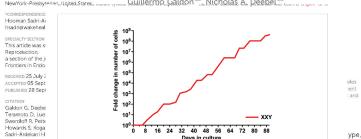
Guillermo Galdon 1.2 Nicholas A. Deebel 1.3

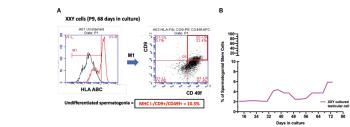
fertility opportunities

In vitro propagation of XXY

human Klinefelter spermatogonial

stem cells: A step towards new





(A) Spermatogonial stem cells (SSC) population was estimated by combining HLA-/CD9+/CD49f+ markers on Flow Cytometry analysis. After 68 days in culture and nine passages, the percentage of putative SSC was 10.1% of a 17-year-old KS patient (B). Several time points were analyzed to evaluate the evolution of this population over time in all subject samples in culture. The graph shows the average of the SSCs population during the culture in KS patients (B)



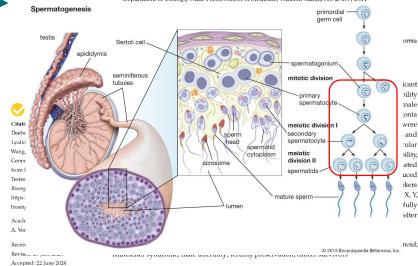


Published: 3 July 2024

In Vitro Generation of Haploid Germ Cells from Human XY and XXY Immature Testes in a 3D Organoid System

Guillermo Galdon 1,2,*0, Nima Pourhabibi Zarandi 1,30, Nicholas A. Deebel 1,40, Sue Zhang 1,5, Olivia Cornett 1, Dmitry Lyalin ^{6,7}, Mark J. Pettenati ⁶, YanHe Lue ⁸, Christina Wang ⁸, Ronald Swerdloff ⁸, Thomas D. Shupe ¹, Colin Bishop 1, Kimberly Stogner 1,6, Stanley J. Kogan 1, Stuart Howards 1,4, Anthony Atala 1,40 and Hooman Sadri-Ardekani 1,4,6,*

- Wake Forest Institute for Regenerative Medicine (WFIRM), Wake Forest School of Medicine, Winston-Salem, NC 27101, USA
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- Department of Urology, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA



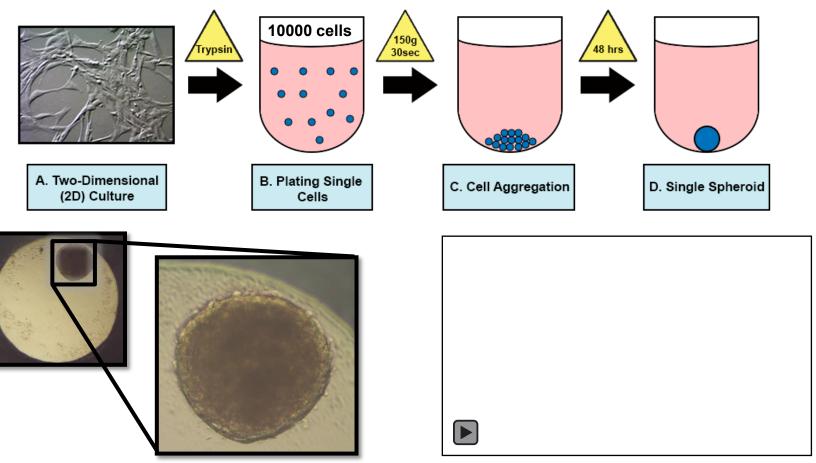




Creating the 3D Organoids (HTO); Methods



Ultra Low Attachment Round-bottom plates

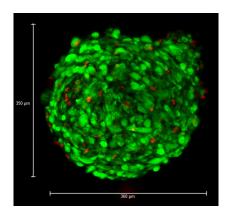


Pendergraft et al 2017 Galdon et al 2024

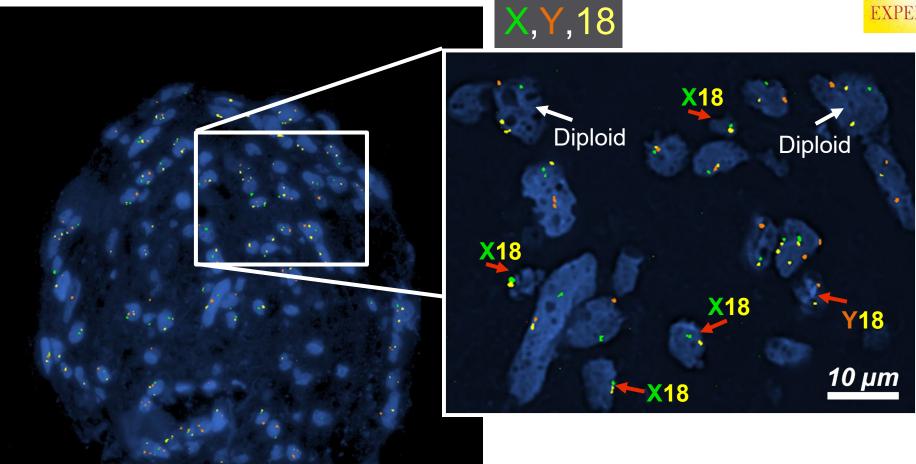


In Vitro Formed HUMAN Haploid Germ cells; DNA FISH





Human Testicular Organoid (HTO)



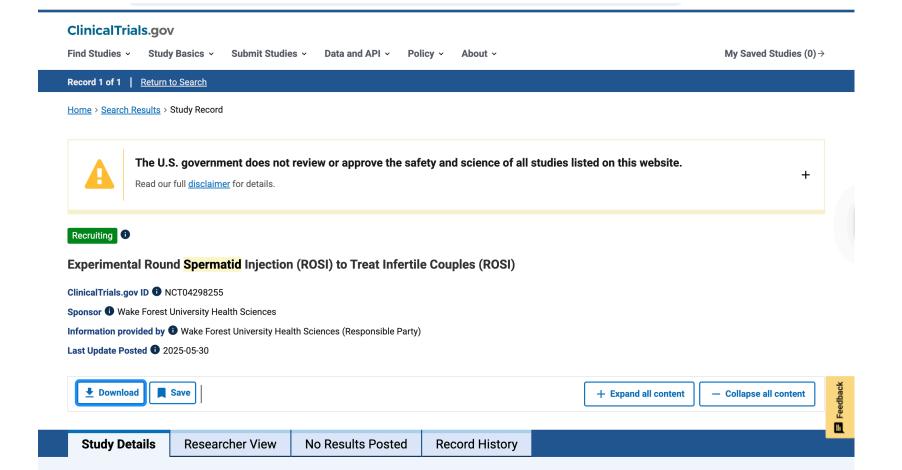
100 µm

Galdon et al 2024











Ninety babies born after round spermatid injection into oocytes: survey of their development from fertilization to 2 years of age

Atsushi Tanaka, M.D., Ph.D., a Kohta Suzuki, M.D., Ph.D., M.P.H., Motoi Nagayoshi, M.D., a Akihiro Tanaka, M.B.J.T., Youichi Takemoto, Sejiji Watanabe, Ph.D., Satoru Takeda, M.D., Ph.D., d Minoru Irahara, M.D., Ph.D., Naoaki Kuji, M.D., Ph.D., Zentaro Yamagata, M.D., Ph.D., 9

"Asam Morthe Obsettics and Gynecology Clinic and Institute for Assisted Reproductive Technologies, Fukuoka, Japan,
"Department of Health and Psychosocal Medicine, Aich Medical University School of Medicine, Aich, Japan,
"Department of Commission of Medicine, Aich Medical University School of Medicine, Aich, Japan,
"Department and Gynecology, Institute of Department of Observation School of Medicine, Observation of Observation School of Observation School Observatio

Objective: To compare physical and cognitive development of babies born after round spermatid injection (ROSI) with those born after

natural conception.

Design: Comparison of efficiencies of ROSI and ICSI using testicular spermatozoa, performed in the St. Mother Clinic. Physical and

Design: Comparison of efficiencies of ROSI and ICSI using testicular spermatorous, performed in the St. Mother Clinic. Physical and cognitive devolopment of ROSI balles revoided by parents in the government-bound Mothers. And Handbook was checked and verified by attending pediatricians. Data included bally's weight gain and response to parents' voice/gesture. Staffing: Assister proposition technicology practice.

Pathentis: A total of 22 in men participated in ROSI; 90 ROSI bables were followed for 2 years for their physical and cognitive development: Control subjects were 1 all in startingly born balles.

Pathentis: A total of 22 in men participated in ROSI; 90 ROSI bables were followed for 2 years for their physical and cognitive development of ROSI bables (e.g., bady weight increase, response to parents, and understanding and speaking simple languaged compared with naturally born bables.

Resultifich: 670 ROSIO bables, there also congenited aberentions a britch, which corrected spontaneously electricular septsa) or after surgery (left tip and omphaloeted). Physical and cognitive development of ROSI bables was similar to those of naturally born bables.

Resultifich: 670 ROSIO bables, there there are differences between ROSI and naturally conceived bables in either physical or cognitive development of ROSI bables was similar to those of naturally born bables. Conclusionists: There were no significant differences between ROSI and naturally conceived bables in either physical or cognitive development of ROSI bables was similar to those of naturally born bables. On the action of the wave of the particular starting of the particular starting or cognitive development of ROSI bables was similar to those of naturally born bables. On the effect of the wave of natural differences between ROSI and naturally conceived bables in either physical or cognitive development of ROSI bables was similar to those of naturally to organize administration of the particular starting organization of the particular starting or the parti

El resumen está disponible en Español al final del artículo.

Key Words: Assisted fertilization, human egg, physical and cognitive development, round spermatid injection

Discuss: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/users/16110-fertillity-and-sterility/posts/32485-25452

eived December 13, 2017; revised April 9, 2018; accepted April 24, 2018.

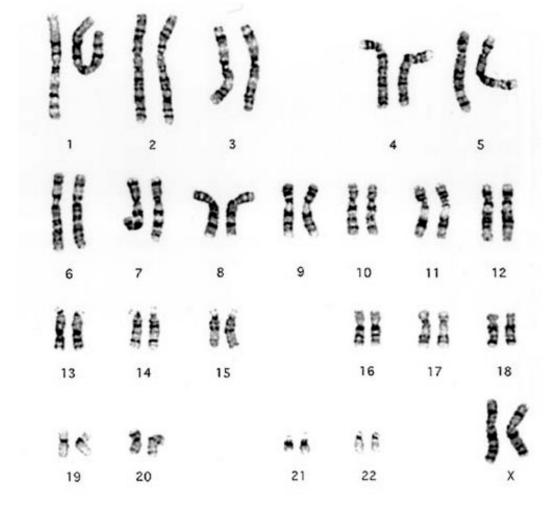
Abushi T. has nothing to disclose. K.S. has nothing to disclose. M.M. has nothing to disclose. Addition T. has nothing to disclose. Y.T. has nothing to disclose. M.K. has nothing to disclose. M.K. has nothing to disclose. T. has nothing to disclose. M.K. has nothing to disclose. R.Y. has nothing to disclo

ouring to discose.
All and K.S. should be considered similar in author order.
Reprint requests: Atushi Tanaka, M.D., Ph.D., Saint Mother Obstetrics and Gynecology Clinic, 4-9-12 Orio Yahatanishi-ku Kitakyushu, Fukuoka, Japa
(E-mail: Indo-Ostmother.com).

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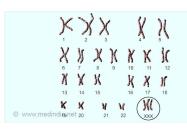




Normal Karyotype Female







Triple X Syndrome

It is a genetic disorder seen in females, characterized by the presence of an extra X chromosome



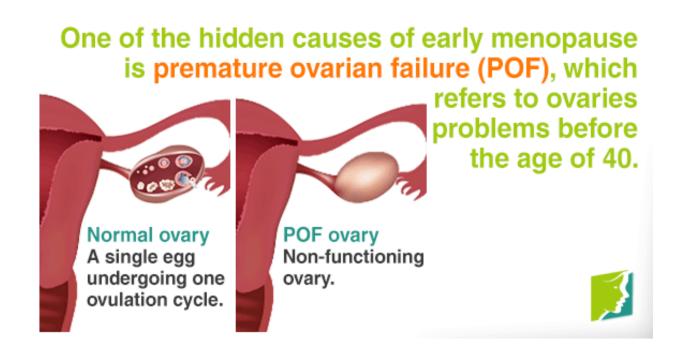
History

- The first published report of a woman with a 47,XXX karyotype was by Patricia A. Jacobs, in Edinburgh, Scotland in 1959. She was a 35-year-old, 5 ft. 9 in., 128 lb. woman who had premature ovarian failure at age 19; her mother was age 41 and her father was 40 at the time of her conception.
- Occurs more often when older men and women conceive vs. younger couples.



Triple X Syndrome

- One in every 1000 females has an extra X chromosome
- The most common sex chromosome abnormality in females
- Most individuals with 47,XXX are diagnosed incidentally on prenatal genetic screening
- The physical phenotype shows earlier growth and longer legs. 47,XXX females have a tendency to be tall, with many reaching the 80th percentile in height by adolescence, but with an average head circumference between the 25th to 35th percentile
- Puberty and fertility are generally in the normal range, but premature ovarian failure can occur



Premature ovarian failure (POF) is a condition in which the ovarian functions of **hormone production** and **oocyte (egg) development** become impaired before the typical age for menopause.

POF occurs in approximately 1% of all women

Studies on the prevalence of POF in adolescents or adults with trisomy X have not yet been performed Premature ovarian failure (POF) seems to be somewhat more common than in the general population



Summary

- Infertility is common in general population (15%)
- More than 98% of Klinefelter individuals deal with infertility
- Early Fertility Preservation is recommended before long term Testosterone replacement
- Microsurgical Testicular Sperm Extraction (Micro-TESE) and Intra Cytoplasmic Sperm Injection (ICSI) is the most successful clinical option in Klinefelter syndrome
- Spermatogonial Stem Cell Technology is a great hope for the future
- Infertility is not an issue in most of the Triple X individuals; however they need a good reproductive health management
- Egg Freezing (Triple X)





Appointment for initial evaluation and consultation (In Person Only):

336.713.1493

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• Appointment for initial evaluation and consultation (Virtual for Non-NC Residents or

In-Person):

336.448.9100





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