Introduction

- In this module, case studies are used to demonstrate how IVF can be applied in special and often uncommon circumstances for an eventual successful outcome.

Contributors

These case studies on male infertility, genetic diseases, and other conditions were provided by:

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- Atsushi Tanaka, MD
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Learning Objectives

By the end of this module, you will be able to:

- Demonstrate how IVF can be applied in uncommon situations to achieve a successful pregnancy
- Apply the knowledge gained for any appropriate applications in the future

Introduction

- Triad syndrome consists of dextrocardia, bronchiectasia, and chronic bronchitis
- Most sperm of patients with Kartagener syndrome are immotile
- Eosin-Y staining and HOST (hypo-osmotic swelling test) are useful tests to detect viable sperm
- Transmission electron microscopy (TEM) shows abnormal findings with connecting pieces, shortened mid-pieces with attenuated mitochondrial sheaths, a poorly developed annulus, abnormal outer dense fibres, and axonemes missing the two central microtubules
- Pregnancy is possible with intracytoplasmic sperm injection (ICSI) using viable but immotile sperm

Patient Presentation

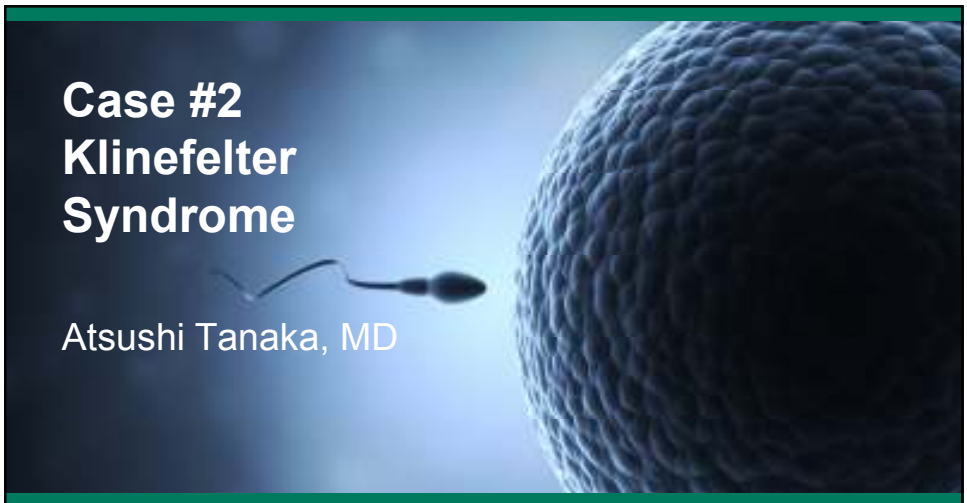
- 28-year-old man trying for three years to father a child
- Completely immotile sperm with normal sperm count
- Physical exam remarkable for dextrocardia, bronchiectasia, and chronic bronchitis
- Deformity of sperm flagella confirmed with TEM

Treatment

- 63% of ejaculated sperm were viable (positive eosin-nigrosin test)
- Selection of motile sperm carried out with HOST
- Two normal boys were born following ICSI using the viable but immotile sperm

Conclusions

- Completely immotile sperm can remain viable
- Sperm found to be viable by performing HOST have the potential to fertilise an oocyte
- The resulting embryos can implant and progress to normal, healthy deliveries



Introduction

- Non-obstructive azoospermia with a 47,XXY chromosomal abnormality
- 47,XXY in 80-90%, and mosaic 46,XY/47,XXY in 10-20%
- Estimated frequency 1/500-1/1000
- Candidates for ICSI based on high collection rate of sperm or spermatids under microdissection testicular sperm extraction (MD-TESE)

Introduction (con't.)

- Small increased risk for aneuploidies in children born from fathers with Klinefelter syndrome
- Origin of XXY aneuploidy is from the father and mother equally
- The extra sex chromosome appears to be eliminated during spermatogenesis

Patient Presentation

- 31-year-old azoospermic man with 47,XXY karyotype
- Tall (187 cm) with small testicles
- FSH: 57 mIU/mL
- Otherwise healthy

Treatment

- Collection of motile sperm with normal morphology under MD-TESE
- A healthy baby boy with 46,XY karyotype was born following the first trial of ICSI

Conclusions

- There appears to be a small increased risk for aneuploidies in children born of fathers with Klinefelter syndrome
- Although mosaic Klinefelter syndrome karyotype (of lymphocytes) is 47,XXY, sperm or spermatids found in seminiferous tubules show a karyotype of 46,XY
- This discrepancy seems to be derived from the gonadal mosaic that preserves partly normal spermatogenesis
- Use of ICSI can be very effective in Klinefelter syndrome

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Introduction

- Functional azoospermia
- The most frequent cause of spinal injury is a motor vehicle accident
- Two methods for sperm collection
  - Electro-ejaculation
  - Microsurgical epididymal sperm aspiration (MESA)
  - Vibratory stimulation

Patient Presentation

- 25-year-old male diver
- Diving injury at 18 years old
- Paralysis below C7

Treatment

- Anal electrical stimulation resulted in immotile sperm with 5% viability
- MESA at the caudal region resulted in normal sperm, which were cryopreserved
- Normal healthy baby born after ICSI using thawed epididymal sperm

Conclusions

- A treatment method including MESA + ICSI for spinal cord-injured patients with ejaculatory dysfunction was evaluated as very effective
- Especially useful for patients with serious complications

Introduction

- Cryopreservation of an extremely small number of sperm is now applied clinically
- This approach has resulted in normal deliveries
- Using this approach, repeated surgical sperm retrieval can be avoided

Patient Presentation

- 28-year-old man
- Four years of childlessness due to azoospermia
- One or two sperm were found every three or four trials of ejaculation following centrifugation of the semen

Treatment

- One to three sperm frozen by vitrification
- Survival rate was 60% (9/15)
- ICSI was successful
- One blastocyst transfer resulted in delivery of a healthy baby girl

Conclusion

- Cryopreservation of individual or small numbers of human spermatozoa has the potential to replace repeated surgical sperm retrieval
- The approach has been clinically validated to result in a live, healthy birth

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Introduction

- In 1993, Ogura and Yanagimachi reported the possibility of achieving conception following ROSI into the oocyte[1]
- In 1994, Edwards and colleagues proposed the use of spermatids from azoospermic men[2]
- In 1996, normal babies were born following spermatid injection into human oocytes by Tesarik and colleagues[3]
- There have been few new reports on ROSI since 2000
- Issues concerning extremely low success rates following ROSI were related to difficult cytodifferentiation of spermatogenic cells and immature oocyte activation
- ROSI might be useful for the treatment of azoospermic men once these issues have been resolved

1. Ogura A, Yanagimachi R. Round spermatid nuclei injected into hamster oocytes from pronuclei and participate in syngamy. *Biol Reprod*. 1993;48:219-225.
2. Edwards RG, Tarin JJ, Dean N, Hirsch A, Tan SL. Are spermatid injections into human oocytes now mandatory? *Hum Reprod*. 1994;9:2217-2219.
3. Tesarik J, Mendoza C. Spermatid injection into human oocytes. I. Laboratory techniques and special features of zygote development. *Hum Reprod*. 1996;11:772-779.

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Patient Presentation

- 30-year-old azoospermic man with a normal karyotype of 46,XY
- No Y-chromosome microdeletion
- High FSH concentration (15 mIU/mL)

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Treatment

- MD-TESE was performed, and round spermatids were found in the biopsied tissues after the enzymatic preparation
- Pathologic assessment was maturation arrest at the spermatid stage
- An enzymatically prepared cell suspension was cryopreserved
- ROSI was performed after oocyte activation with electrical stimulation
- Seven out of twelve oocytes collected after a GnRH agonist long protocol were fertilised; five were cleaved, two developed further into blastocysts
- Two blastocysts were transferred
- A healthy baby girl was delivered with a 46,XX karyotype

Conclusion

- ROSI has the potential to help many non-obstructive azoospermic men become fathers
- Previous technical barriers appear to have been largely overcome

Introduction

- Poor oocyte quality or intrinsic sperm defects may lead to fertilisation failure despite normal sperm counts and "morphologically normal" metaphase II oocytes
- Overall unexplained fertilisation failure occurs about 4% of the time after conventional IVF and about 2% with ICSI
- Intrinsic sperm defects are mainly responsible for fertilisation failure when performing ICSI

Patient Presentation

- Mr. AS, age 37 years, had two consecutive ICSI cycles because of borderline male factor infertility (10 million sperm/mL, 32% motility, and normal sperm morphology) after three years of primary infertility
- His wife was 33 years old, G0P0, and had a completely unremarkable medical history
- In the first cycle she produced 14 oocytes but only 1/14 (7%) fertilised, and no pregnancy ensued
- In the second ICSI cycle there was no fertilisation (0/16 oocytes)
- In both cycles the oocytes showed no morphologic abnormalities

Treatment

- In a third ICSI cycle artificial oocyte activation using Ca^{2+}-ionophore was performed soon after ICSI to prevent recurrent fertilisation failure
- Oocyte activation initiated the fertilisation process, and 5/12 oocytes (41%) showed fertilisation, and 4/5 cleaved normally
- Two embryos were transferred and the couple achieved a singleton live birth

Conclusions

- No routine semen analysis or sperm test can reliably predict whether a couple will experience fertilisation failure
- In this case, after two ICSI cycles with extremely poor or no fertilisation, oocyte activation with Ca^{2+}-ionophore was utilised
- Alternatively, polarisation microscopy can be used to visualise spindles during ICSI, or a high-magnification microscope can be used

1. Sakkas D, Alvarez JG. Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis. *Fertil Steril.* 2010;93:1027-1036.
2. Henkel R. Sperm preparation: state-of-the-art--physiological aspects and application of advanced sperm preparation methods. *Asian J Androl.* 2012;14:260-269.

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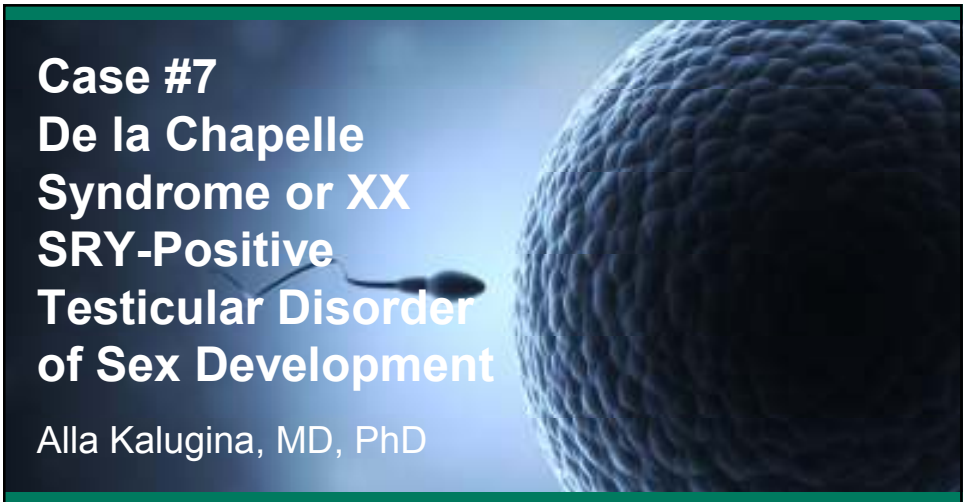

Case #7 De la Chapelle Syndrome or XX SRY-Positive Testicular Disorder of Sex Development

Alla Kalugina, MD, PhD

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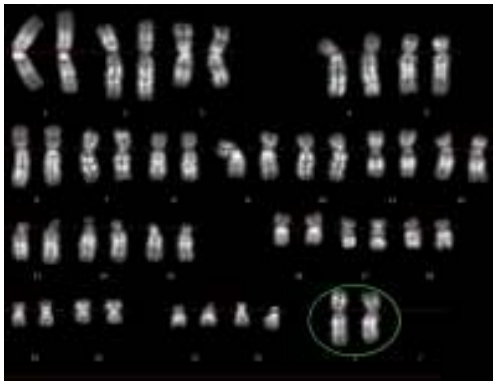
Introduction

- An XX SRY-positive testicular disorder of sex development is a rare form of sex reversal with an incidence of about 1:20,000 in newborn males
- Important cause of hypergonadotropic hypogonadism in which the diagnosis can be delayed or missed
- Such patients are unable to achieve successful conception

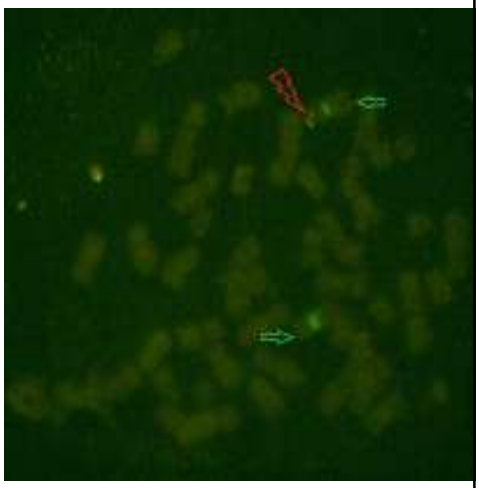
Patient Presentation

- 30-year-old man trying for five years to have a child
- Azoospermia without erectile dysfunction
- Hypergonadotropic hypogonadism
- Chromosome karyotyping in peripheral blood culture: 46,XX



Diagnosis

- Chromosome analysis showed a 46,XX karyotype
- Translocation of *SRY* gene (testis-determining factor) from chromosome Y to chromosome X was identified by fluorescence in situ hybridization (FISH)
- *SRY*: Yp11.3



Green: alpha-satellite DNA-probe for centromere of X-chromosome (*DXZ1*, Xp11.1-q11.1)
Orange: locus-specific DNA-probe for *SRY* (LSI *SRY*, Yp11.3 region)

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Treatment

- Treatment: donor sperm
- Healthy baby boy was born following IUI with donor sperm

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Conclusions

- Male patients with severe infertility of unknown origin should be routinely offered genetic counselling to avoid unnecessary diagnostic and treatment interventions
- Use of donor sperm is an appropriate option

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Introduction

- Azoospermia factor locus, which contains one or more genes required for normal spermatogenesis, has been mapped to the Yq11 region
- 7-10% of Y microdeletions cause severe oligozoospermia, and 15-20% cause idiopathic azoospermia
- Patient phenotypes with *AZFc* deletion range from moderate oligozoospermia to azoospermia, with various histologic aspects

Patient Presentation

- 35-year-old with a 31-year-old wife
- Varicocele
- FSH: 15.8 mIU/mL; Testosterone: 5.6 ng/mL
- Azoospermia (no spermatozoa found in the ejaculate after high-speed centrifugation in two samples)

Diagnosis

- Karyotype: 46,XY
- Origin of the *AZF* deletion: deletion of *AZFc*
- Testicular sperm extraction (TESE) results: Fewer than normal testicular spermatozoa present

Treatment

- As the patient had testicular spermatozoa, the couple chose ICSI with their own gametes as the first option
- PGD is usually proposed to couples in whom men have Y-microdeletion as a means to better ensure conceiving a "healthy" non-Y-microdeleted baby
- PGD is not permitted in France even in such cases, thus was not performed
- ICSI result: no implantation following fresh embryo transfer

Conclusions

- This couple should be recommended for genetic counselling
- They can either attempt a second ICSI with their own genetic material or consider sperm donation

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Case #9
Advanced Maternal Age Patient Undergoing Preimplantation Genetic Screening (PGS) Cycles

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Introduction

- Aneuploidy rate in human embryos is highly correlated with maternal age, sharply increasing when the female partner is older than 35 years
- PGS is highly recommended for infertile couples whose female partner is older than 35 years and approaching an IVF cycle
  - Especially with history of previous IVF failures and/or miscarriages

Patient Presentation

- 37-year-old woman trying unsuccessfully to conceive for three years
- No history of previous miscarriages
- Normal 46,XX karyotype without any common mutations
- Male partner has a normal 46,XY karyotype without any common mutations

Diagnosis and Treatment

- The couple was offered a PGS cycle because of advanced maternal age
- Oocyte retrieval and fertilisation conducted on day 0
- Insemination carried out by ICSI
- Embryo development carried out in a controlled environment in a time-lapse incubator slide up, to the blastocyst stage (day 5, 6, or 7 of preimplantation development)
- Checks of embryo development performed without disturbing the embryo

Diagnosis and Treatment (con't.)

- Trophectoderm biopsy was performed
- Blastocysts were vitrified soon after the biopsy in order to be singularly thawed and transferred in a natural non-stimulated cycle (only if diagnosed as euploid)
- Because comprehensive chromosome screening (CCS) looking for entire chromosomes imbalances was needed, qPCR is often selected as the diagnostic method where available

Capalbo et al. Sequential comprehensive chromosome analysis on polar bodies, blastomeres and trophoblast: insights into female meiotic errors and chromosomal segregation in the preimplantation window of embryo development. Hum. Reprod. 2013;28(2):509.518.

Outcome

- Eight cumulus-oocyte complexes were retrieved
- Six mature eggs were found and ICSI was performed
- Five oocytes were found to be fertilised on day 1
- Only one embryo reached the expanded blastocyst stage at day 7 of embryo development
  - Classified as a "good morphology" blastocyst according to criteria of Gardner and Schoolcraft[1]
  - Trophectoderm biopsy was performed and the blastocyst was vitrified soon after

1. Gardner DK, Schoolcraft WB. Culture and transfer of human blastocysts. *Curr Opin Obstet Gynecol.* 1999;11:307-311.

Outcome (con't.)

- qPCR was conducted by a referral centre and the blastocyst was found to be euploid
- Embryo transfer was performed in a natural non-stimulated cycle after blastocyst thawing
- Clinical pregnancy was verified by three hCG-positive tests
- Miscarriage occurred 13 weeks after embryo transfer

Second PGS Cycle Outcome

- In a second PGS cycle, 13 cumulus-oocyte complexes were retrieved
- ICSI was performed on the 10 mature eggs that were found
- Seven oocytes were fertilised on day 1
- Four embryos reached the expanded blastocyst stage and were classified as follows according to Gardner and Schoolcraft:[1]
  - Embryo n1: "excellent morphology" blastocyst at day 6
  - Embryo n2: "average morphology" blastocyst at day 7
  - Embryo n3: "good morphology" blastocyst at day 7
  - Embryo n4: "poor morphology" blastocyst at day 7

1. Gardner DK, Schoolcraft WB. Culture and transfer of human blastocysts. *Curr Opin Obstet Gynecol.* 1999;11:307-311.

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Second PGS Cycle Outcome (con't.)

- Trophectoderm biopsy was performed and the blastocysts were singularly vitrified soon after
- qPCR was conducted by a referral centre:
  - Embryos n1 and n4 were aneuploid (45,X0 and monosomy 10)
  - Embryos n2 and n3 were euploid
- Embryo n2 was transferred in a natural non-stimulated cycle after blastocyst thawing
- A clinical pregnancy was verified by three hCG-positive tests and is ongoing

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Conclusions

- Advanced maternal age (>35 years) is associated with a decrease in fertility rate due to increased aneuploidy rate in preimplantation embryos
- Poor-quality or developmentally slow embryos should also be tested for aneuploidy as they may be euploid and able to implant
- The failure of a PGS cycle is not predictive of the success or failure of a subsequent attempt
- qPCR is a reliable method to perform CCS for aneuploidy testing

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Introduction

- Reciprocal translocations can cause:
  - Fertility reduction
  - Spontaneous abortions and birth defects
  - Meiotic process impediment
  - Production of genetically unbalanced gametes
  - Failure of meiosis and subsequent elimination of germ cells
- If non-homologous pairing involves X and Y chromosomes during meiosis I, it will interfere with X inactivation, resulting in a lethal gene-dosage effect on the germ cells
- Interaction between translocation chromosomes and other parts of the nucleus may produce errors in meiosis and cell death

Couple Presentation

- Female partner: 32 years old with a normal 46,XX karyotype
- Male partner: 32 years old and reciprocal translocation carrier 46,XY,t(4,11)(p13;q21)
- History of four previous early miscarriages between the 5th and 10th weeks of pregnancy

Treatment

- The couple was offered a PGD cycle because of reciprocal translocation
- Oocyte retrieval and fertilisation (through ICSI) were conducted on day 0
- Embryo development was carried out in a controlled environment in a time lapse incubator, slide up, to the blastocyst stage (day 5, 6, or 7 of preimplantation development)
- Check of embryo development was performed without disturbing the embryo using a camera and time-lapse imaging system

Treatment (con't.)

- Trophectoderm biopsy was performed
- Blastocysts were vitrified soon after the biopsy in order to be singularly thawed and subsequently transferred in a natural non-stimulated cycle if euploid
- Array CGH (aCGH)* was chosen as the CCS** platform because it can detect chromosomal imbalances in the male partner

*Array Comparative Genomic Hybridisation
**Comprehensive Chromosome Screening

Outcome

- 11 cumulus-oocyte complexes retrieved
- ICSI was performed on the seven mature eggs
- Seven oocytes were fertilised on day 1
- Three embryos reached the expanded blastocyst stage and were classified on day 5 according to the criteria of Gardner and Schoolcraft:[1]
  - Embryo n1 = "excellent morphology" blastocyst
  - Embryo n2 = "good morphology" blastocyst
  - Embryo n3 = "good morphology" blastocyst

1. Gardner DK, Schoolcraft WB. Culture and transfer of human blastocysts. *Curr Opin Obstet Gynecol.* 1999;11:307-311.

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Outcome (con't.)

- Trophectoderm biopsy was performed and the blastocysts were singularly vitrified
- aCGH was conducted by a referral centre
  - Embryos number one and number two were euploid
  - Embryo number three was aneuploid (trisomy 2)
- Embryo number one was transferred in a natural non-stimulated cycle after blastocyst thawing
- A clinical pregnancy was verified by three hCG-positive tests
- A normal female infant (2890 g, 51 cm) was born 38 weeks after embryo transfer

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Conclusions

- Reciprocal translocation can cause infertility and increase spontaneous abortion rates even in young couples
- aCGH (and eventually aSNP assays) can detect the imbalances in embryos as well as other possible aneuploidies
- Application of aCGH with ICSI resulted in a healthy live birth

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Introduction

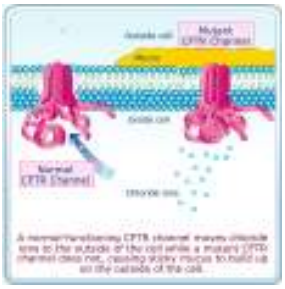
- The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene encodes an ABC transporter-class ion channel that transports chloride and thiocynate ions across epithelial cell membranes
- *CFTR* is located on human chromosome 7
  - More than 1000 mutations have been described that affect the *CFTR* gene
  - Mutations can cause two genetic disorders:
    - Congenital bilateral absence of vas deferens
    - Cystic fibrosis (CF), also known as mucoviscidosis
  - Both arise from the blockage of the movement of ions and water into and out of cells

Introduction (con't.)

- ΔF508 is the most common mutation and results from a three-nucleotide deletion (Δ) that leads to the absence of phenylalanine (F) at the 508th position on the protein
- Consequently, the protein does not fold properly and is degraded at a higher-than-normal rate
- The CFTR protein is found in the epithelial cells of many organs, such as lungs, liver, pancreas, digestive tract, reproductive tract, and skin
  - Normally, the protein moves chloride and thiocyanate ions (with a negative charge) out of epithelial cells to the covering mucus
  - Positively charged sodium ions follow these anions out of the cell, which increases the total electrolyte concentration in the mucus and results in the movement of water out of cells by osmosis

Cystic Fibrosis (CF)

- CF is an autosomal recessive genetic disorder that affects mainly the lungs, but also the pancreas, liver, and intestine
- The most important pathogenic mechanism at the basis of the disease is the abnormal transport of chloride and sodium across the epithelium, which leads to thick viscous secretions
- Breathing difficulty results from common lung infections, and other symptoms due to the effects of the disease on various parts of the body, which include:
  - Sinus infections
  - Poor growth
  - Infertility



Couple Presentation

- The couple had been trying to conceive naturally for four years before deciding to undergo an IVF cycle
- Female partner was 33 years old with a normal 46,XX karyotype, but a carrier of the R668C mutation in *CFTR*
- Male partner was 37 years old with a normal 46,XY karyotype, but a carrier of the common ΔF508 mutation in *CFTR*
- No history of previous miscarriage or IVF failures

Treatment

- The couple was offered a PGD cycle because both partners were carriers of a *CFTR* gene mutation
- Blood samples were taken from both partners to help develop probes for PGD
- Once the probes were ready, the female partner underwent a stimulation protocol
- Oocyte retrieval and insemination were conducted on day 0
- Insemination was carried out by ICSI

Treatment (con't.)

- Embryo development was carried out in a controlled environment in a time lapse incubator, slide up, to the blastocyst stage (day 5, 6, or 7 of preimplantation development)
- Checks of embryo development were performed without disturbing the embryo using a camera and time-lapse imaging system
- Trophectoderm biopsy was performed
- The blastocysts were vitrified soon after the biopsy to be singularly thawed and transferred in a natural non-stimulated cycle only if diagnosed as normal or as a carrier of a single *CFTR* mutation
- PCR was chosen to screen the embryos for mutations in the *CFTR* gene either in heterozygous or homozygous

Outcomes

- 20 cumulus-oocyte complexes were retrieved
- 14 mature eggs were found, and ICSI was performed
- 11 oocytes were found to be fertilised on day 1
- Seven embryos reached the expanded blastocyst stage:
  - Embryos n1, n9, and n10 on day 5
  - Embryos n2, n3, n6, and n11 on day 6
- Trophectoderm biopsy was performed and the blastocysts were singularly vitrified soon after

Outcomes (con't.)

- PCR was conducted by a referral centre
  - Embryos n3, n6, and n11 were normal
  - Embryos n1 and n10 were carriers
  - Embryos n2 and n9 were affected
- Embryo n3 was transferred in a natural non-stimulated cycle after blastocyst thawing
- A clinical pregnancy was verified by three hCG-positive tests; the pregnancy is ongoing

Conclusions

- An infertile couple requiring an IVF/ICSI cycle needs to undergo screening for the most common causative disease mutations, including those that cause CF
- If both partners are carriers of a causative mutation, PGD is highly recommended
- Blood samples from both partners are obtained to help prepare the probes
- PCR can detect mutations in the embryos produced in either heterozygous or homozygous
- However, PCR does not detect aneuploidies; thus PGS should be performed

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Introduction

- Endometrial cancer is a leading gynecological cancer
- About 5% of cases are in patients <40 years who are potentially interested in preserving childbearing options
- Endometrial cancer is classified as:
  - Hormone dependent (type 1, endometrioid type): majority of cases
  - Hormone-independent (type 2, papillary serous or clear cell type)
- For patients not opting for fertility preservation, the standard treatment is surgery with hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymph nodes dissection, and/or omentectomy

Patient Presentation

- 30-year-old female, G0P0, BMI 26, with primary infertility for two years and irregular menstrual cycles (hypermenorrhea and menorrhagia)
- Family history was non-contributory and husband had a completely normal semen analysis
- Physical and bimanual pelvic exams were normal
- Transvaginal ultrasound exam (cycle day 12) revealed a thick endometrial stripe (18 mm)

Endometrial Cancer - Ultrasound Features

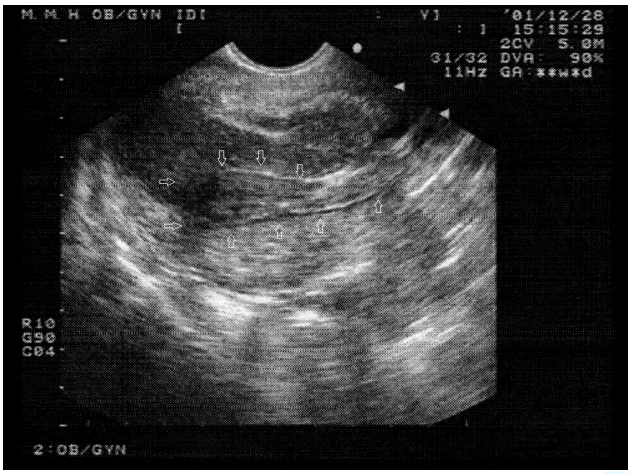


Photo courtesy of Dr. M. Azodi, Yale Gynecologic Oncology

Patient Presentation (con't.)

- Endocrine laboratory tests (FSH, LH, AMH, TSH, PRL) were normal, but the absence of luteal progesterone confirmed anovulatory cycles
- Hysteroscopy with D&C was carried out and the pathology findings were consistent with endometrioid adenocarcinoma, architecture grade 1, nuclear grade 1
  - The cancer tissue was immunoreactive for oestrogen and progesterone receptors
- MRI revealed no distant or local metastases

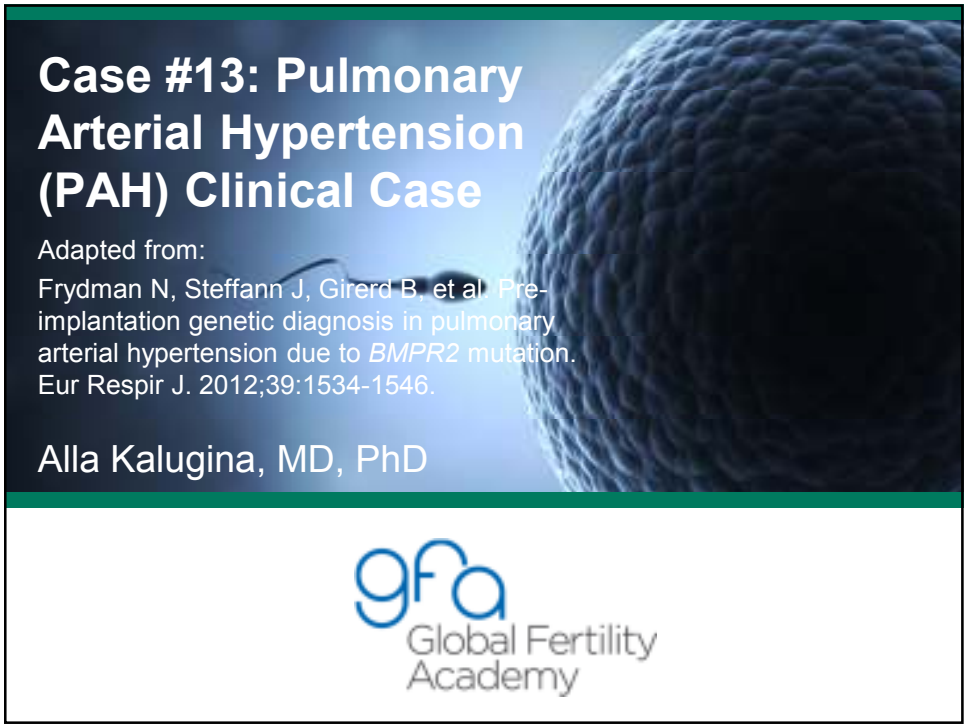
Treatment

- To preserve the patient's fertility, treatment with continuous high-dose megestrol acetate was started
- Endometrial re-biopsies were performed at one, two, and three months after starting megestrol
- Complete cancer remission was documented at the one-month biopsy, but treatment was continued for four months
- After the third negative D&C, clomiphene citrate was used to induce ovulation
  - The patient achieved a total of three pregnancies (one miscarriage and two term deliveries)

Conclusions

- The pathogenesis of type 1 endometrial cancer is believed to be due to excessive unopposed exposure of oestrogen
  - Endometrial atypical hyperplasia is generally the pre-cancer lesion
- In young women, conservative hormone therapy with progesterone is effective in reversing endometrial hyperplasia or well-differentiated cancer without myometrial or cervical invasion (by MRI)
- Alternatives to megestrol include:
  - Medroxyprogesterone acetate
  - Levonorgestrel IUD

1. Sala E, Wakely S, Senior E, Lomas D. MRI of malignant neoplasms of the uterine corpus and cervix. *AJR Am J Roentgenol.* 2007;188:1577-1587.
2. American Cancer Society. Cancer facts and figures 2012. American Cancer Society website. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf.
3. Kim MK, Yoon BS, Park H, et al. Conservative treatment with medroxyprogesterone acetate plus levonorgestrel intrauterine system for early-stage endometrial cancer in young women: pilot study. *Int J Gynecol Cancer.* 2011;21:673-677.
4. Kesterson JP, Fanning J. Fertility-sparing treatment of endometrial cancer: options, outcomes and pitfalls. *J Gynecol Oncol.* 2012;23:120-124.



Introduction

- Pulmonary arterial hypertension (PAH) is a rare and severe condition
- May be familial/heritable
- Consists of progressively debilitating symptoms and carries high mortality
- Familial PAH is an autosomal dominant trait with offspring having a 50% chance of inheriting the disease allele

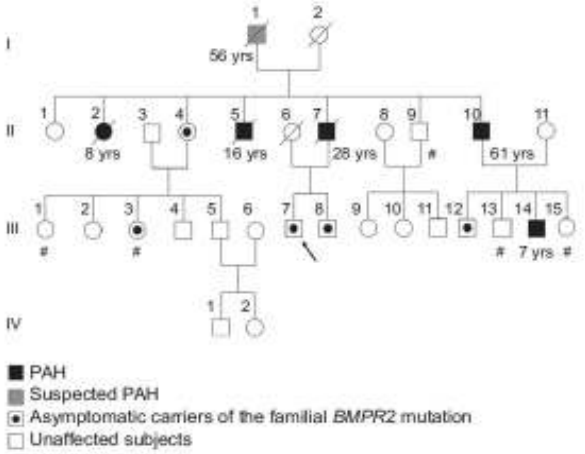
Introduction (con't.)

- Recent finding: mutations in the bone morphogenetic protein receptor 2 gene (*BMPR2*) in 70–80% of familial cases
- *BMPR2* mutations: incomplete but variable penetrance
  - 10–20% of mutation carriers develop PAH
  - This can be much higher in some families
- Genetic anticipation phenomenon in familial PAH
  - Increased risk in children and young adults

Patient Presentation

- A couple was referred for PGD
  - Extensive family history of PAH
  - Cause: *BMPR2* mutation

Family Tree of the Subject for PGD



#: noncarriers of the familial *BMPR2* mutation
Age in years correspond to age at PAH diagnosis

Diagnosis

- Husband's father (II.7)
  - Diagnosed with PAH at 28 years of age
  - Died 11 years later despite lung transplantation
- An aunt (II.2) and an uncle (II.5) had fatal paediatric PAH (death at 13 and 16 years of age, respectively)
- Another uncle (II.10) and his son (III.14) had severe PAH diagnosed at 61 and 7 years of age, respectively

Diagnosis (con't.)

- Grandfather (I.1) had sudden death at 56 years of age, presumably from PAH
- Husband (III.7) is a *BMPR2* mutation carrier with no clinical or echocardiographic PAH
- Genetic tree analysis: high *BMPR2* mutation penetrance in this family
- The future mother had no personal or familial history of PAH

Treatment

- 20 oocytes were harvested for ICSI
- 12 embryos obtained, seven of which were suitable for biopsy
- Genetic analysis was performed on two blastomeres for each embryo
  - Two embryos were unaffected
  - Five embryos were *BMPR2* mutation carriers
- An unaffected embryo was implanted
- Outcome was a successful pregnancy resulting in a healthy child not carrying a *BMPR2* mutation

Conclusion

- PGD may be considered in selected families with familial/heritable PAH, which still remains a dramatic and incurable disease

Module Summary

- The case studies presented in this module have demonstrated the useful application of IVF
- IVF has enabled successful pregnancies in women who would have otherwise not conceived

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