Genetics Aspects of Male infertility

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Introduction

- Etiology of infertility
- Female Factor
- Male factor
- Combination of M & F
- Unexplained infertility
• 15% of couples do not achieved pregnancy after one year of sexual intercourse & at the end of their reproductive life, 2-7% of couples remain childless
• Male factor infertility accounts for about half the cases of couple infertility.
• Up to 40% of MF the etiology remains unknown (de Kretser, 1997).

• These cases of idiopathic MF the question arises whether these could be explained by genetic factors
Genetics of male factor infertility (MF)

- MF & Chromosomal abnormalities
- MF & the Y chromosome
  - *microdeletions of the Y chromosome*
- MF & autosomal or X-linked monogenic disorders
- MF & candidate genes; mouse models
- MF & multifactorial
Genetics of male factor infertility (MF)

- Frequency of **chromosomal aberrations** range from
- 2.2% in subfertile men (*sperm count* > $20 \times 10^6$/ml)
- 6.0% oligozoospermia (*sperm count* < $20 \times 10^6$/ml)
- 19.6% azoospermia
- in total 4.2 up to 21%
- The aberrations include numerical & structural abnormalities of the sex ch. & structural ab. of autosome
chromosomal abnormalities

Type of chromosomal abnormality

Numerical
- 10

Structural
- 6
Klinefelter Syndrome:
47,XXY, n=5
47,XXY/46,XY, n=4
47,XXYY n=1

46XY, dup; (4)(q31.1;q32)
46,XY,del(13)(p)
46,XY,del 13p
46,XY/47,XY,+8 del (8)(pter)
46,XY,t7;14(10p;10q)
NVP:
13, 21, Y( pst+/pst-),(pstk+-/)
Inversion 9, Y qh+/-
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of egg</th>
<th>No. of embryo</th>
<th>No. of Cycle</th>
<th>βhCG</th>
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</thead>
<tbody>
<tr>
<td>Normal K</td>
<td>5±1.3</td>
<td>2±0.7</td>
<td>17/105</td>
<td>17/105 (16.2%)</td>
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<tr>
<td>Abnormal K</td>
<td>5±1.6</td>
<td>1.8±0.8</td>
<td>1/16</td>
<td>1/16 (6.25%)</td>
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<tr>
<td>χ²</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td></td>
<td>&lt;0.01</td>
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SMK, Lusan, 2010
Genetics of male factor infertility (MF)

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- MF & multifactorial

Azoospermic Factor (AZF), located on the Y ch.
- There are 4 distinct AZF loci in the region q11 of Y ch.
- Most of these deletions map to Yq11.23 (Yq5 & 6) on the long arm of Y ch.
Sex determination factor

Spermatogenesis
AZF gene deletions

- AZFa: certoli cell only syndrome
- AZFb: spermatogenenic arrest at the pachytene spermatocyte stage
- AZFc: spermatogenenic arrest at the spermatid stage
- AZFd: mild oligospermia or even normal sperm count with abnormal sperm morphology
STS primers

• For AZFa: sY84, sY86
• For AZFb: sY127, sY134
• For AZFc: sY254, sY255 (both in DAZ gene)
• SRY gene (TDF)
• ZFY gene
Treatment of MF

- Assisted reproduction techniques such as IVF and ICSI alone, or in association with testicular sperm retrieval, represent an efficient therapy for these patients.
• However the potential of these techniques (PESA, TESE, injection of spermatid,..) to transmit genetic defects causing male infertility raises the need for a systematic genetic screening and genetic counseling of these patients.
Intracytoplasmic Sperm Injection (ICSI) – What are the risks?

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Abstract

In vitro fertilization (IVF) used in combination with intracytoplasmic sperm injection (IVF/ICSI) allows otherwise sterile couples to become parents. Despite the fact that the oldest IVF conceived baby\textsuperscript{1} is now over 30 years of age, questions about the safety of assisted reproductive technologies persist. The long term follow-up of the first generation of IVF/ICSI offspring offers a clearer picture of the safety of these technologies; despite these recent studies, however, there is still only an incomplete picture of the risks associated with the usage of these assisted reproductive techniques (ART) to offspring. The risk of multiple gestation continues to be of major concern because of its association with low birth weight, preterm delivery and increased perinatal mortality. Other ART outcomes typically assessed include: 1) congenital abnormality 2) developmental delay or abnormality 3) hormonal dysfunction 4) epigenetic effect. Existing maternal or paternal factors may confound any analysis of ART and spontaneous conception cohorts making it difficult to draw firm conclusions. This review outlines the risks associated with IVF/ICSI as a well defined treatment for couples with severe male factor infertility. Importantly, no discussion of the risks associated with IVF/ICSI can be conducted outside of the context of the existing IVF safety data. As such, both the safety of IVF and IVF/ICSI are considered here. Overall, the total body of data points to the conclusion that ICSI conceived children are at a higher absolute risk of the following conditions: 1) multiple gestation and its associated sequelae, 2) congenital defects (in particular genitourinary defects), and 3) epigenetic syndromes (such as Beckwith Wiedemann). Nevertheless, the absolute incidence of these events remains rare.
Infertility, infertility treatment, and congenital malformations: Danish national birth cohort

Jin Liang Zhu, Olga Basso, Carsten Obel, Camilla Bille, Jørn Olsen

Abstract

Objectives To examine whether infertile couples (with a time to pregnancy of >12 months), who conceive naturally or after treatment, give birth to children with an increased prevalence of congenital malformations.

Design Longitudinal study.

Setting The Danish Medical Birth Registry, from 1973 to 1998.

Participants 1,887,471 births, of whom 1,04,806 were to infertile couples.

Main outcome measures Prevalence of congenital malformations in infants born to infertile couples, compared with naturally conceived infants.

Results The prevalence of congenital malformations was not different in the infertile group compared with the naturally conceived group.

Conclusions Infertile couples do not appear to be at increased risk of giving birth to infants with congenital malformations.
Conclusion: The observed frequency of Y-chromosome microdeletions was 6.2% among Japanese azoospermic and oligozoospermic males; no microdeletions were identified among our African study patients. In this population of couples undergoing IVF+ICSI, there was no statistically significant difference in embryo characteristics or pregnancy outcome between patients with Y-chromosome microdeletion and those with an intact Y-chromosome.
• The results indicate that men with poor semen quality may have an increased risk for meiotic non-disjunction

• it has been showed an increased risk of mild delays in development in ICSI children (Brown, 1998)

• Data on follow-up of the “ICSI children” are not yet available.
Single Gene disorders
GENETIC DISORDERS IN INFERTILITY

- **Chromosomal abnormalities**
  - Sex chromosome abnormalities (Klinefelter’s syndrome and variants [47,XXY; 46,XY/47, XXY mosaicism])
  - Autosomal abnormalities
  - Sperm chromosomal abnormalities

- **Gene defects**
  - *X*-linked genetic disorders and male fertility
  - *Kallmann syndrome*
  - *Mild androgen insensitivity syndrome*
  - *Y*-chromosome and male infertility
  - *Y-chromosome: ‘gr/gr’ deletion*
  - Cystic fibrosis mutations and male infertility
  - Unilateral or bilateral absence/abnormality of the vas and renal anomalies

- **Unknown genetic disorders**
- **DNA fragmentation in spermatozoa**
- **Genetic counseling and ART, ICSI**
Conclusions and Recommendations for Genetic disorders in male infertility
Conclusions

New insights into the genetic basis of infertility and the advent of ICSI require a good understanding of genetics by clinicians and the general public.

Diagnostic advances will allow us to identify the genetic basis of more disorders and diagnose known disorders at a lower cost. For some of these disorders, gene therapy might be practical in the future.

In men with spermatogenic damage there is a higher prevalence of chromosome abnormalities reaching the highest frequency in NOA men.

AZF deletions are clear-cut causes of spermatogenic impairments with diagnostic and prognostic value for TESE.

AZF deletion will be obligatorily transmitted to the son.

gr/gr deletion has been confirmed as a significant risk factor for impaired sperm production, whereas further evidence of the prognostic significance of gr/gr and development of a testicular germ cell tumour is needed.
## II- Recommendations

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<td>From a diagnostic view point, standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa &lt; 10 million/mL) who are seeking fertility treatment by IVF.</td>
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<td>Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.</td>
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<td>All men with Klinefelter's syndrome need long-term endocrine follow-up and usually require androgen replacement therapy.</td>
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<td>Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.</td>
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<td>Men with severely damaged spermatogenesis (spermatozoa &lt; 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling.</td>
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<td>If complete AZFa or AZFb microdeletions are detected, micro-TESE should not be performed because it is extremely unlikely that any sperm will be found.</td>
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<td>If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.</td>
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<td>When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.</td>
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*IVF = in vitro fertilisation; OA = obstructive azoospermia; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction; CF = cystic fibrosis.*