


**ESHRE Andrology Campus Course**  
**Reproductive Andrology**  
**Brussels 8-10 November 2007**


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**To treat the man or his sperm? When to treat the man?**  
 Conventional non-surgical treatment of male infertility

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 European Academy of Andrology Training  
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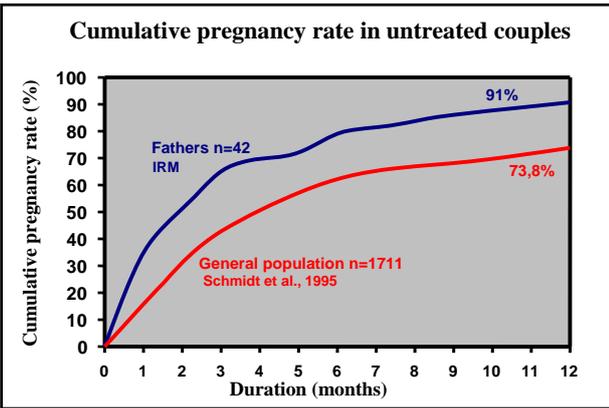
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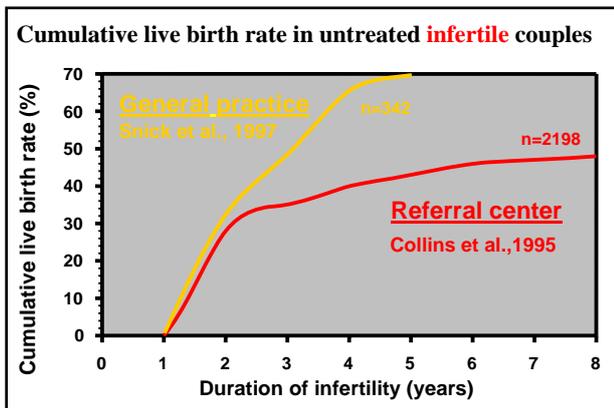
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### Effectiveness of treatment

"Treatment effectiveness can be judged fairly only in randomized clinical trials, because conception without therapy can occur in most infertile couples over time."

The ESHRE Capri workshop 1996. Guidelines to the prevalence, diagnosis, treatment and management of infertility. Hum. Reprod. 11: 1775 - 1807, 1996

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Walcheren prediction model of live birth among untreated subfertile couples, seeking reproductive health care for the first time. Snick et al., Hum. Reprod. 12: 1582-88, 1997

| Expectant management | Average baseline prognosis of live birth (%) |
|----------------------|--|
| 3 Months             | 13.0   |
| 6 Months             | 18.9   |
| 12 Months            | 27.4   |
| 24 Months            | 41.9   |
| 36 Months            | 46.2   |

| Prognostic multiplication factor (MF) | Effect on the baseline prognosis |
|---------------------------------------|----------------------------------|
| Prior pregnancy in partnership        | 1.5                              |
| Duration of infertility <24 months    | 1.5                              |
| Female age < 30 years                 | 1.4                              |
| Male sperm defect (WHO)               | 0.6                              |
| Ovulation defect                      | 0.4                              |
| Tubal defect                          | 0.1                              |

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**Example estimation for the Walcheren Prediction model**

Example Couple A:

Couple with primary infertility of 1 year duration (MF 1.5); female partner aged 24 years (MF 1.4); man with moderate (12.2 Mill/ml) oligozoospermia (MF 0.6)

Example Couple B:

Couple with secondary infertility (MF 1.5) of 2.5 year duration; female partner aged 34 years with ovulation defect (MF 0.4); man with moderate (12.2 Mill/ml) oligozoospermia (MF 0.6)

| Expectant management | Prognosis of live birth (%)     |                                 |
|----------------------|---------------------------------|---------------------------------|
|                      | Couple A                        | Couple B                        |
| 3 Months             | $13.0 * 1.5 * 1.4 * 0.6 = 16.4$ | $13.0 * 1.5 * 0.4 * 0.6 = 4.7$  |
| 6 Months             | $18.9 * 1.5 * 1.4 * 0.6 = 23.8$ | $18.9 * 1.5 * 0.4 * 0.6 = 6.8$  |
| 12 Months            | $27.4 * 1.5 * 1.4 * 0.6 = 34.5$ | $27.4 * 1.5 * 0.4 * 0.6 = 9.9$  |
| 24 Months            | $41.9 * 1.5 * 1.4 * 0.6 = 52.8$ | $41.9 * 1.5 * 0.4 * 0.6 = 15.1$ |
| 36 Months            | $46.2 * 1.5 * 1.4 * 0.6 = 58.2$ | $46.2 * 1.5 * 0.4 * 0.6 = 16.6$ |

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**Classification of treatments for male infertility**

- No therapy
  - Normal examination results
  - Complete Sertoli Cell Only syndrome
  - Anorchia
- Preventive therapy
  - Maldescended testes
  - Cryopreservation of sperm

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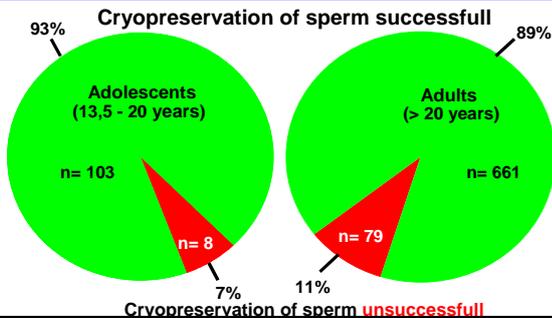
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**Cryopreservation of semen samples in patients with malignant diseases**

Kamischke et al. J. Androl. 25: 586- 592, 2004




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**Pregnancies from cancer patients with artificial reproduction techniques and use of cryopreserved semen samples**

**Intrauterine insemination (IUI)**

- total: 467 patients, 1631 cycles, 124 pregnancies
- pregnancy rate per couple: 27%
- pregnancy rate per cycle: 8%

**In-Vitro-Fertilisation (IVF)**

- total: 69 patients, 96 cycles, 31 pregnancies
- pregnancy rate per couple: 45%
- pregnancy rate per cycle: 32%

**IntraCytoplasmatic Sperm Injection (ICSI)**

- total: 46 patients, 71 cycles, 29 pregnancies
- pregnancy rate per couple: 63 %
- pregnancy rate per cycle: 41%

modified from Sanger et al., 1992; Kelleher et al., 2001 and IRM

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  - Cryopreservation of sperm
- Rational therapy
  - Infections / Obstructions of the genital tract
  - Secondary hypogonadism
  - Anejaculation / retrograde ejaculation

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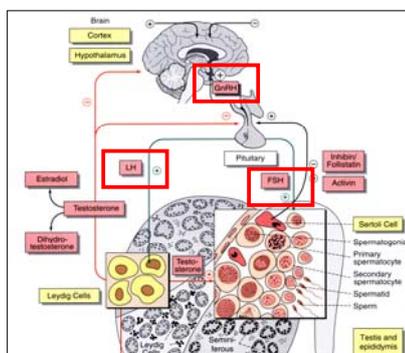
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Nieschlag & Behre, Andrology, Male reproductive health and dysfunction, Springer, 2000

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**Induction of spermatogenesis in patients with secondary hypogonadism**

| Treatment                                       | Route of application        | Dose                                |
|---|-----------------------------|-------------------------------------|
| GnRH pulsatile                                  | s.c. via external mini-pump | 5- 20 ug per puls every 120 minutes |
| <b>AND/OR</b>                                   |                             |                                     |
| human chorionic-gonadotropin (hCG)              | s.c. or i.m.                | 1000- 2500 IU<br>2 times /week      |
| <b>+</b><br>human menopausal-gonadotropin (hMG) | s.c. or i.m.                | 150 IU<br>3 times /week             |

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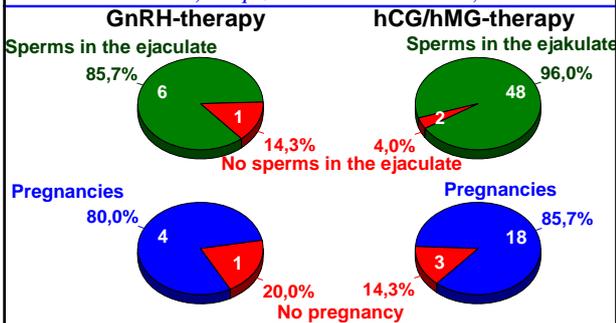
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**Effectiveness of GnRH or hCG/hMG therapy in patients with secondary hypogonadism**

*Büchter et al., Europ. J.Endocrinol. 139: 298-303, 1998*




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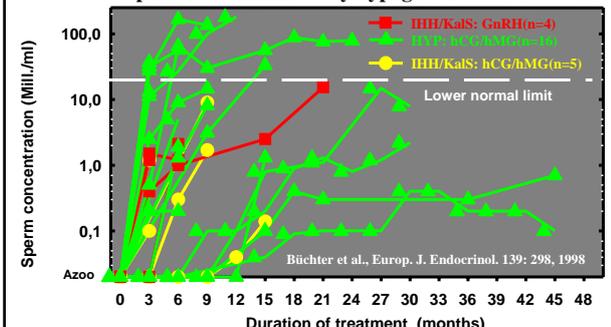
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**Development of sperm concentrations until induction of pregnancy after treatment with gonadotropins or GnRH in patients with secondary hypogonadism**




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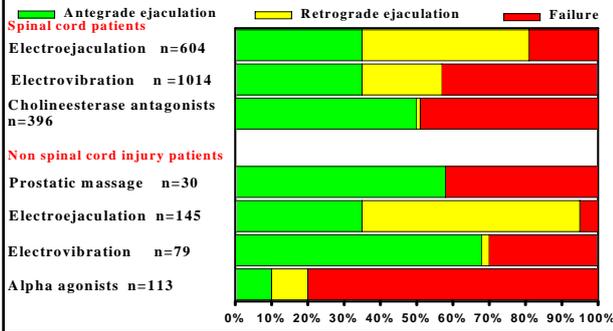
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### Comparison of treatments for anejaculation therapy

Kamischke & Nieschlag, Int. J. Androl. 25: 333, 2002




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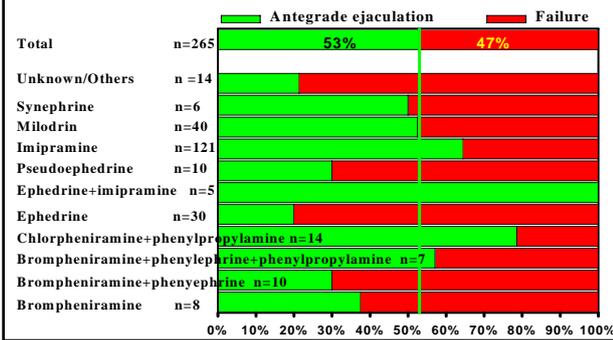
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### Efficacy of drugs used to reverse retrograde ejaculation

Kamischke & Nieschlag, Int. J. Androl. 25: 333, 2002




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### Classification of treatments for male infertility

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  - Cryopreservation of sperm
- Rational therapy
  - Infections / Obstructions of the genital tract
  - Secondary hypogonadism
  - Anejaculation /retrograde ejaculation
- Empirical therapy
  - Immunological therapy
  - Varicocele
  - Idiopathic infertility

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**Aulus Cornelius Celsus**  
C. 25 B.C. - 50 A.D.

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### History of varicocele treatment

|            |   |
|------------|---|
| 23-35 A.D. | Celsus first detailed report of a varicocele and its operative therapy.                           |
| 1856       | Curling suggested a relationship between infertility and varicocele.                              |
| 1885       | Barwell reported a pregnancy after varicocelectomy.   |
| 1942       | Bernadi introduced the supravaginal operation technique.  |
| 1977/80    | Sclerosing and embolization of the spermatic vein were introduced.                                |
| 1979       | First randomized controlled clinical efficacy trial on varicocelectomy from Nilsson et al.        |
| 1986       | According to McClure and Hricak varicocelectomy is the most common operation for male infertility |

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### Characteristics of randomized controlled studies

Laven et al., 1992; Paduch et al., 1997;  
**Major criticism: Adolescents, not infertile; no pregnancy rates**

Nilson et al.; 1979; Breznik et al., 1993; Yamamoto et al., 1996;  
**Major criticism: Female factors might have been overlooked as many men had normozoospermia or normal sperm concentration**

Magdar et al., 1995; Grasso et al., 2000; Unal et al., 2001  
**Major criticism: Unexplained low pregnancy rates in the treatment groups, Unal et al. 2001: clomiphene citrat treated control group**

Hargreave et al., 1997;  
**Major criticism: Several protocol violations, high loss to follow up**

Nieschlag et al., 1998;  
**Major criticism: Drop out rate 38%**

Krause et al., 2002;  
**Major criticism: More than 50% lost in follow up, treatment crossovers**

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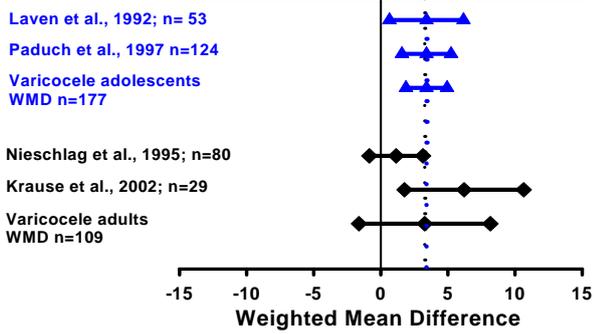
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### Testicular volume weighted mean differences of varicocele treatment based on controlled, randomized trials




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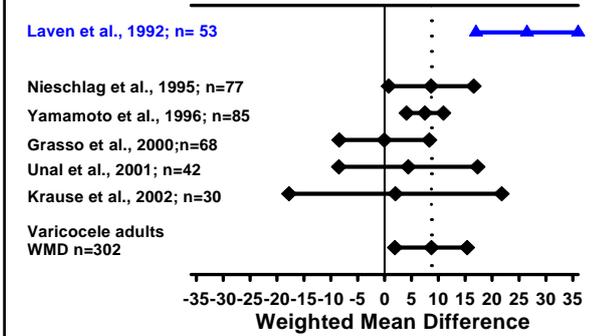
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### Sperm concentration weighted mean differences of varicocele treatment based on controlled, randomized trials




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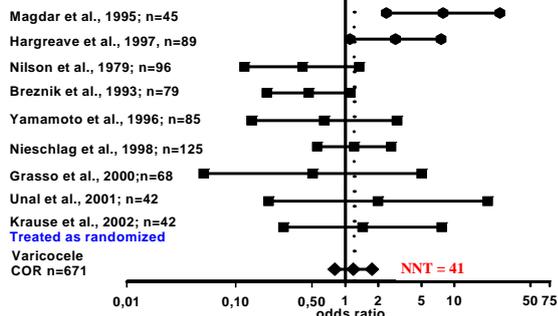
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**Pregnancies odds ratios of varicocele treatment based on truly randomized controlled clinical trials**



Modified from: Kamischke and Nieschlag, Hum. Reprod. Update 7: 65-9, 2001

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**Pregnancy rates in the treatment and control groups of the randomised, controlled clinical trials for varicocelectomy**

| Study;                  | n     | Follow up (months) | Treatment pregnancy | Control pregnancy |
|-------------------------|-------|--------------------|---------------------|-------------------|
| Magdar et al., 1995;    | n=45  | 12                 | 60 %                | 10%               |
| Hargreave et al, 1997;  | n=89  | 12                 | 35 %                | 16%               |
| Nilson et al;1979;      | n=96  | 53                 | 8 %                 | 18%               |
| Breznik et al., 1993;   | n=79  | 48                 | 34 %                | 54%               |
| Yamamoto et al., 1996;  | n=85  | 12                 | 6 %                 | 10%               |
| Nieschlag et al., 1998; | n=125 | 12                 | 29 %                | 25%               |
| Grasso et al., 2000;    | n=68  | 12                 | 3 %                 | 6%                |
| Unal et al., 2001       | n=42  | 15                 | 12,5%               | 6,5%              |
| Krause et al., 2002;    | n=42  | 12                 | 20 %                | 15%               |

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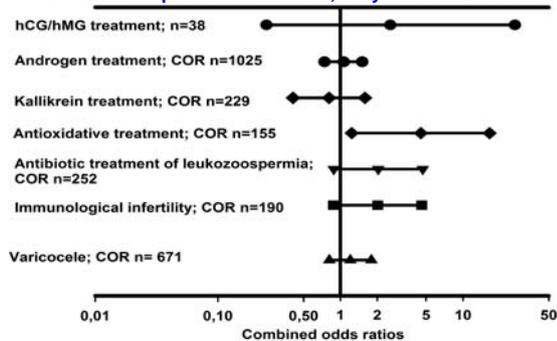
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**Pregnancy odds ratios of infertility treatments based on individual or combined placebo controlled, truly randomized trials**



Update von Kamischke & Nieschlag, Hum. Reprod. 14 (Suppl. 1): 1, 1999

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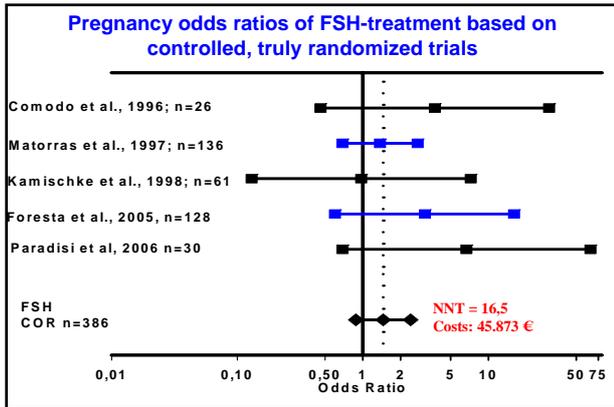
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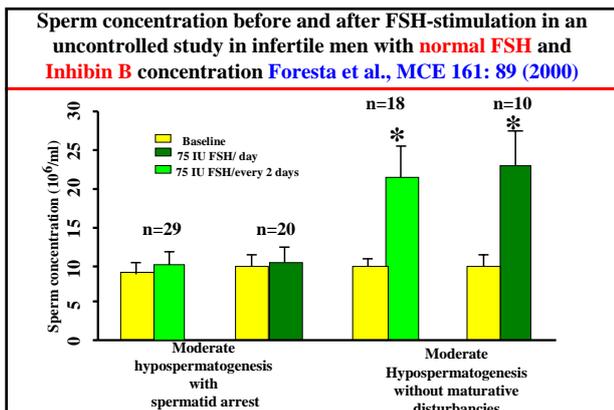
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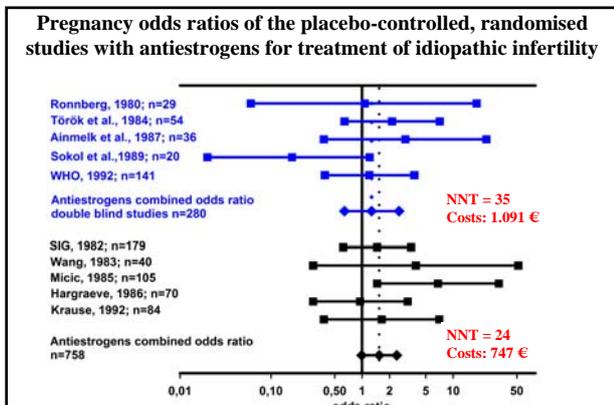
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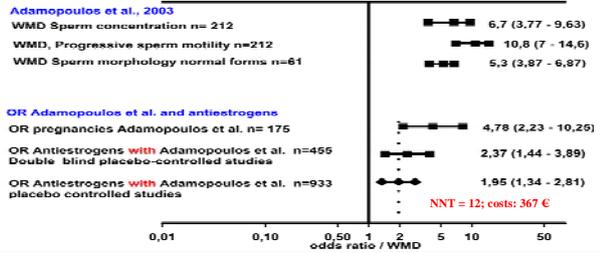
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**Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia**

Adamopoulos et al. Fertil. Steril. 80: 914, 2003

**Design:** Prospective, randomized, placebo-controlled trial

**Treatment:** Tamoxifen citrate, 20 mg/d, and testosterone undecanoate, 120 mg/d or placebo treatment for 6 months.




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**Classification of treatments for male infertility**

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  - Cryopreservation of sperm
- Rational therapy
  - Infections / Obstructions of the genital tract
  - Secondary hypogonadism
  - Anejaculation /retrograde ejaculation
- Empirical therapy
  - Varicocele
  - Idiopathic infertility
  - Immunological therapy
- Symptomatic therapy
  - Severe fertility disturbances

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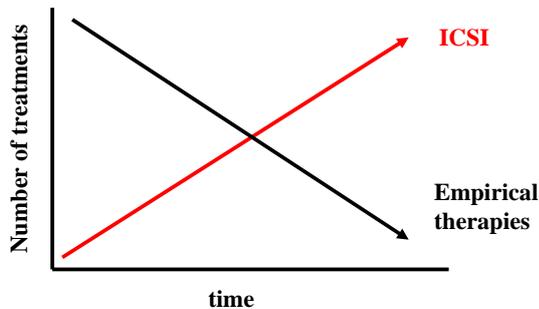
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**Therapy of male infertility in the age of „Evidence-based Medicine“**




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