DOES VARICOCELECTOMY RESULT IN MORE SPONTANEOUS PREGNANCIES?

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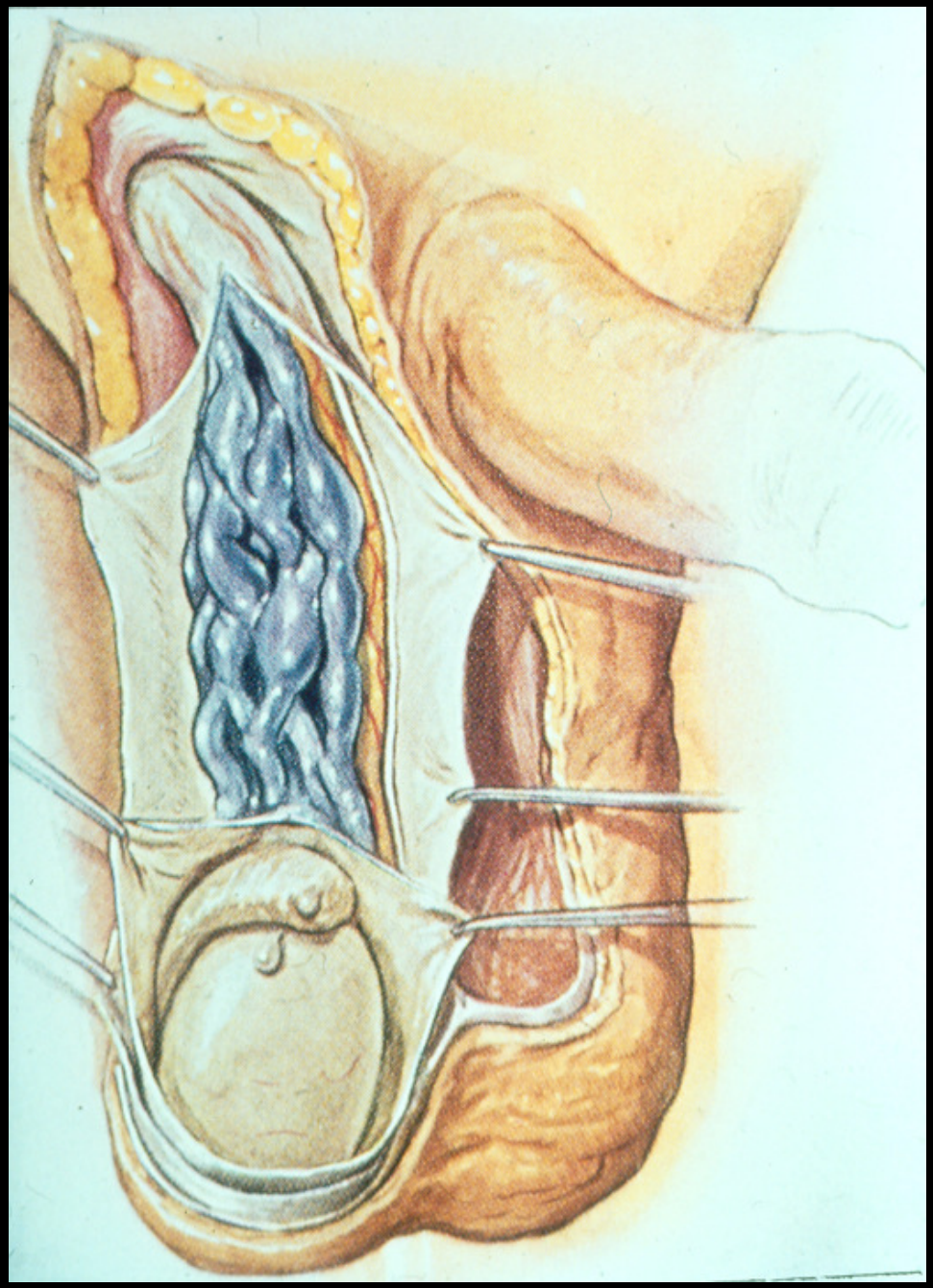
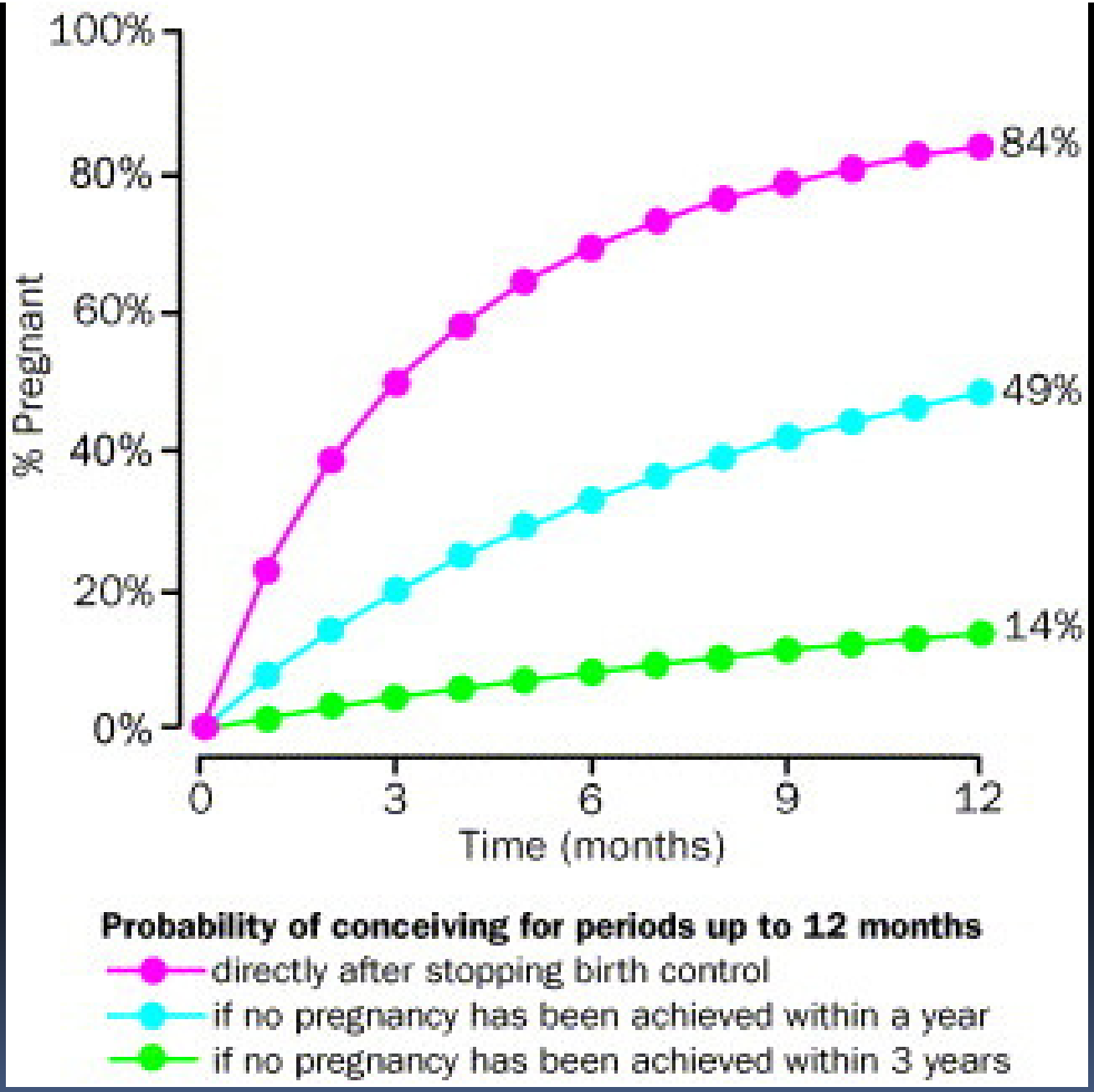


Some facts about varicoceles

- 11% of men with normal sperm count have a varicocele, 25% of subfertile men have a varicocele (WHO 1992)
- Most men with a varicocele have no problems achieving spontaneous pregnancy
- Profylactic treatment is only advised in case of documented growth deterioration of the testis or in case of impaired semen quality
- After treatment 85% of these men will show an improvement of their semen quality.
- Spontaneous pregnancies after varicocele treatment is observed in 25-35% of the couples within one year
- Treatment usually has little influence on hormonal parameters.



From: te Velde E. et. al., Lancet 2000;355:1928-29

RECOMMENDATIONS

Treatment of male infertility

Dohle GR et. al. EAU guidelines on male infertility 2005

- *Infertility treatment should not start before 2 years of unprotected intercourse, unless there are gross abnormalities found that exclude spontaneous pregnancy, such as azoospermia or extreme oligozoospermia, anovulation and tubal blockage.*

- *In case of female age >35 years treatment should start after 1 year.*

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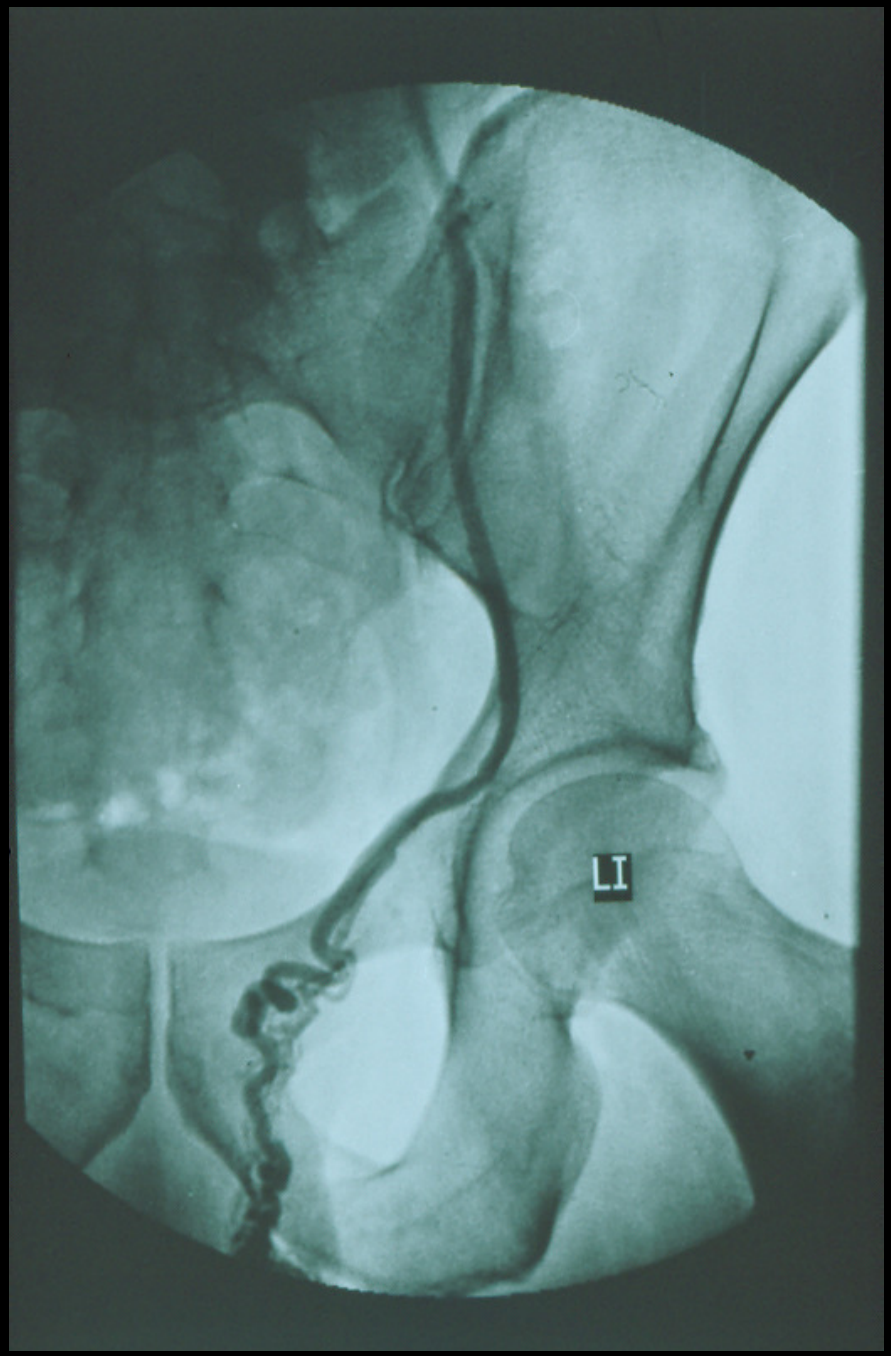
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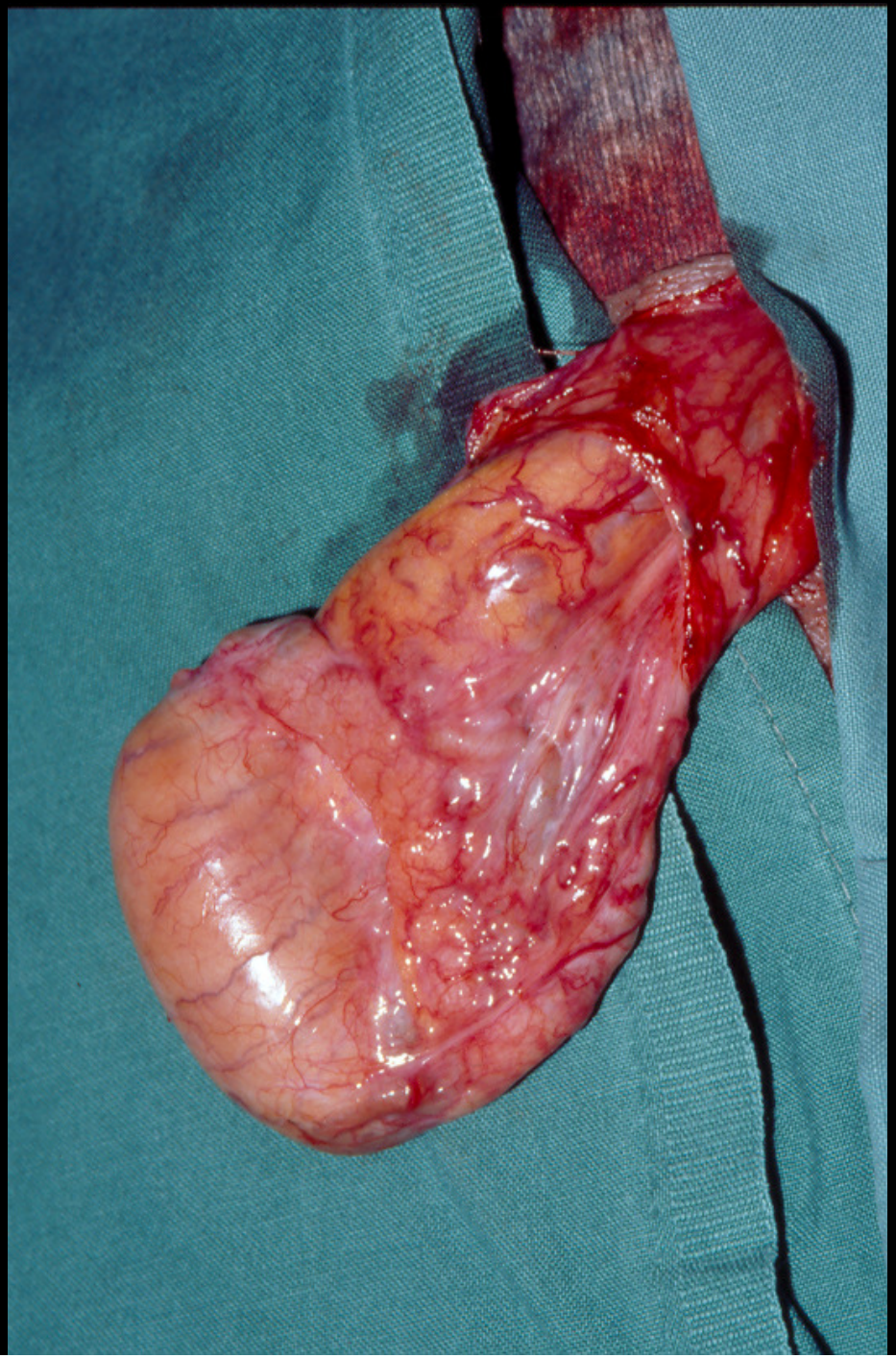
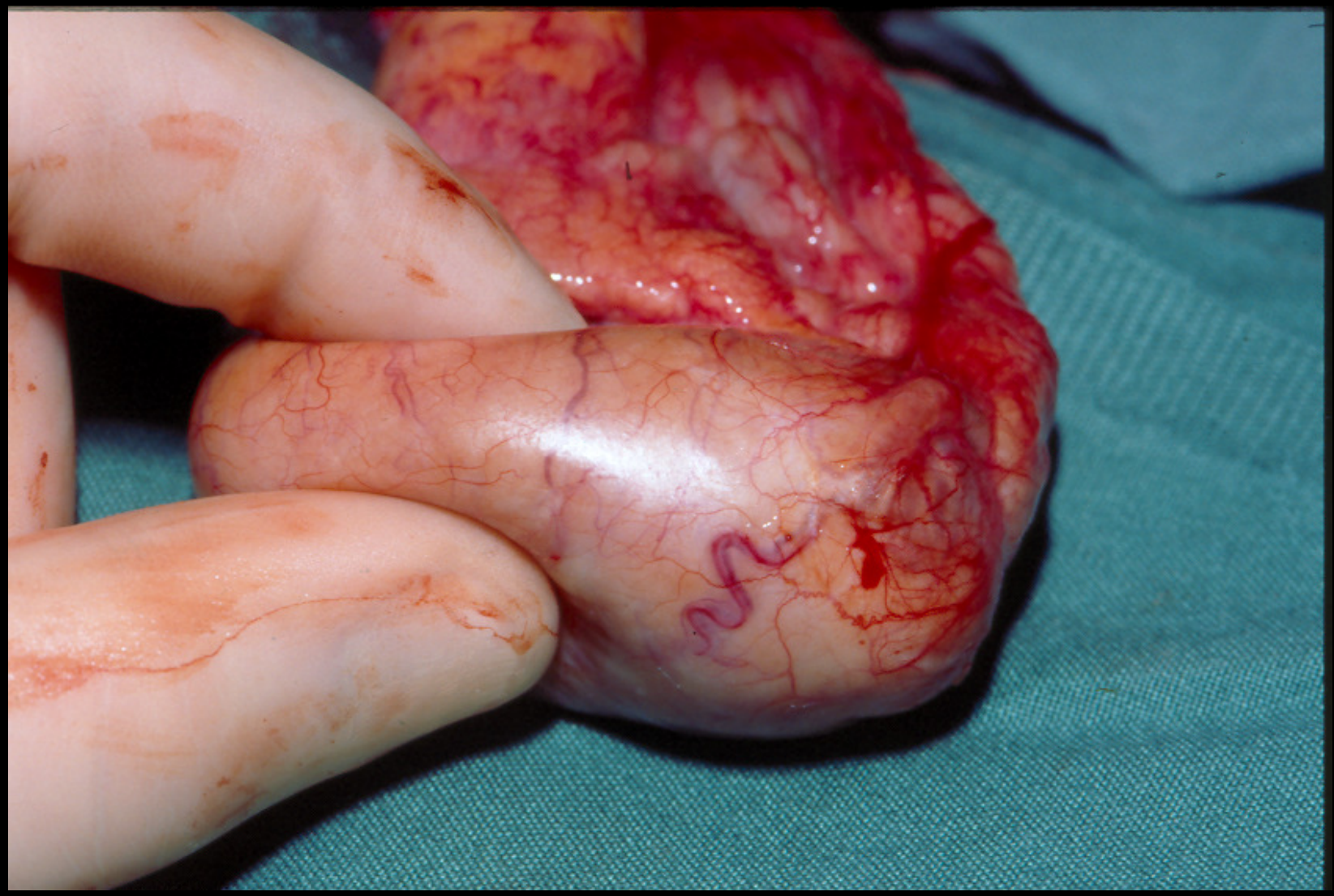




Treatment results in retrospective studies

- Dubin and Amelar (1977): 986 operations, 53% pregnancies, follow-up of 5 years, 30% within one year
- Aafjes and v.d. Vijver (1985): 38% pregnancies in oligospermic men after 2 years, but no benefit in normospermic men compared to controls (32% versus 20% inj controls)
- Other non-randomised studies also did not show any benefit in varicocele treatment in normospermic men over non-treatment (Nilsson, Baker, Rodriguez, Cokett, Breznik).

Treatment Results prospective studies

- Nieschlag et al., (1998):
  - Randomisation in treatment versus counselling, 120 couples.
  - Sperm concentration improved in the treatment group from 16 -> 24 million/ml.
  - In the treatment group pregnancies occurred in 29% versus 25% in the counselling group (non-significant).

- WHO-study (Hargreave et al, 1996):
  - Randomisation in immediate treatment or delayed treatment after 1 year (controls), 260 couples.
  - Sperm concentration improved from 16 -> 25 Million/ml in the immediate treatment group.
  - Pregnancies: 34,8% in the immediate treated group versus 16.7% pregnancies in the control group (significant).

Subclinical varicocele – Yamamoto et al J Urol 1996 155:1636-38

- 85 patients with a subclinical varicocele randomized for treatment or no treatment
- Sperm improvement was found only in the treated group: concentration improved from 15 million/ml to 21 million/ml
- No difference in pregnancy rates between the treatment group (6,7%) and the controls (10%)
- Conclusion: Treatment of a subclinical varicocele has no benefit for the couple.
- Similar results reported from 2 other studies (Grasso et.al. en Unal et al.)

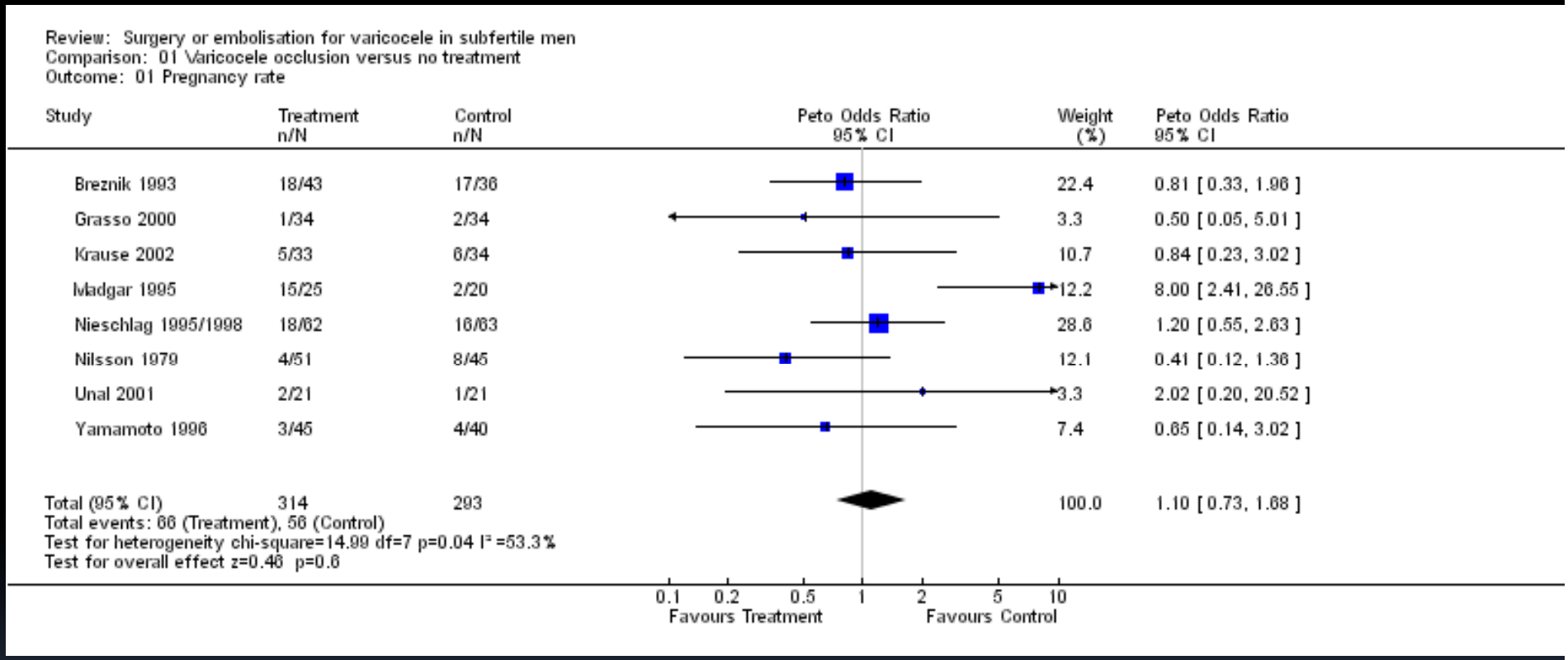
RCT from the WHO-study
Madgar I. et.al. Fertil.Steril 1995 63:120-124

- 45 subfertile men with palpable varicocele were randomized for immediate treatment (High ligation) of treatment after one year.

- In the treatment group (N=25) 15 spontaneous pregnancies (60%) occurred within one year.
- In the control group (N=20) 2 spontaneous pregnancies (10%) occurred within one year. Treatment after one year resulted in another 8 spontaneous pregnancies (44%).

The German RCT on varicocele treatment by embolisation (Krause et. Al., Andrologia 2001)

- RCT comparing embolisation of a varicocele to no treatment in men with oligospermia with a follow-up of 1 year
- Poor recruitment: from a calculated number of case needed of 460 men only 67 patients were randomized for treatment (embolisation) or no treatment in a period of 5 years.
- Loss to follow-up was present in more than half of the randomized men (no conception was assumed in these couples)
- No difference in pregnancies between the two groups: 15,7% versus 20,8%.



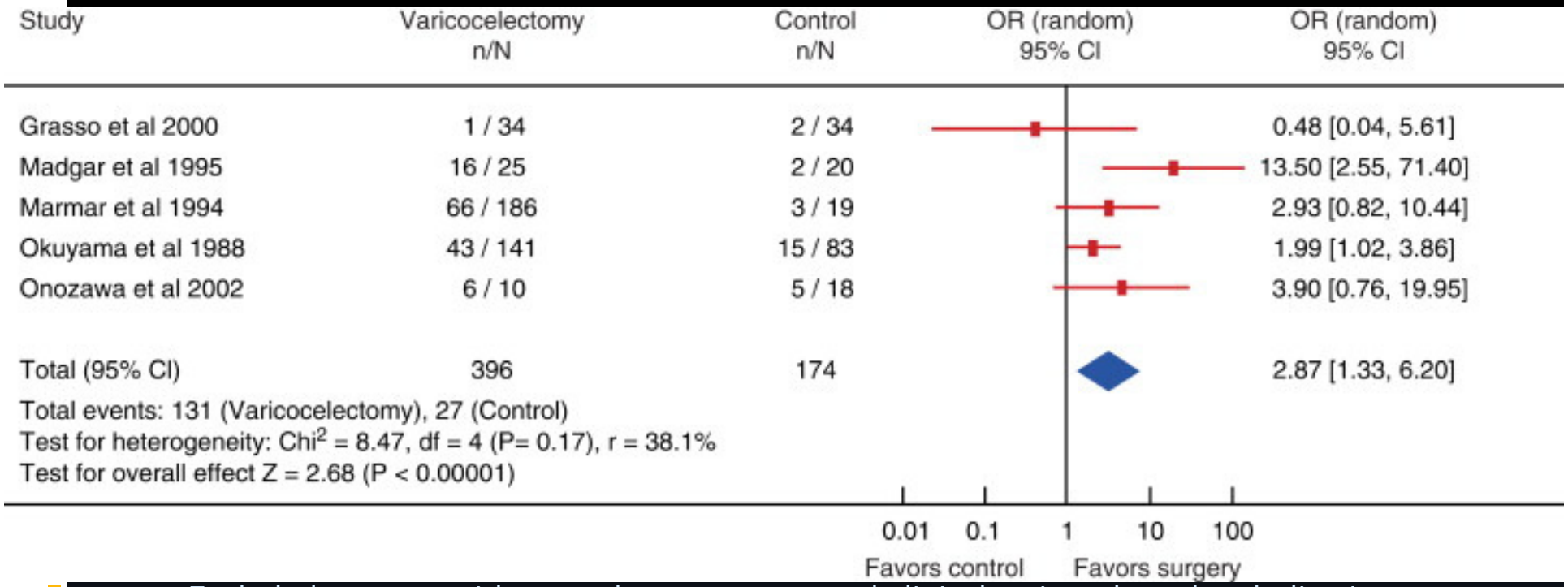
Evers JL and Collins JA, Cochrane analysis 2004

Re-analysis of the Cochrane meta-analysis

Ficara V. et. al. Eur Urol 2006 49:258-263

- Studies with either normal sperm analysis and subclinical varicoceles were excluded.
- Only 3/8 studies from the Cochrane analysis remain
- 3 studies analyzed are Nieschlag, Krause and Madgar:
  - 120 men treated and 117 controls
  - Pregnancies in 36% of the treated group versus 20% of the controls
  - A meta-analysis of poor quality studies cannot result in a recommendation against of in favor of varicocelectomy.

From Marmar J et al. Fert. Steril. 2007 88: 639-648



Excluded are men with normal sperm counts, subclinical varicocele and embolisation as treatment. (i. e. the studies of Nieschlag and Breznik)

Included are some observational studies

Does varicocele repair result in more spontaneous pregnancies? A prospective randomized trial. Study design

- Inclusion/exclusion
  - Infertility duration of at least 1 year
  - Oligospermia: <20 million sperms/ml., but not azoospermia
  - No other abnormality than a clinical varicocele (grade 1-3)
  - Female partner younger than 36 years of age and no obvious fertility problems
- Randomisation
  - Immediate treatment (surgical varicocelectomy or embolisation)
  - or
  - delayed treatment (controls) after 1 year (ART or varicocelectomy)

STUDY DESIGN

CLINICAL EVALUATION

- Semen analysis twice (WHO, 1999), interval of one month
- Endocrine screening (FSH, Inhibin-B)
- Scrotal ultrasound, criteria for varicocele:
  - diameter >3mm after valsalva maneuver
  - reflux > 2 sec. into the venous plexus
- Informed consent (take home video, explain the study and randomization)
- Follow-up of at least 1 year with semen analysis at 3 and 6 months, scrotal ultrasound and endocrine evaluation at 3 months

STANDARD

Final analysis

- Treatment group N=65
- Loss to FU =5

- Age partner 29,6 years
- Infert. duration 2,5 years

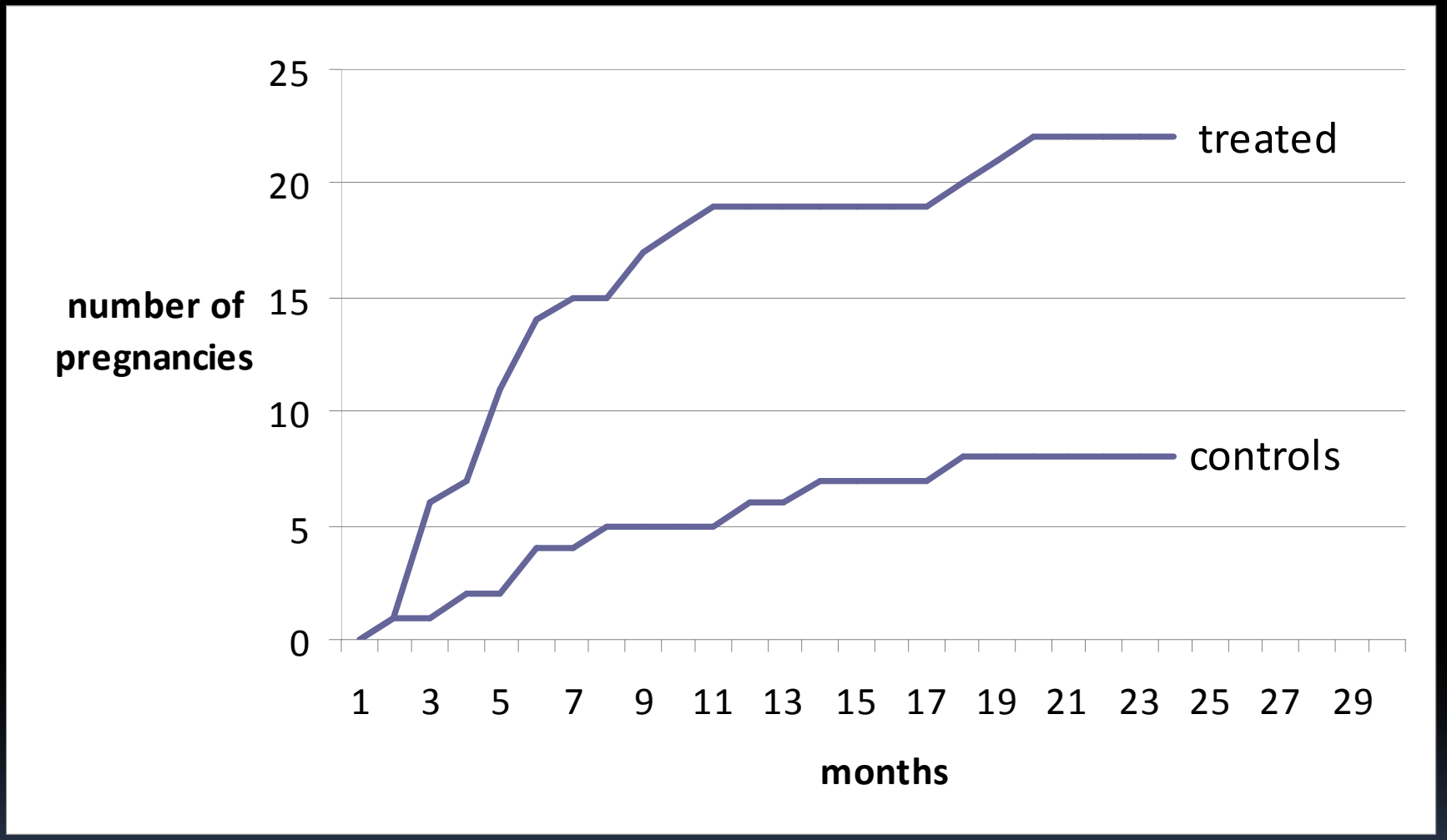
- Semen analysis
  - concentration 9,7->18,5
  - motility 19% -> 24%

- **Spontaneous pregnancies 19/60 (31%) within 1 year**
- **After 2 years FU: (37%) spontaneous pergnancies**

- Controls N =65
- Loss to FU = 7

- Age partner 29,3 years
- Infert. duration 2,3 years
- Semen analysis
  - concentration 8,5 -> 11,0
  - Motility 22% -> 23%

- **Spontaneous pregnancies 6/58 (10%) within 1 year**
- **After 2 years FU: (14%) spontaneous pregnancies**


number of pregnancies
25
20
15
10
5
0
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
months
treated
controls

TREATMENT

- Operation/Embolisation
  - High-inguinal (Palomo): 43 x, 4 reccurrences (9%)
  - Embolisation 7 x, 3 reccurrences (42%)
  - Microsurgery (Goldstein procedure) 7 x, no recurrences

Table 1. Recurrence and complication rates of different treatment methods for variocele

Treatment	Recurrence Rates	Complications
Antegrade Sclerotherapy	9%	Epididymitis - Testicular atrophy - Flank erytema
Retrograde Embolisation	10-15%	Trombophlebitis – Bleeding/heamatoma – Vene perforation Dislocation of the coil – Contrast allergy
Open Operation	13-30%	Hydrocele – Testicular atrophy – Haematoma
Laparoscopy	7-15%	Intestinal damage – Peritonitis – Pulmonary embolism
Microsurgery	1-4%	Testicular atrophy – Hydrocele – Scrotal heamatoma

Surgical treatment after 1 year

- 23 men from the no treatment group had a varicocele repair after their follow-up period of 1 year.
- This resulted in 7/23 (30,4%) spontaneous pregnancies.

Artificial Reproductive Techniques (After 1 year)

- 52 couples treated (IUI, IVF, ICSI)
- 20 ongoing pregnancies (38,4%)

Summary of the studies

- Treatment is recommended if:
  - The duration of infertility is about 2 years or longer
  - There is a significant oligozoospermia: <20 milj. spermatozoa/ml.
  - The partner is younger than 36 years of age and without obvious fertility problems

- Treatment was not shown beneficial in men with normospermia and in case of a subclinical varicocele.