MALE INFERTILITY

CHALLENGES IN TREATMENT

MASTER, MD MAI BA TIEN DUNG

HEAD OF ANDROLOGY DEPARTMENT – BINH DAN HOSPITAL

INTRODUCTION

Infertility: 15% in the community – 14% of causes of infertility are azoospermia.

Vas deferens, epididymis interventional surgery failure ⇨ permanent infertility.

1992: Palermo performed ICSI (intracytoplasmic sperm injection) ⇨ Male infertility can be treated with in vitro fertilization (IVF).

1998: Tu Du hospital performed ICSI with sperms in semen.

1992: Prof. Ngo Gia Hy and MD Nguyen Van Hiep have laid the foundation for andrology in Binh Dan hospital

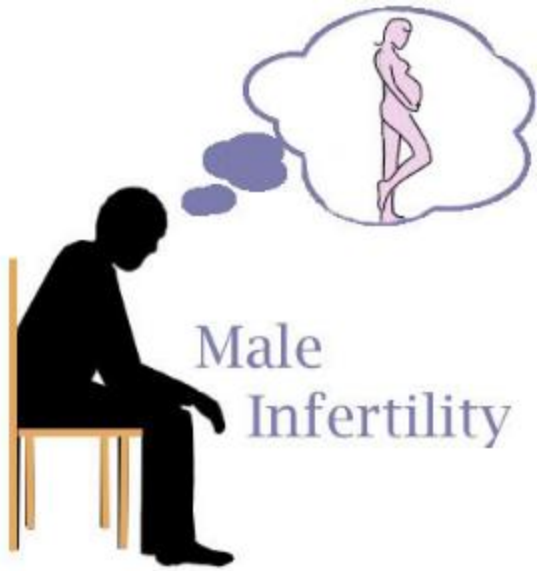
1999: Binh Dan hospital andrology clinic was established

2004: Viet Duc hospital andrology center

1. *World Health Organization (2000),Cambridge: Cambridge University Press.*
2. *Palermo G, Joris H, Deroey P (1992), Lancet*
3. *Ho Mai Thong et al (2000), Medical and pharmaceutical news*
4. *Nguyen Thanh Nhu et al (2002), Medical and pharmaceutical news*

⇒ Male infertility is interested and treated actively

DEFINITION OF INFERTILITY



- Pregnancy opportunity in normal couples Spira, 1986):
  - 20-25% in 1 month
  - 75% in 6 months
  - 90% in 1 year
- WHO: Couples, after one year marriage, do not apply family planning measures but still do not have children = infertility.
- *Causes: wife (40%), husband (30%), both (20%) and 10% of unknown causes.*

World Health Organization. WHO Manual for the Standardised Investigation, Diagnosis and Management of the Infertile Male. Cambridge: Cambridge University Press, 2000.

Daily Mail

WORLD EXCLUSIVE

And here she is...

THE LOVELY LOUISE

Louise Brown (1978) the world's 1st IVF baby

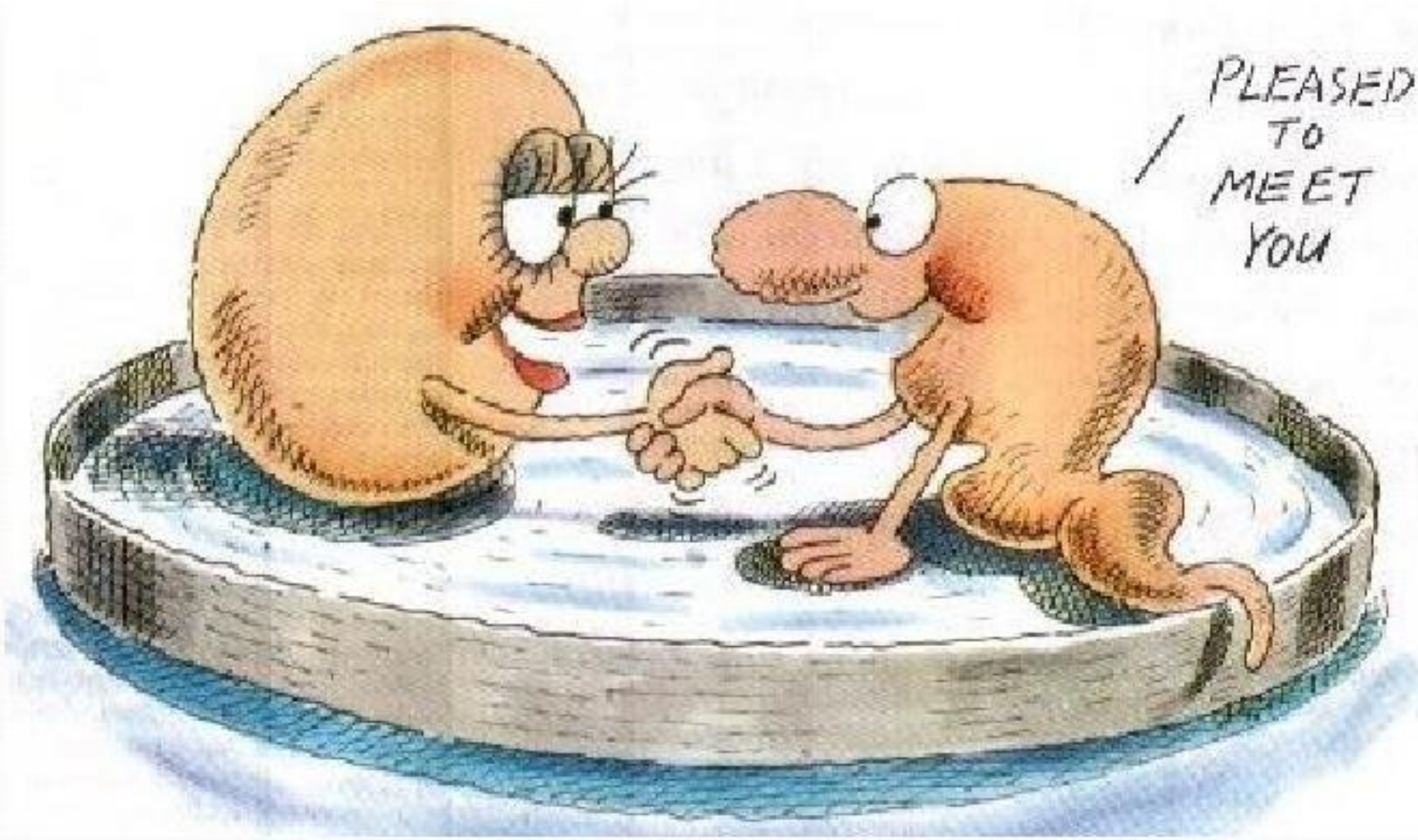

Evening News

Meet Louise, the world's first test-tube arrival

SUPERBABE

Worlds first test tube baby, Louise Brown turns 36 in 2014

In 2010, Sir Edwards was awarded the Nobel Prize in Physiology or Medicine "for the development of in vitro fertilization"


PLEASED TO MEET YOU

ANATOMY OF TESTES

- TESTES – EPIDIDYMIS:
  - Endocrine and exocrine function.
  - Testis has 250 – 300 lobules.
  - Seminiferous tubules account for 90% of testicular volume.
  - Epididymis: in the upper back, covering the testes.
  - Head of epididymis: 6-8 tubes, body and tail of epididymis only have one tube.

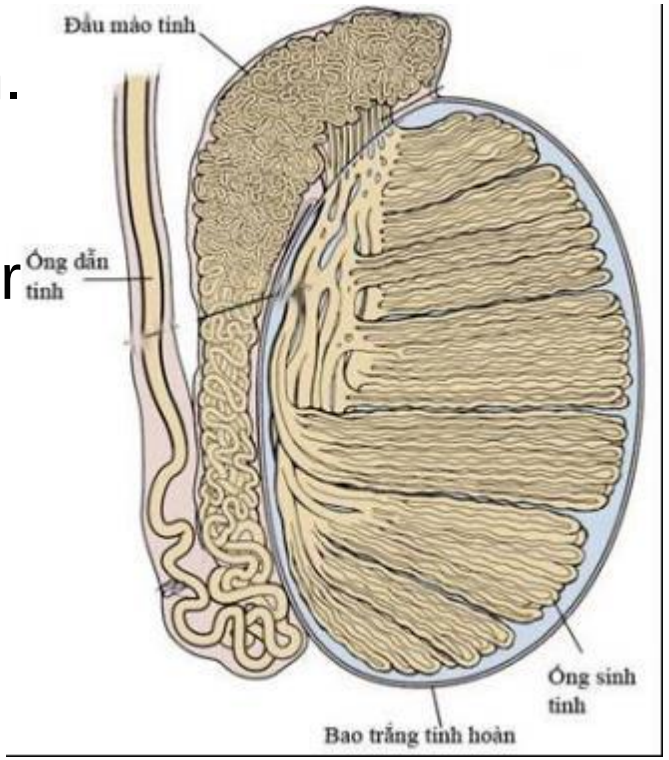
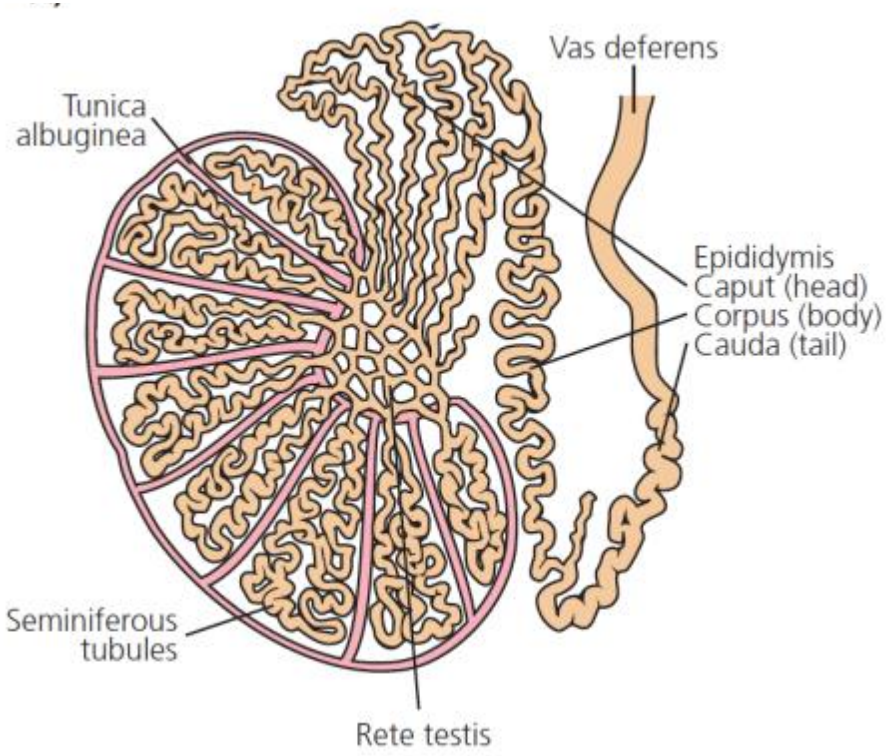
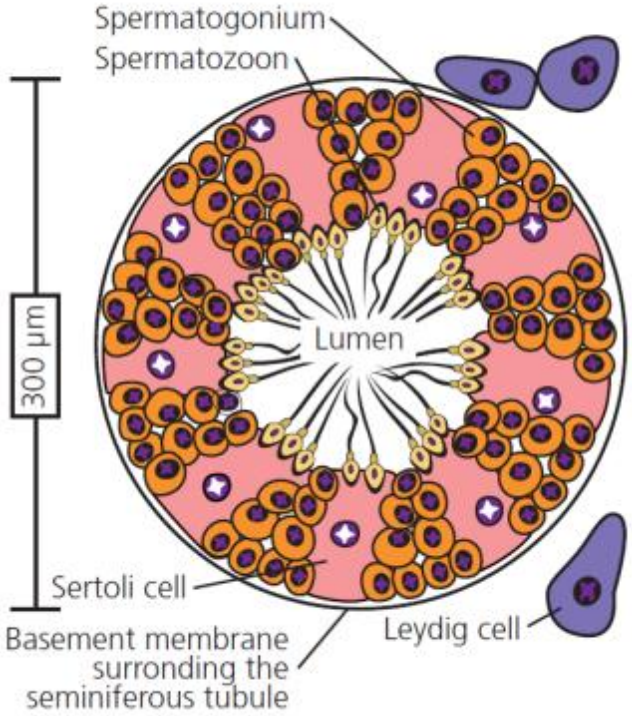


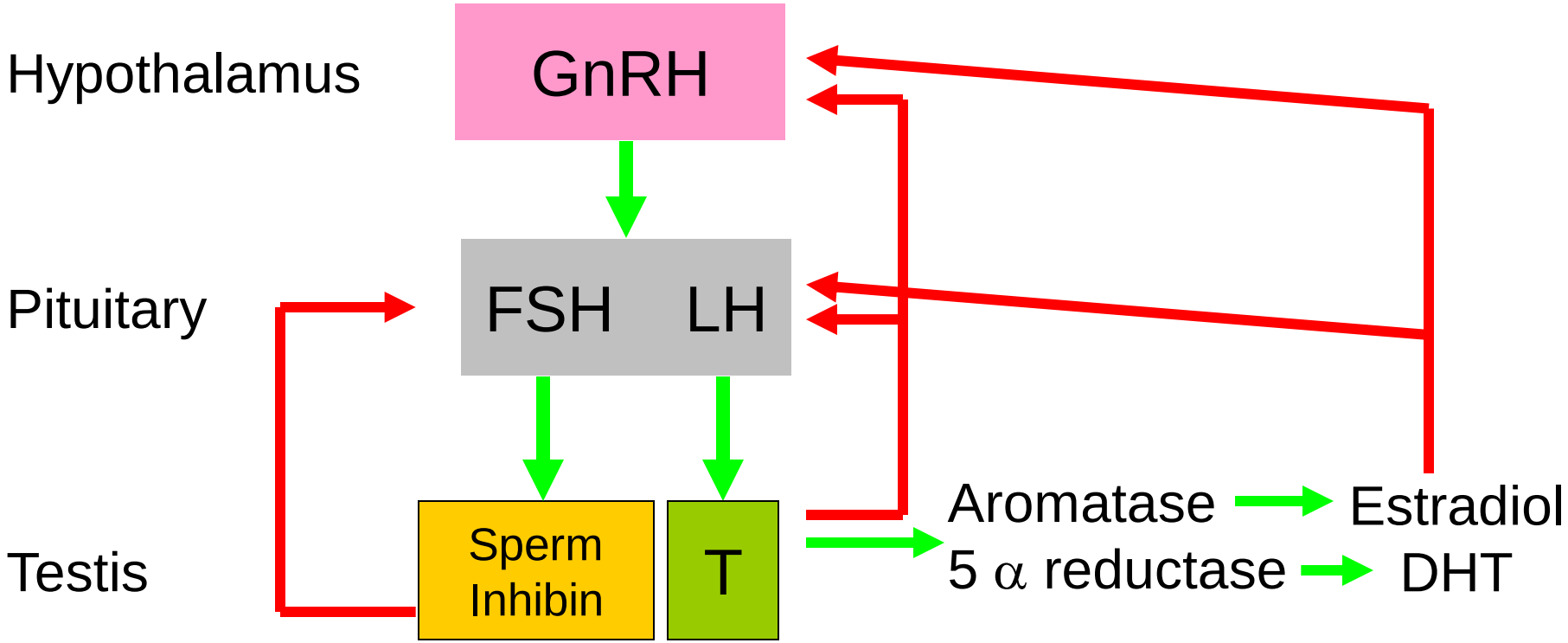
Figure 1.1: Longitudinal section of testes (Source: Hirsh AV, 1995)





Reference: Rhoades RA, Bell RB. *Medical Physiology: Principles for Clinical Medicine*. Fourth ed. Philadelphia: Lippincott Williams & Wilkins, Wolters Kluwer; 2013.

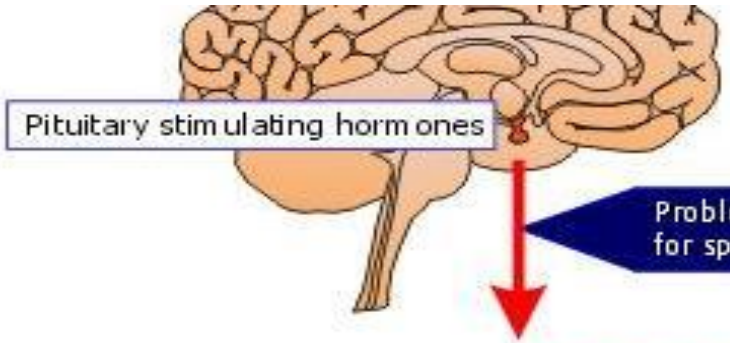
HYPOTHALAMUS – PITUITARY – TESTIS AXIS



Sertoli cell
Seminiferous tubule

Leydig cell

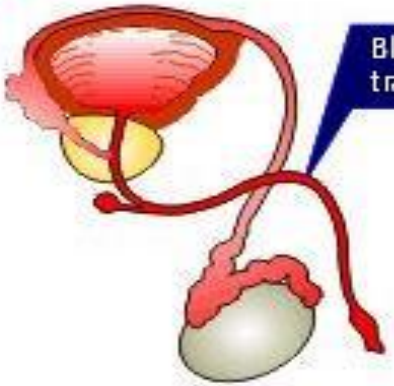
T=testosterone
GnRH=Gonadotropin-releasing hormone;
FSH= Follicle-stimulating hormone; LH = Luteinizing hormone; DHT: dihydrotestosterone



Pituitary stimulating hormones

Problems in producing hormones for sperm production

Hormonal control



Blockage of sperm transport

- Infection
- Prostate-related problems
- Absence of vas deferens
- Vasectomy

sperm

Erection & ejaculation problems

- Prostate Surgery
- Damage to Nerves
- Ejaculation Problems
- Timing of Intercourse
- Medication

Sperm production problems

- Genetic Causes
- Failure of testes to decend
- Infections
- Torsion
- Varicocele
- Drugs
- Radiation damage
- Sperm Antibodies

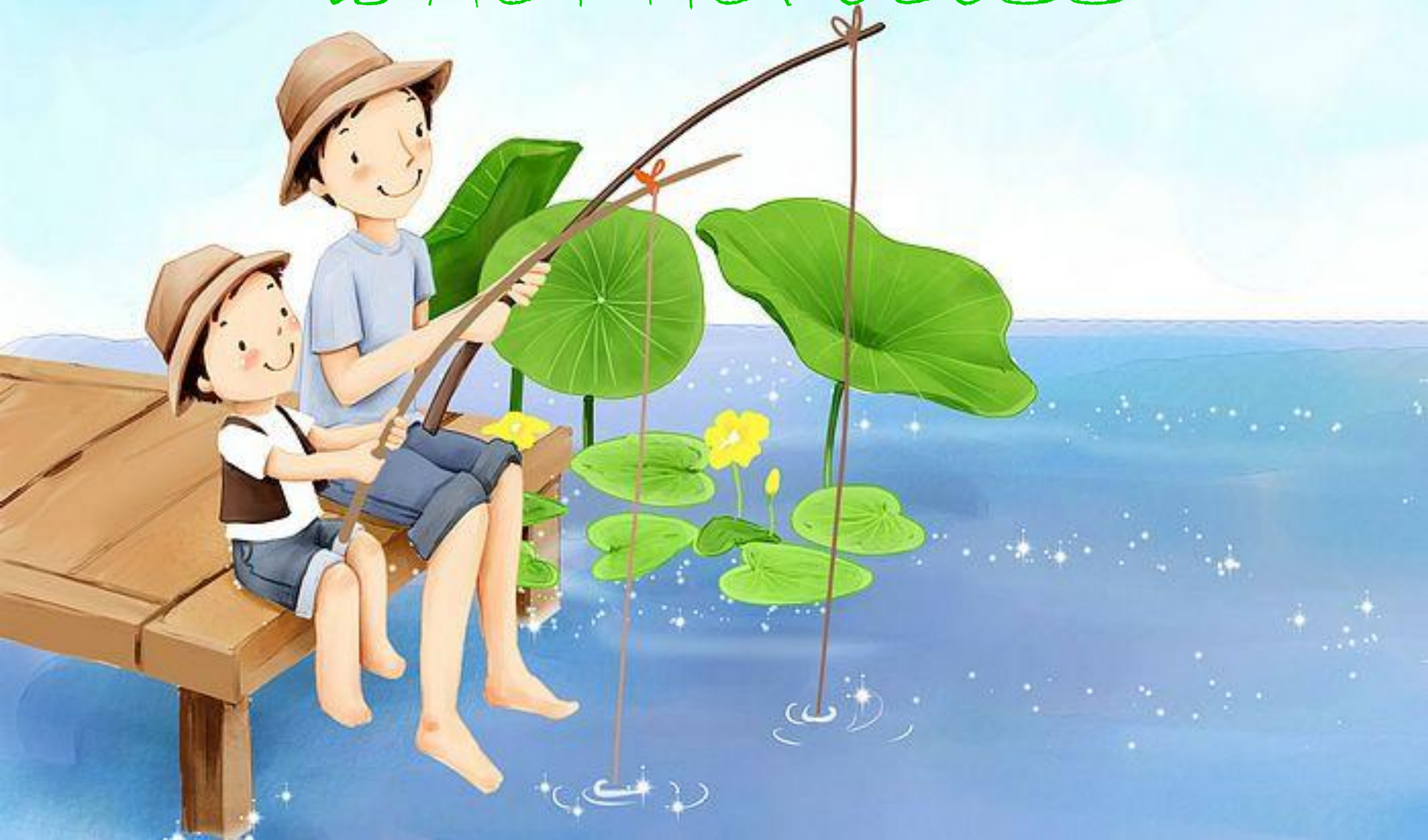
CAUSES OF MALE INFERTILITY

Classification	Percentage %
Testicular varicose veins	38
Unknown causes	23
Obstruction	13
Occult testes	3
Testicular failure	5
Antibody to sperm	2
Ejaculation disorder	2
Endocrine	1
Gene abnormalities	0,5
Testicular torsion	0,5
Erectile dysfunction	0,4
Testicular cancer	0,4
Systemic diseases	0,2
Low urethra	0,05

WHICH SPECIALIZED DOCTOR WILL HELP PATIENTS?

Nieschlag E. Andrology (Eds), Male reproductive health and dysfunction, 2nd Ed. Springer Verlag, Berlin,

MALE INFERTILITY
is NOT HOPELESS




WE JUST DEAL WITH IT

BỆNH VIỆN PHỤ SẢN TRUNG ƯƠNG
National Hospital of Obstetrics and Gynecology

KNOWLEDGE AND BEHAVIOR OF SEEKING MALE INFERTILITY EXAMINATION AND TREATMENT SERVICES AT ANDROLOGY DEPARTMENT OF HO CHI MINH CITY BINH DAN HOSPITAL AND SOME INFLUENCING FACTORS

Topic title	Expected results
The popularity of male infertility	Doctors' assessment on the popularity of male infertility.
Patient knowledge of male infertility	Patient knowledge about male infertility: causes, symptoms and possibility of treatment. Effects of male infertility on the patient itself and his family.
	Doctors' assessment on patient knowledge relating to male infertility.
Education information, communication about male infertility for patients	Patient knowledge on places where provide male infertility examination and treatment services. What sources patients know information.
	Patient knowledge on male infertility communication activities that the patient has received previously: content and form of communication, effectiveness of changing the patient's behavior.
	Doctors's knowledge on actual status and effectiveness of communication programs for infertility patients today.
Male infertility examination and treatment	Patient knowledge on whether to go for male infertility examination and treatment early or late, reasons. Medical facility - where patients choose for first treatment of male infertility and reason of choice. Thoughts, inmost feelings before deciding to go to Binh Dan Hospital for inpatient treatment.
	Doctors' knowledge on the effectiveness of current male infertility regimen ; Common difficulties during treatment arising due to improper treatment for patients before hospitalization.
Factors supporting patients to make decision to select Binh Dan hospital to treat male infertility due to varicocele.	Factors that prevent patients from going for infertility examination and treatment. How to overcome these factors. Supportive role of family, friends, relatives Role of local health facilities Internet impact, how do the media change patient perceptions.

Characteristics		Percentage (%)
Duration of infertility	≤ 5 years	38.3
	> 5 years	61.7
Status of infertility	Primary	82.5
	Secondary	17.5
Consulted by medical staffs on male intertility	Have been consulted	11.0
	Not yet consulted	89.0
Sources of information on male infertility	Friends, relatives	48.7
	Internet	35.7
	Television, newspapers, radio	11.0
	Traditional medicine practitioners	3.2
	Medical staffs in communes, wards	1.9
	Medical staffs in hospitals	1.9
	Herbalist, fortune-teller	0.6
	Leaflets, posters	0
	Other sources	5.8

Table 3.2. Some epidemiological characteristics of study subjects

Table 3.3. Understand the diagnostic criteria for male infertility in late time having children

Period enough for diagnosis of male infertility	Percentage (%)
6 months	*14.9*
1 year	*9.1*
2 years	*14.9*
Over 2 years	*33.1*
Unknown	*27.9*

"Infertility is due to women, every man thinks so." PVS NB1.

"I often see infertility in women, seeing in men when paying attention" PVS NB2.

"Often the causes of infertility are due to more women than men. Men have infertility who experienced the bad luck" PVS NB5.

Table 3.11. Practical selection of male infertility treatment facility for the first time

Facility for male infertility treatment for the first time	Percentage (%)
Home-remedy facility	*26.5*
Private infertility clinic	*17.9*
Hospital has andrology department	*17.2*
Province/city hospital	*13.9*
Traditional medicine facility	*11.3*
Herbalist	*7.3*
Communes, wards, towns health stations	*1.3*
Other options	*1.3*
No response	*5.3*

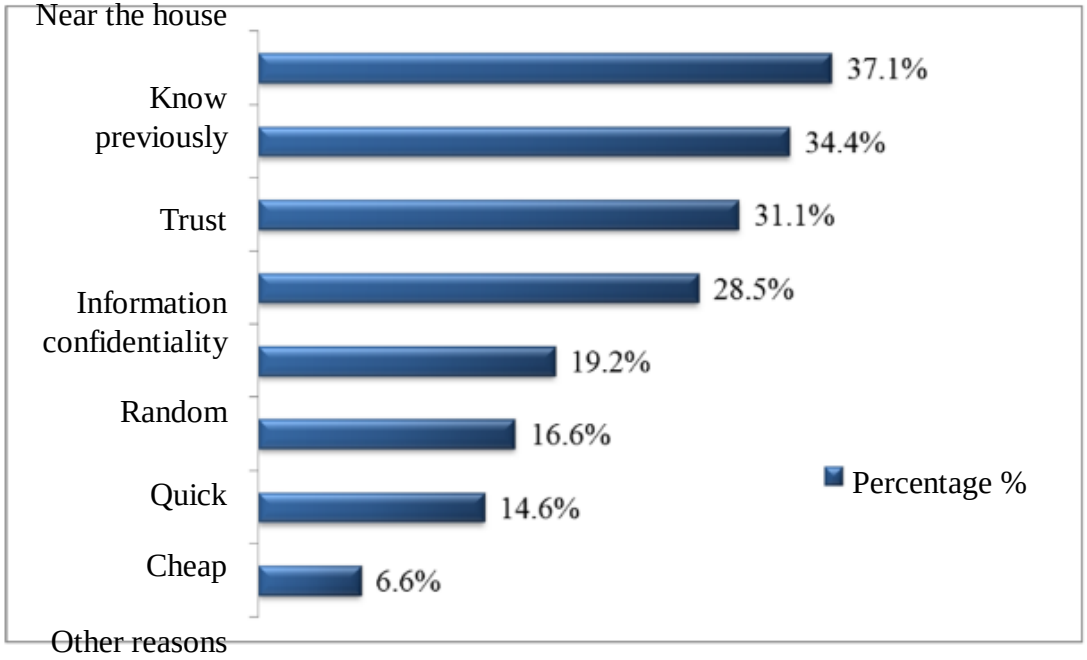


Table 3.12. Number of infertility treatment facilities that patients have experienced

Number of infertility treatment facilities that patients have experienced	Percentage (%)
1 to 2 facilities	*43.6*
3 - 5 facilities	*46.1*
Over 5 facilities	*4.5*
Does not remember	*5.8*

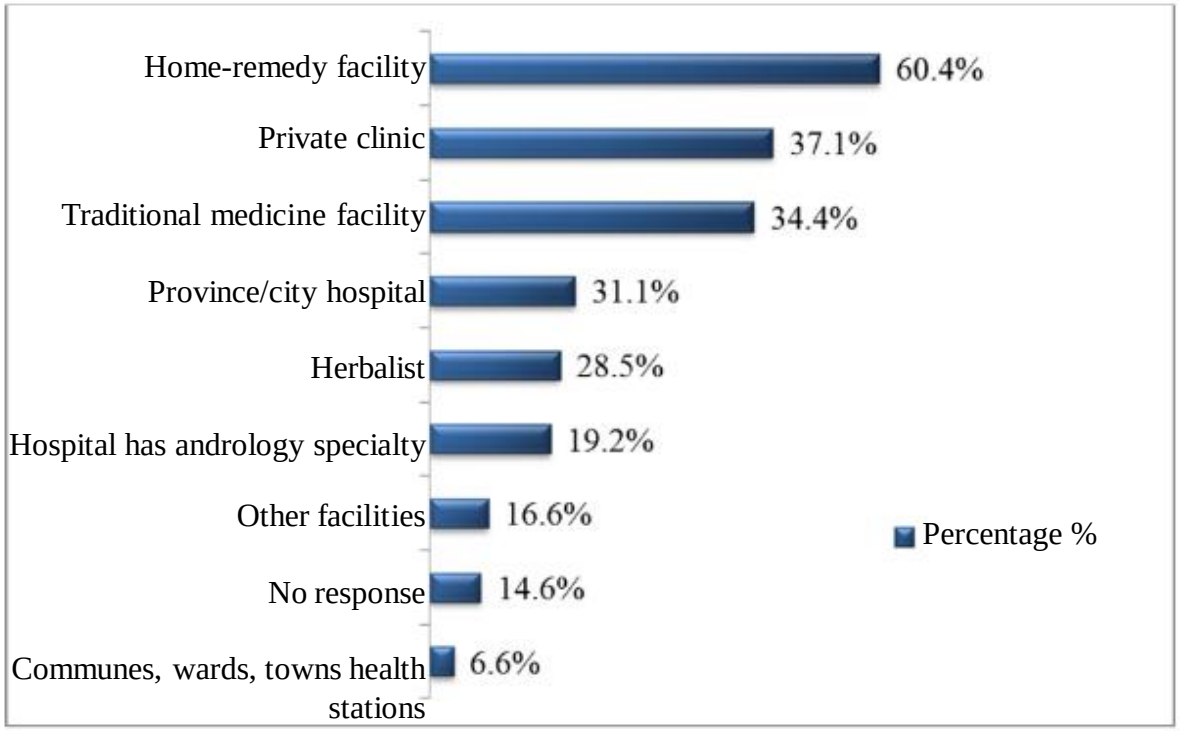
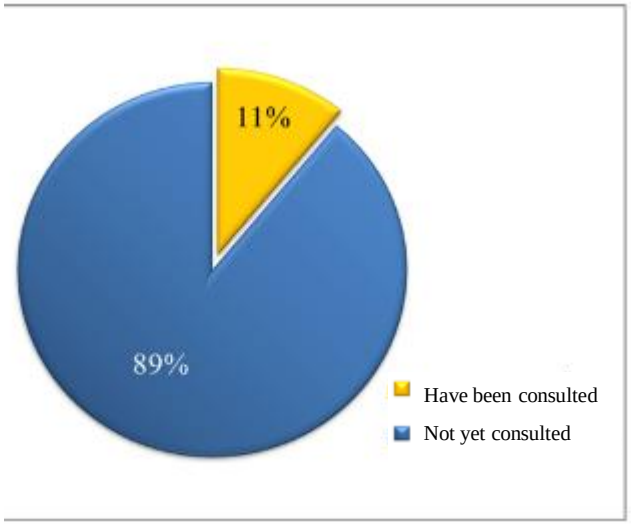


Chart 3.3. Infertility treatment facilities that patients have experienced

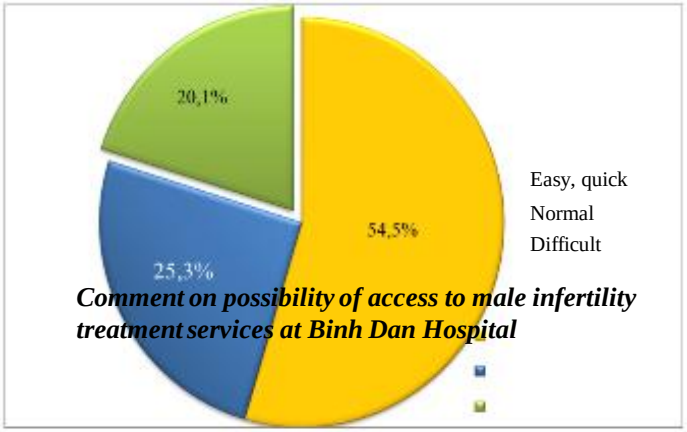
Table 3.3. Reasons that male infertility patients do not go to Binh Dan hospital from the beginning

Difficulties when accessing services	Percentage (%)
Lack of information about Binh Dan Hospital	*38.3*
House is far from hospital	*23.4*
Patients are crowded, waiting a long time	*14.3*
High cost of treatment	*7.8*
Not yet consulted for clear understanding of male infertility	*6.5*
Patients are not enough confident to go to hospital for male infertility treatment	*1.9*
Total	***100***



"I have never been consulted about male infertility before." PVS NB4.
"I have not been consulted about this disease." PVS2.

"Often the causes of infertility are due to more women than men. Men have infertility who experienced the bad luck" PVS NB5.



Comment on possibility of access to male infertility treatment services at Binh Dan Hospital

2. Some factors affecting the behavior of seeking male infertility services

•Factors of each individual patient: lack of information about medical facilities that are capable of treating male infertility (38.3%), lives far from hospital (23.4%), anxiety to wait a long time (14.3%), lack of treatment expense (7.8%).

•Patients lack support from the reproductive health care system, especially at the primary level, so they do not receive necessary information and psychological support leading to disorientation of treatment. The proportion of patients who have been consulted was 11%.

•The cost of infertility treatment in hospitals is high, the pressure of having to give birth prematurely to keep family happiness, to maintain the lineage makes it easy for patients to trust and accept unscientific treatments.

- Binh Dan Hospital is a good facility for male infertility treatment but the hospital overload reduces the ability to attract patients due to lack of privacy, long waiting time.

OVERCOME

Role of media

Reform the health system

Improve knowledge

Treat couples

Co-ordinate with infertility specialists - andrologists

Evaluate treatment under an overall picture

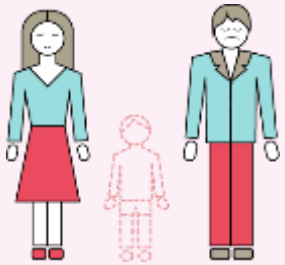
Classification	Percentage %
Testicular varicose veins	38
Unknown causes	23
Obstruction	13
Occult testes	3
Testicular failure	5
Antibody to sperm	2
Ejaculation disorder	2
Endocrine	1
Gene abnormalities	0.5
Testicular torsion	0.5
Erectile dysfunction	0.4
Testicular cancer	0.4
Systemic diseases	0.2

TREATMENT ?

Nieschlag E. Andrology (Eds), Male reproductive health and dysfunction, 2nd Ed. Springer Verlag, Berlin,

Causes of male infertility

- Pathology and injury
- Reduced sperm quality

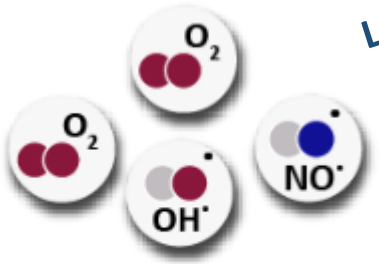


Infertile men with unknown cause have high concentrations of ROS

Very high concentrations of ROS are found in 25-40% of infertile men

ROS (Reactive oxygen Species)

The destruction of biological macromolecules by ROS and RNS is the cause of many dangerous diseases



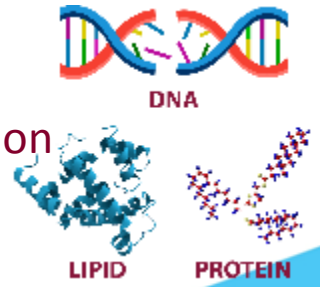
FREE OXIDATIVE RADICALS

LOW CONCENTRATION*

- Regulate cell division
- Activate transcription factors
- Regulate the expression of genes coding for antioxidant enzymes

HIGH CONCENTRATION**

- DNA mutation
- Protein denaturation
- Lipid oxidation



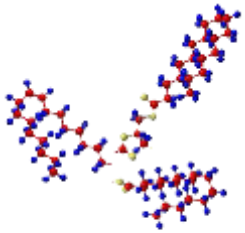
*(Favier, 2003; Pincemail & cs., 1998; Pincemail, 2006)
**(Favier, 2003; Pincemail & cs., 1998).

Antioxidants

Antioxidants are compounds that can slow down, prevent or reverse the oxidation of compounds contained in the body cells*.

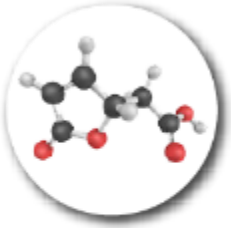
ANTIOXIDANTS

Internal



PROTEIN

- Ferritin
- Transferrin
- Albumin
- Heat shock proteins



ANTIOXIDANT ENZYMES

- Superoxide dismutase
- Glutathion peroxydase
- Catalase

External

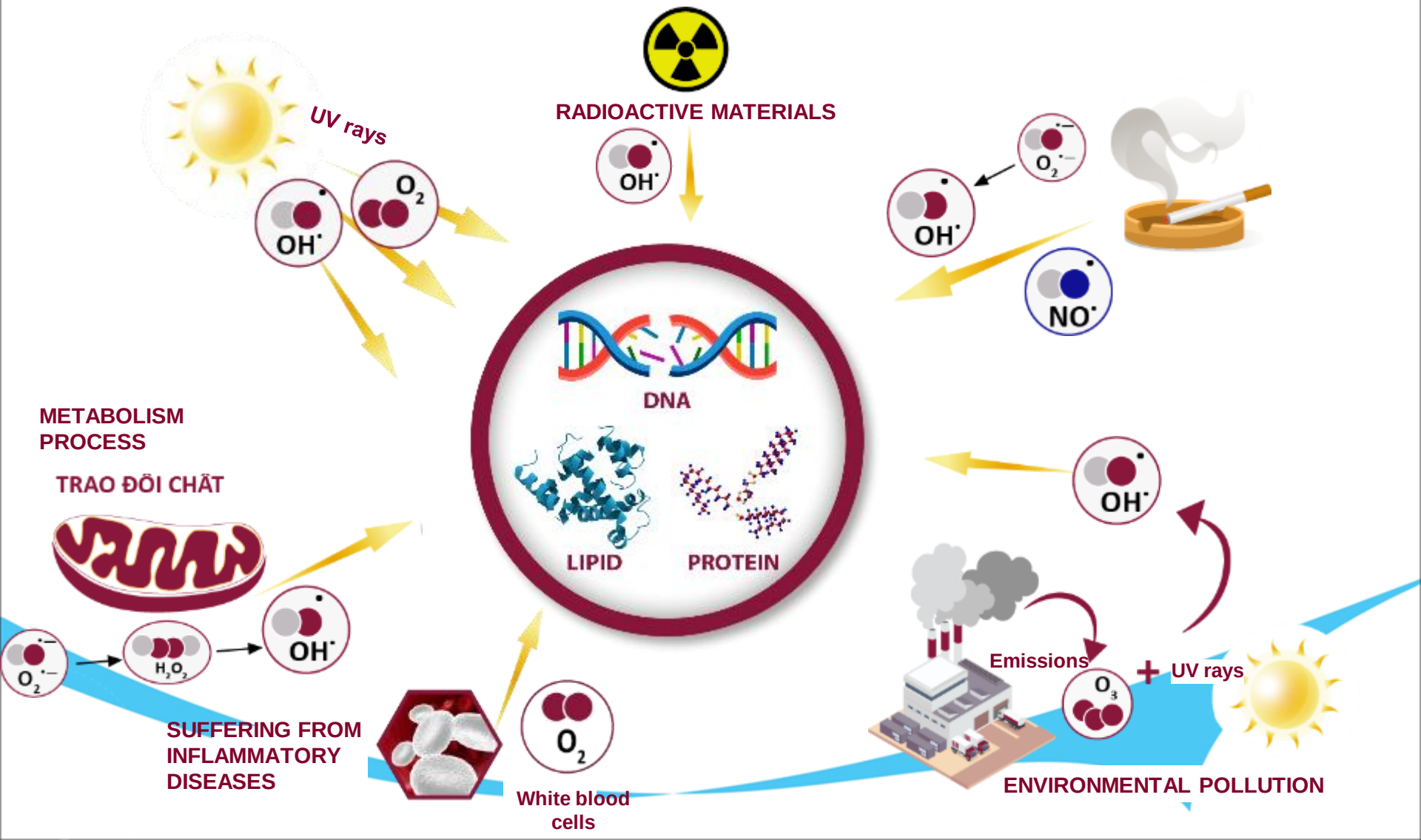
Vitamin C

Vitamin E

- Vitamin E
- Vitamin C
- Carotenoids and phenolic compounds**

**Jovanovic và Simic, 2000; Lachman & cs., 2000; Singh và Rajini, 2004).*
***Niki & cs., 1995; Lachman & cs.,2000; Pincemail & cs., 1998; Vansant & cs. 2004).*

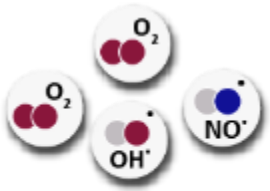
ROS & RNS – Formation causes and impacts



Effects on fertilization process

Vitamin B2, B3

Neutralize



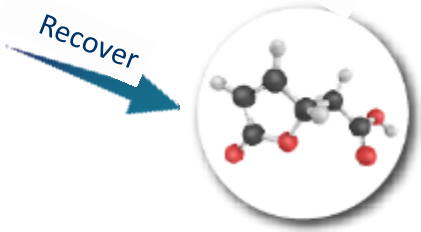
FREE OXIDATIVE RADICALS
Bad effects

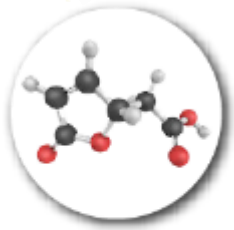
Neutralize

Recover

Vitamin C

Recover





Recover

Vitamin E

Irritate

ANTIOXIDANTS

Recover

Yeast flower

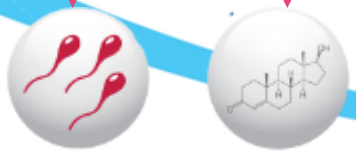
Mangan (Mn)

Selen (Se)

Kẽm (Zn)

INCREASE

FERTILIZATION PROCESS

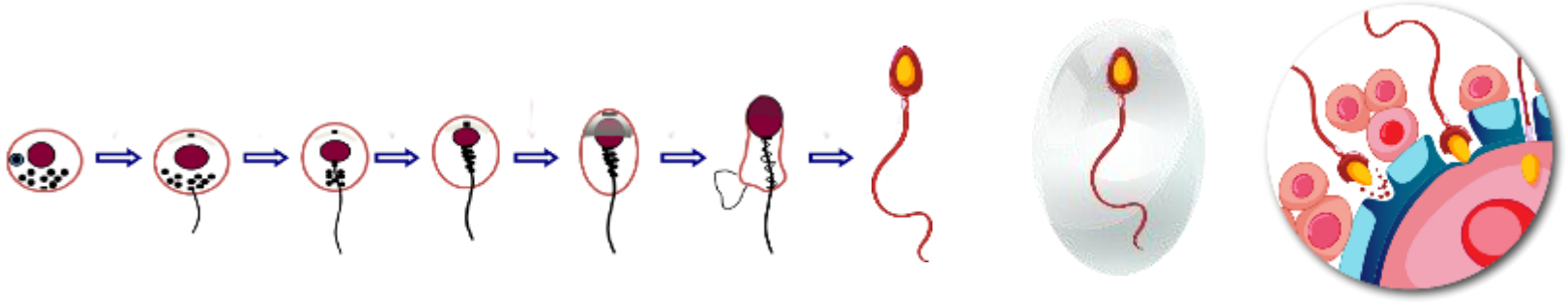


Sperm production

Testosterone concentration

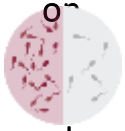
Hughes *et al. 1998; Balercia et al.* 2004; Greco *et al. 2005; Piomboni et al. 2008;*Ghanem *et al. 2010; Wang et al. 2010; Zini et al.*2010; Moslemi and Tavanbakhsh, 2011; Chen *et al. 2012; Safarinejad, 2012; Walczak*–Jedrzejowska *et al. 2013; Durairajanayagam et al.*2014; Haghighian *et al. 2015; Thakur et al. 2015].*

Sperms are affected by ROS during growth, storage and fertilization processes [7,8,9,10]



SPERMS MAY BE AFFECTED BY ROS/RNS

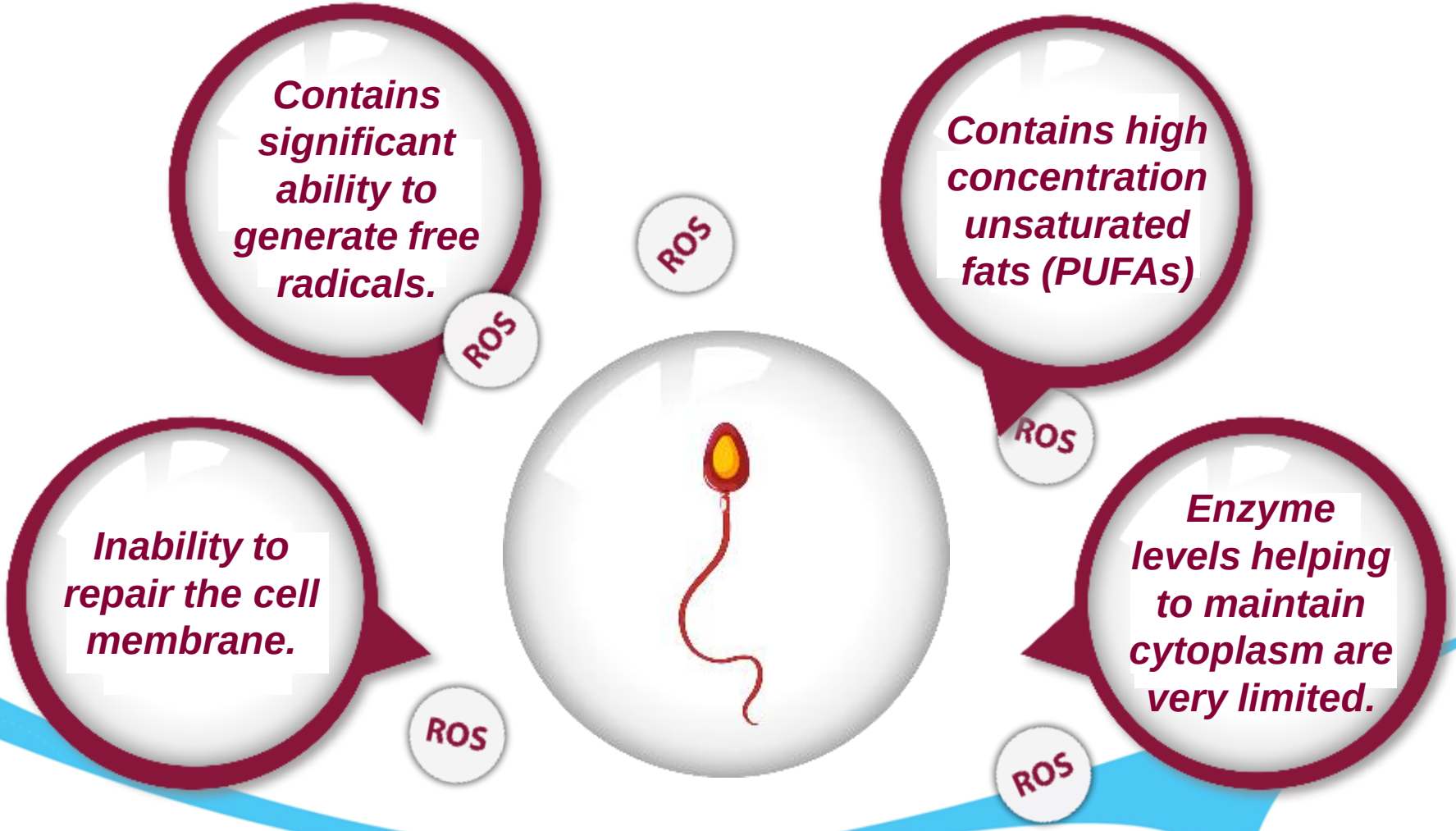

Deformati
o


Reduced count

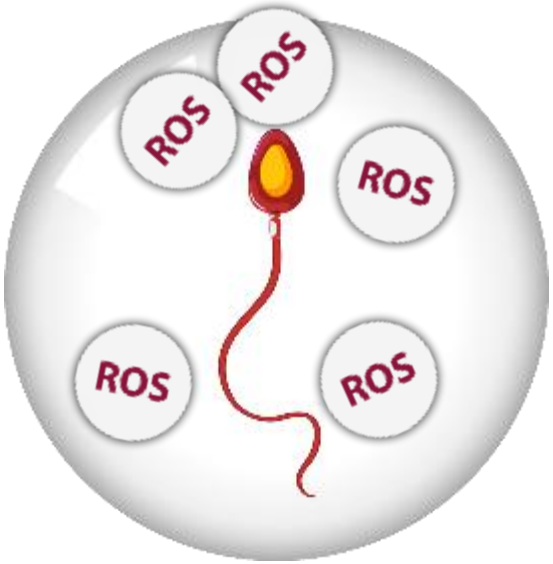

Motility

- Reduced sperm count & quality
- Sperm DNA damage
- Reduced conception rate

Why are sperms prone to oxidation?



Characteristics of sperms damaged by ROS



- Increase the viscosity of semen
- High white blood cells in semen
- Poor motility
- Deformed sperms
- Low conception ability

Evaluation of sperm quality

Semen analysis

Main diagnostic tool

Semen analysis
(at least 2 times)

Evaluation

Quality and count of
sperms

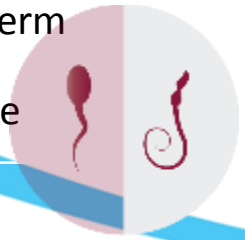
Sperm shape deformity

Reduced sperm count

Sperm motility

Evaluation of sperm quality
Semen analysis

	WHO 2010	Pathology
Semen volume	1.5ml	
Total sperm count	39 million	
Overall motility	40%	
Sperm concentration	15 million/ml	**Oligozoospermia**
Progressive motility	32%	**Asthenozoospermia**
Normal morphology	25%	**Teratozoospermia**
Vital sperm	58%	
pH value	7.2	



Sperm shape deformity

Reduced sperm count

Sperm motility

Evaluation of sperm quality

DNA fragmentation assay

Compromise male fertility

Evenson et al 1980; Aitken 1999, Henkel et al 2004, Agarwal Int. Braz. J. Urol 2011)

Predispose to genetic diseases, birth defects and childhood cancer

(Fraga et al 1996, Ji et al/ Aitken et al 2003).

Recurrent pregnancy loss and poor outcomes in Intrauterine insemination (IUI) and in-vitro fertilisation (IVF)

(Agarwal Int. Braz. J. Urol 2011)

ROS – DF TEST RESULTS

TINH DỊCH ĐỒ
SEMEN ANALYSIS

Mã hồ sơ 701BD.170906376
ID

Họ tên : **SẦN KÝ DẬU** Năm sinh: **1988** Giới tính: **Nam**
Name YoB Sex

Địa chỉ: Cây Giáo -, Huyện Trảng Bom, Đồng Nai SĐT: 0977.316235
Address Tel

Bác sĩ điều trị : **BS. Lê Vũ Tân**
Clinician

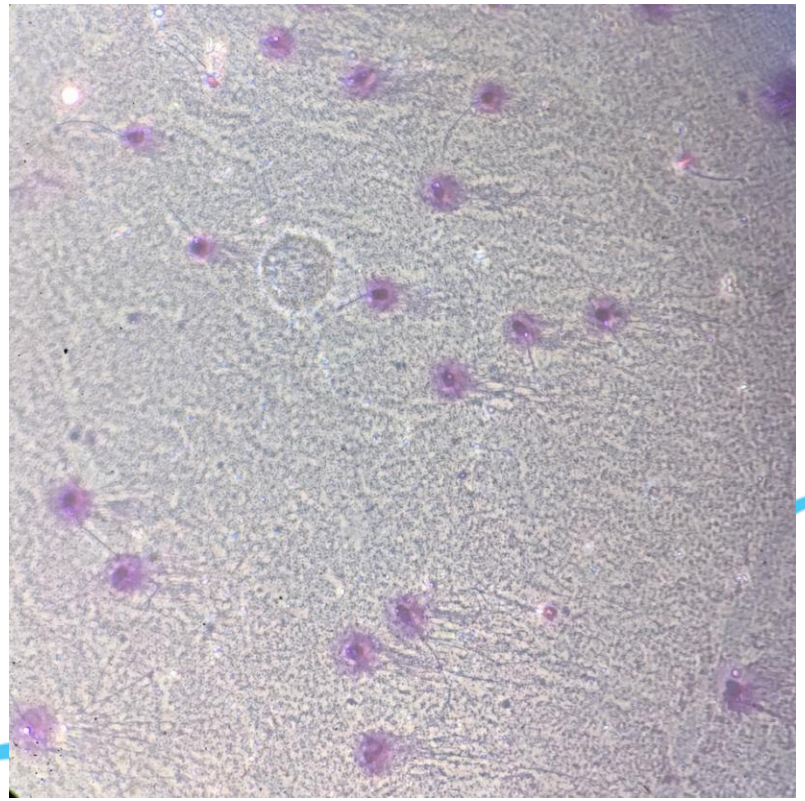
Nơi lấy mẫu : **Bệnh viện Bình Dân (Binh Dan hospital)**
Collection

				Chuẩn tham khảo (WHO,2010) *Reference values*
Thời gian lấy tinh dịch trước khi xét nghiệm Time from ejaculation to analysis		**10**	phút	≤ 60 phút (minutes)
Kiêng giao hợp Abstinence period		**4**	Ngày	3 - 5 ngày (days)
Thể Tích Volume		**7,3**	ml	≥ 1,5 ml (ml)
Ly giải Liquefaction		**30**	phút	≤ 60 phút (minutes)
pH pH		**7,4**		≥ 7,2
Mật độ Concentration		**12**	x 10^6 TT/ml	≥ 15 x 10^6 TT/ml (sperms/ml)
Tổng số tinh trùng Total sperm number		**87,6**	x 10^6	≥ 39 x 10^6
Di Động: Motillity	PR.Tiến tới Progressive	**02**	%	≥ 32%
	NP.Không tiến tới Non-Progressive	**11**	%	PR + NP ≥ 40%
	IM.Không di động Immotile	**87**	%	
Tỉ lệ sống Vitality		**14**	%	≥ 58%
Hình dạng bình thường Normal Morphology		**01**	%	≥ 4%
Bạch cầu White blood cells		**2**	x 10^6 BC/ml	≤ 1 x 10^6 BC/ml (WBC/ml)

Nhận xét khác
Other observations

ROS: Moderate levels

SDF = 20.33%



TREATMENT OF REDUCED SPERM QUALITY

- Anti-free radicals are becoming the most common treatment today for male infertility due to sperm abnormalities.
- The process of fighting free radicals for sperm protection can be combined by:
  - Provides substances that help activate and restore the body's antioxidant enzymes such as Vitamin B2, Vitamin B3, Zn, Cu, Mn, Selenium.
  - Provides external antioxidants such as quercetin, xanthohumol, Vitamin C, Vitamin E

Esteves and Agarwal, 2011

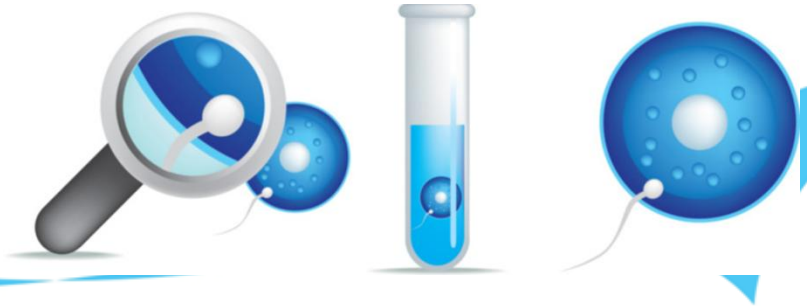
Study and antioxidant	*Antioxidant*	*Duration and dose*	*R/C/B*	*Sample size*	*Study population*	*Follow-up*	*Improvement in semen parameters*	*No improvement in semen parameters*
Lenzi *et al.*, 1993	Glutathione	2 months 600 mg/alternate day	Y/Y/Y	21	MFI (varicocoele and MAGI)	1 month	Motility, morphology	Concentration
Costa *et al.*, 1994	L-Carnitine	4 months, 3 g	N/N/N	100	Asthenozoo-spermia	2 months	Concentration, motility, morphology	
Lenzi *et al.*, 1994	Glutathione	2 months, 600 mg/alternate day	N/N/N	10	MFI (varicocoele, MAGI)	No	Concentration, motility, morphology	
Kessopoulou *et al.*, 1995	Vitamin E	3 months, 600 mg	Y/Y/Y	30	MFI patients with high ROS	4 months	Zona-binding assay (unfertilized human oocyte)	Concentration, motility, morphology, ROS
Moilanen and Hovatta, 1995	Vitamin E	3 weeks, 600 mg, 800 mg, 1200 mg	N/N/N	15	Infertility screening and volunteers	No		Concentration, motility, viability
Iwanier and Zachara, 1995	Selenium	3 months, 200 µg	N/N/N	33	Subfertile	No		Concentration, motility, morphology
Geva *et al.*, 1996	Vitamin E	3 months, 200 mg	N/N/N	15	ART patients	No	MDA concentration	Ultra morphology
Vezina *et al.*, 1996	Vitamin E, selenium	6 months, 400 mg vitamin E, 100 µg 1 month and 200 µg 5 months Se µg 2 months Se	N/Y/N	9	MFI (OAT)	2 months	Motility, morphology, viability	Concentration,
Suleiman *et al.*, 1996	Vitamin E	6 months, 300 mg	Y/Y/Y	110	Asthenozoo-spermia	No	Motility, MDA concentration	
Okada *et al.*, 1997	Pentoxifylline	300 mg 4 months then 1200 mg 4 months	N/N/N	33	Asthenozoo-spermia	No	Motility	ROS, zona-free hamster egg penetration test
Kodama *et al.*, 1997	Vitamins E, C, glutathione	2 months, 200 mg vitamin C, 200 mg vitamin E, 400 mg GSH	N/N/N	36	Infertile	No	Concentration, MDA concentration, DNA damage	Motility, morphology
Lewin and Lavon, 1997	Coenzyme Q_{10}	103 days, 60 mg	N/N/N	17	MFI	No	Fertilization rate	Concentration, motility, morphology
Scott *et al.*, 1998	Selenium, vitamins E, C, A	3 months, 100 µg Se, or Se with 1 mg vitamin A, 10 mg vitamin C, 15 mg vitamin E	Y/Y/Y	64	46 OAT, 16 subfertile	1 month	Motility	Concentration

IMPORTANCE OF SPERM DNA PROTECTION IN IUI

- Sperms with damaged DNA are more susceptible to attack than normal sperms when undergoing self-destruction during the period in the genital tract.
- Sperms having intact genetic components have the opportunity to meet and fertilize eggs better.
- The normal DNA preservation of sperms is an important factor for fertility when two spermatozoa are combined during spontaneous conception and IUI

IMPORTANCE OF SPERM DNA PROTECTION IN IVF

- There is an inverse correlation between sperm DNA damage levels and the development of embryo-fetus or trophocytes (
- The conception rate of women who undergo IVF reduces if her husband has high levels of sperm DNA damage (Li, 2006)
- The rate of miscarriage in women using assisted reproductive measures increases twice if the sperm DNA damage is high.



Eveson, 2006; Li, 2006; Taozzi, 2007)

Human Reproduction Vol.20, No.9 pp. 2590–2594, 2005
Advance Access publication June 2, 2005

doi:10.1093/humrep/dei091

ICSI in cases of sperm DNA damage: beneficial effect of oral antioxidant treatment

Ermanno Greco[1], Stefania Romano[1], Marcello Iacobelli[1], Susanna Ferrero[1], Elena Baroni[1], Maria Giulia Minasi[1], Filippo Ubaldi[1], Laura Rienzi[1] and Jan Tesarik[2,3]

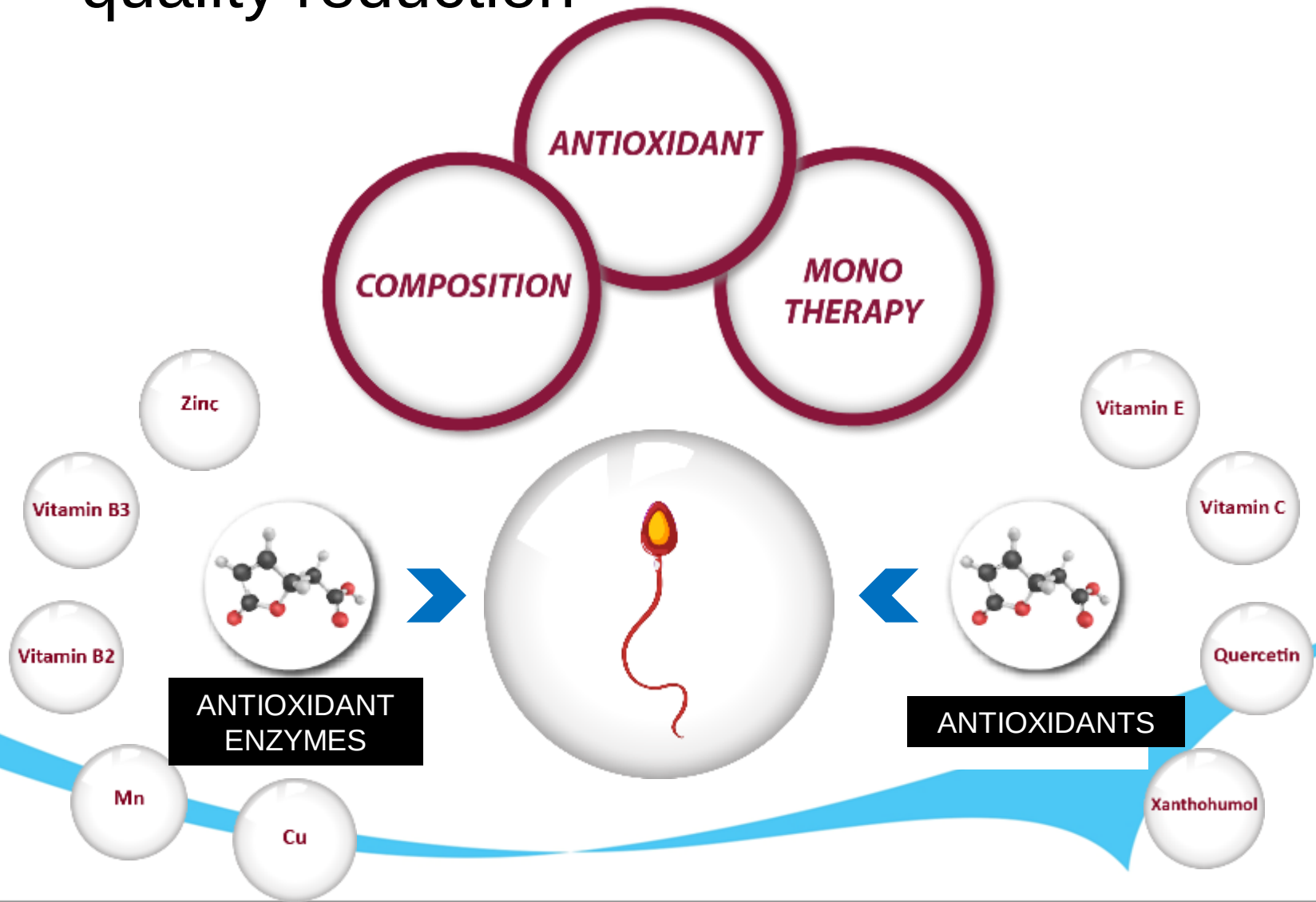
[1]Centre for Reproductive Medicine, European Hospital, Via Portuense 700, 00149 Rome, Italy and [2]MAR&Gen, Molecular Assisted Reproduction and Genetics, Gracia 36, 18002 Granada, Spain

[3]To whom correspondence should be addressed. E-mail: cmendoza@ugr.es

BACKGROUND: Most studies examining the use of ICSI for cases of elevated sperm DNA fragmentation report poor pregnancy and implantation rates. ICSI with testicular sperm samples has recently been suggested for these cases. Here we test a less invasive approach based on oral antioxidant treatment prior to ICSI with ejaculated spermatozoa. METHODS: Thirty-eight men with an elevated (≥15%) percentage of DNA-fragmented spermatozoa in the ejaculate were treated with antioxidants (1 g vitamin C and 1 g vitamin E daily) for 2 months after one failed ICSI attempt. In 29 (76%) of these cases this treatment led to a decrease in the percentage of DNA-fragmented spermatozoa, and a second ICSI attempt was performed. Outcomes of the two attempts were compared. RESULTS: No differences in fertilization and cleavage rates or in embryo morphology were found between the ICSI attempts performed before and after the antioxidant treatment. However, a marked improvement of clinical pregnancy (48.2% versus 6.9%) and implantation (19.6% versus 2.2%) rates was observed after the antioxidant treatment as compared with the pretreatment ICSI outcomes. CONCLUSIONS: Oral antioxidant treatment appears to improve ICSI outcomes in those patiens with sperm DNA damage, in whom this treatment reduces the percentage of damaged spermatozoa.

Key words: antioxidant treatment/ejaculated spermatozoa/ICSI/sperm DNA damage/sperm fertilizing ability

Which solution is used for the sperm quality reduction



Original article

Improvement of sperm quality after micronutrient supplementation

Martin Imhof [a,b,*], Jakob Lackner [a,c], Markus Lipovac [a,b], Peter Chedraui [d], Claus Riedl [e]

[a] Fertility Clinic IMI, Dorotheergasse 7, A-1010 Vienna, Austria
[b] Department of Obstetrics and Gynecology, General Public Teaching Hospital Korneuburg, Wiener Ring 3-5, A 2100 Korneuburg, Vienna, Austria
[c] Department of Urology, General Public Hospital Hietzing, Wolkersbergenstrasse 1, A-1130 Vienna, Austria
[d] Institute of Biomedicine, Universidad Católica de Santiago de Guayaquil, Av. Carlos J. Arosemena Km 1.5, Guayaquil, Ecuador
[e] Department of Urology, General Public Hospital Baden, Wimmergasse 19 A-2500 Baden, Austria

ARTICLE INFO

Article history:
Received 6 May 2011
Accepted 16 November 2011

Keywords:
Sperm quality
Oligoasthenoteratozoospermia
Idiopathic male infertility
Sub-fertility

SUMMARY

Background & aims: Nearly 50% of male infertility is idiopathic and to date there still is no proven therapy. We evaluated the effect of a non prescription nutraceutical containing eight micronutrients on sperm quality in males with idiopathic sub-fertility.
Methods: This open comparative pilot study was carried out at the Fertility Center IMI, Vienna, Austria. A total of 132 sub-fertile males (active treatment group) were invited to participate and take two daily capsules of the active compound for a three month period between the first and the follow-up semen analysis. Each capsule contained L-carnitine, L-arginine, zinc, vitamin E, glutathione, selenium, coenzyme Q10 and folic acid. Sub-fertile men receiving no active treatment served as controls ($n = 73$). Main outcome measure was the standardized semen analysis.
Results: All parameters evaluated by semen analysis significantly increased after 3 months of treatment with the active compound. Median ejaculatory volume, sperm cell density, sperm motility (progressive and total) and normal morphology rate increased by 33.3%, 215.5%, 83.1%, 36.4% and 23.0%, respectively. These increments were significantly higher than those observed among controls. In the active treatment group no side effects were encountered and a total of 34 pregnancies were reported after 6 months follow-up whereas 11 were reported in the control group.
Conclusion: Semen analysis significantly improved in sub-fertile men after treatment with an active

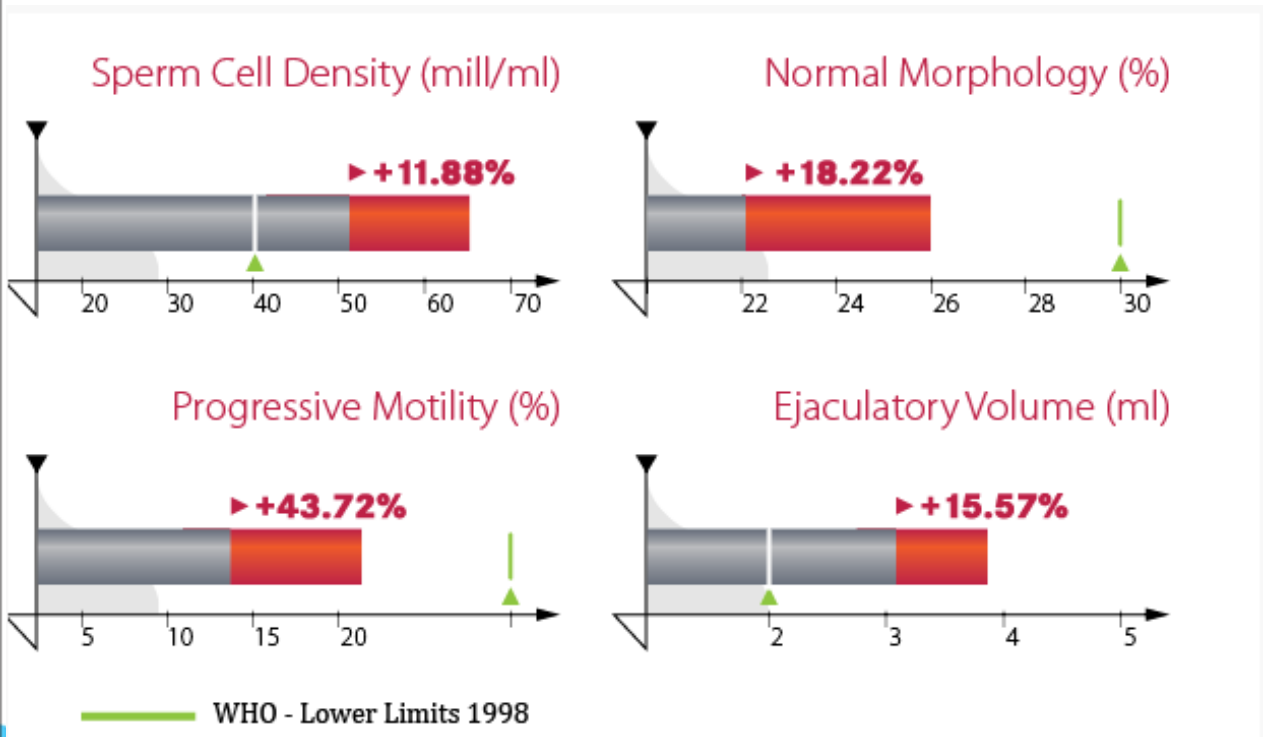
Table 1
Semen analysis data among studied groups (active treatment group and controls).

	Ejaculatory volume (ml)		Sperm cell density (million/ml)		Progressive motility (%)		Total motility (%)		Normal morphology (%)	
	Treatment	Control[c]	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
WHO lower limits	2		20		25		50		30	
Baseline median [IQR]	2.9 [1.5]	3.0 [1.7]	5.0 [6.5]	4.9 [5.8]	30.5 [25]	31 [38.8]	32.5 [23.8]	40.5 [44.8]	29.0 [15.2]	39.0 [38.5]
At three months median [IQR]	3.5 [2.3]	3.2 [1.8]	18.5 [23]	7.5 [9.0]	49 [32]	44.0 [47.2]	47.0 [26.0]	50.0 [40.1]	40.0 [17.5]	35.5 [42.3]
p value[a]	0.0001	0.46	0.0001	0.01	0.0001	0.06	0.0001	0.06	0.0001	0.95
Median % change from baseline	+33.3%	+3.7%[b]	+215.5%	+46.4%[b]	+83.1%	+44.0%[b]	+36.4%	+33.9[b]	+23.0%	−2.4%[b]

Note: Lower limit values for each semen parameter are provided in accordance to the WHO.[16]
[a] p values when comparing 3 months with baseline using Wilcoxon rank test; IQR: interquartile range.
[b] $p < 0.05$ when treatments are compared using Mann Whitney test.
[c] Controls were sub-fertile men ($n = 73$) who did not receive active compound.

Varicocele Study 2009

What is the role of varicocele in male infertility?
"Micronutrients as an alternative to fertility treatment in men with subclinical varicocele"



I.Schauer, R. Jost, M. Imhof: "Micronutrients as an alternative to fertility treatment in men with subclinical varicocele" EAU Bratislava 2010

Conclusion:

Treatment with micronutrients appears to be an option for improving sperm quality and consequently fertility, particularly in men with subclinical and low-grade varicocele, for whom surgical or interventional treatment are not indicated or where risks outweigh the benefits.

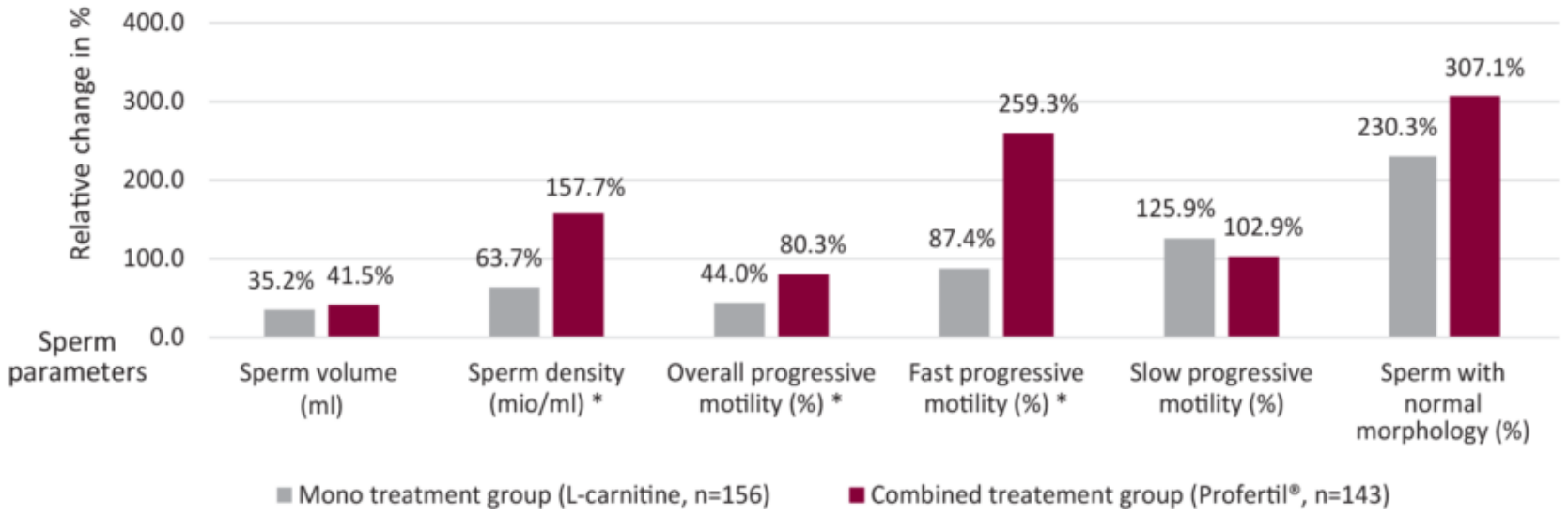
BỆNH VIỆN PHỤ SẢN TRUNG ƯƠNG
National Hospital of Obstetrics and Gynecology

L-carnitine Study 2016

BioMed Central
Reproductive Biology and Endocrinology

"Comparison of the effect of a combination of eight micronutrients versus a standard mono preparation on sperm parameters"

Relative change of sperm parameters after 3 months treatment (PROfertil® group compared to monosubstance group)



*p < 0.05

EMJ

Sperm DNA fragmentation index decreases after micronutrient supplementation

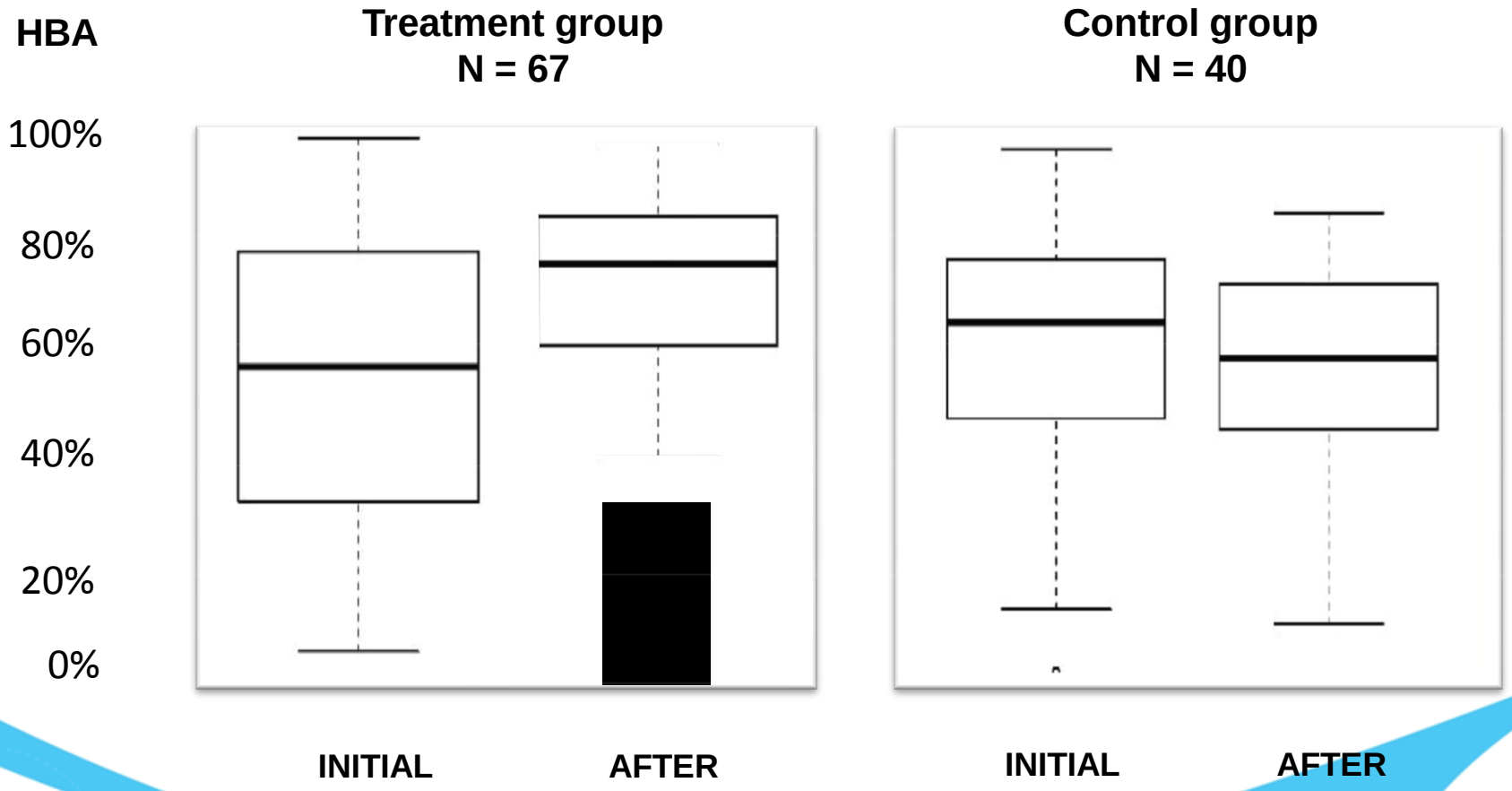
Increased hyaluronic acid binding ability of spermatozoa indicates better maturity and morphology, as well as higher DNA integrity after micronutrient supplementation

Trial setting	Treatment group	Control group
Inclusion criteria	subfertile men (> 1 year) with 2 pathological semen analyses	
Exclusion criteria		
Parameter		
Treatment		

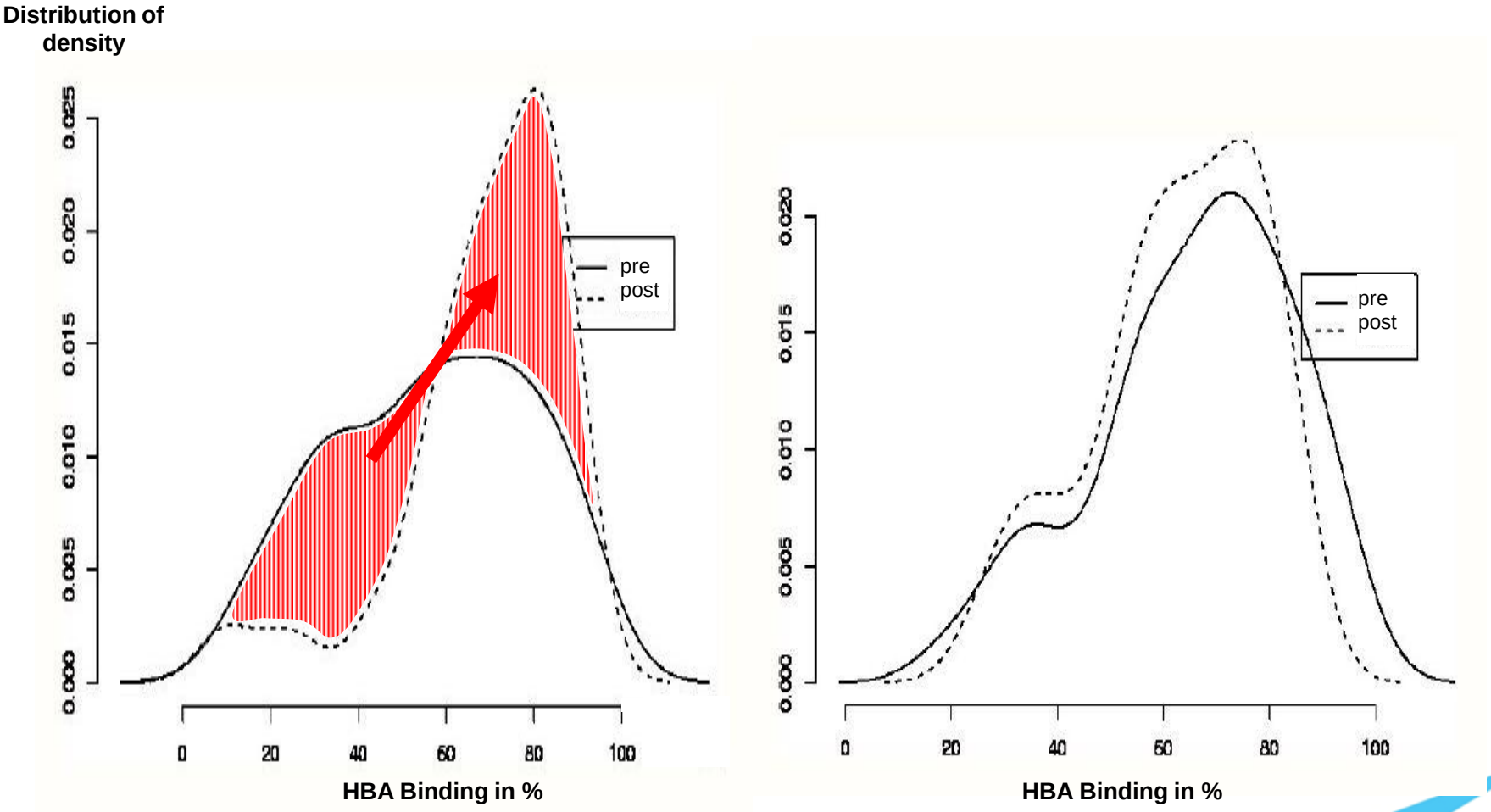
Lipovac M, et al.; EMJ Urology 2014 1:60-65.

EMJ

Results


HBA
Treatment group
N = 67
Control group
N = 40
100%
80%
60%
40%
20%
0%
INITIAL
AFTER
INITIAL
AFTER

Data before and after treatment, compared to control group



Therapy group n=67	Control group n=40

"This disease impacts both economically and mentally, family happiness is greatly affected. As a man, I should not say but my wife's psychology is clearly not good. Sometimes I feel optimistic but sometimes I think there is no hope anymore." PVS NB4.

"Because of wanting to have children, someone - sometimes as friends, sometimes as our relatives, told me some places then I went immediately to there for treatment. After 5 years, I took home-remedies of a herbalist who lived nearly to my house for 6 months without results, then I also went to many other herbalists and traditional acupuncture clinics. The cost of each place was from 4 million to 50 million dongs." PVS NB2.

"Previously I saw in internet that there was a place where a home-remedy for infertility treatment was sold, its price was 10 million dongs per month. I took it without any results." PVS NB1.

"Based on my friends' instructions and verbal information, I found a herbalist who prescribed 5-6 packs of traditional medicines at a cost of several million dongs, but they did not have any effect. That place did not have a sign board and surely that it did not have a license." PVS NB4.

Thank You