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The importance of the male in poor responders

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The importance of

- history taking and examination
- semen analysis
- novel diagnostic and prognostic tests

impediments

- the neglect of andrological research since ISCI
- the lack of funding to improve
- but now there is a window of opportunity

Young patients with diminished ovarian reserve undergoing assisted reproductive treatments: a preliminary report

Banu Kumbak[1], Engin Oral, Semra Kahraman, Guvenc Karlikaya, Hale Karagozoglu

Table 1. Distribution of causes of infertility by number and percentage. DOR = diminished ovarian reserve; NR = normal ovarian reserve. There were no statistically significant differences between the two groups.

	Young DOR patients	*Young NR patients*
Tubal factor	14 (20)	11 (21)
Male subfertility	31 (44)	23 (43)
Unexplained infertility	21 (30)	14 (27)
Mixed	4 (6)	5 (9)

Values in parentheses are percentages.

RBM 2005 11 (3) 294-299

How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis

Dimitra Kyrou, M.D., Efstratios M. Kolibianakis, M.D., M.Sc., Ph.D., Christos A. Venetis, M.D., M.Sc., Evangelos G. Papanikolaou, M.D., M.Sc., Ph.D., John Bontis, M.D., Ph.D., and Basil C. Tarlatzis, M.D., Ph.D.

Fertility and Sterility 2009 91 (3) 749-766

TABLE 2

Baseline characteristics of patients included in the studies analyzed in the systematic review.

Study	Baseline characteristics of patients
Bahceci et al., 2006	Not reported
Battaglia et al., 1999	Mean age 40.2 ± 2.1 years, tubal infertility, regular menstrual cycles (28 ± 4 days), fertile partners according to WHO criteria, not receiving any hormonal treatment for 4 months before initiation of treatment. Exclusion criteria: intercurrent illness, BMI >30 kg/m^2, endometriosis, ovarian functional cyst, polycystic ovarian syndrome, unilateral ovarian resection or ovariectomy, regular exercise, heavy smokers (>10 cigarettes/day), hypertension.
Bergh et al., 1994	Regular menstrual cycles (25–35 days), normal semen analysis (according to WHO criteria) and normal basal FSH, LH, and PRL levels. Additionally, normal US appearance of ovaries before stimulation. Exclusion criteria: Severe intercurrent illness, severe endometriosis, BMI >28 kg/m^2, unilateral ovariectomy plus ovarian resection of the other ovary as well as malignancy, HIV infection.
D'Amato et al., 2004	Age 27–39 years, primary or secondary infertility, normal menstrual cycles, BMI <27 kg/m^2, not taking medication for at least 3 months. Exclusion criteria: polycystic ovarian syndrome, stage III–IV endometriosis and hypothalamic amenorrhea.
Dimfeld et al., 1999	Basal FSH levels >9 mIU/mL and <12 mIU/mL on two or more consecutive measurements at 1 month apart Exclusion criteria: Age >42 and irregular menstrual cycles.
Dor et al., 1995	Otherwise healthy patients with basal FSH and LH levels <10 IU/L
Garcia-Velasco et al., 2000	No exclusion criteria and no age limit, 37.1% male factor infertility, 11.4% tubal infertility, 21.4% unexplained infertility, and 30% combination of male and female infertility.
Goswami et al., 2004	One to three unintervened cycles between last and current treatment cycle, evaluation of basal FSH and other endocrinopathy during the cycle preceding the index cycle. Exclusion criteria: severe endometriosis, history of previous pelvic surgery or basal FSH 12 mIU/mL.
Howles et al., 1999	Women aged 18–40 years and with documented tubal or unexplained infertility
Kim et al., 1999	Age: ≤39, normoprolactinemic, with normal liver and kidney function tests, with normal menstrual cycles. In all patients, an interval of at least 2 months was allowed to elapse between IVF-ET cycles. Exclusion criteria: diabetes or hypertension, polycystic ovaries in US.
Malmusi et al., 2005	Basal FSH < 15 mIU/mL at previous IVF attempts. Exclusion criteria: Azoospermia.
Marci et al., 2005	Age: 32–44; mean age: 39
Martinez et al., 2003	Mean age: 38.7 ± 3.9, Basal FSH level: 11.7 ± 5.6 mUI/mL, and mean number of previous IVF cycles: 2.6 ± 1.3
Massin et al., 2006	Age ≤ 42, with no history of previous ovarian surgery or ovarian endometriosis or endocrine and metabolic disorders. FSH > 12 IU/l, E_2 > 70 pg/mL, inhibin B < 45 pg/mL on day 3 of a spontaneous cycle.

Kyrou. Poor responders and pregnancy. Fertil Steril 2009.

Few studies account for male factors

TABLE 2

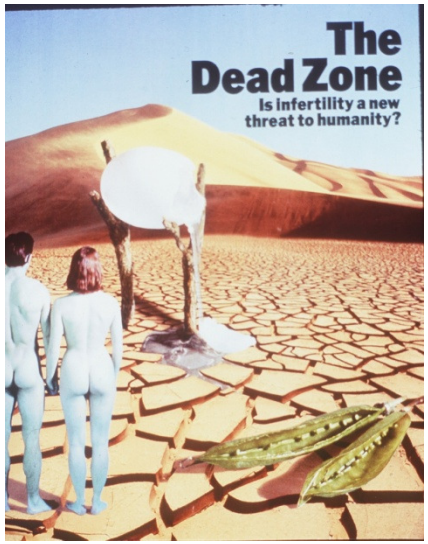
Continued.

Study	Baseline characteristics of patients
Moreno et al., 1998	The mean age of the females was 36.7 ± 0.6 and 35.3 ± 0.6 years respectively. A total of 34.6 and 38.5% of the patients in each group had at least one previous cancelled cycle due to low response. All male partners presented no anti-sperm antibodies and normal sperm samples according to the criteria of the WHO
Morgia et al., 2004	Age: ≤43, regular menstrual cycles (26–39 days) with primary infertility
Owen et al., 1991	Age: < 38, patients with normal as well as polycystic ovaries
Raga et al., 1999	Age: ≤35, normal ovulatory cycles, and good physical and mental health
Schmidt et al., 2005	Age: 25-43, basal FSH <13 mIU/mL and serum E_2 level <75 pg/mL, no follicular development, defined as a follicle >10 mm at the start of gonadotropin stimulation
Suikkari et al., 1996	Age: 25-40 and BMI: 19-27 kg/m^2 basal FSH < 16mIU/mL. Infertility diagnosis: tubal (46.5%), minimal endometriosis (4.6%), male factor (9%) and idiopathic (41%). Exclusion criteria: hypertension (140/90 mmHg), diabetes mellitus, thyroid disorder, hyperprolactinemia (serum PRL <17 ng/ml) or history of acromegaly
Weissman et al., 2003	Basal FSH <20 IU/L
Zhuang et al., 1994	Infertility diagnosis: tubal factor or unexplained

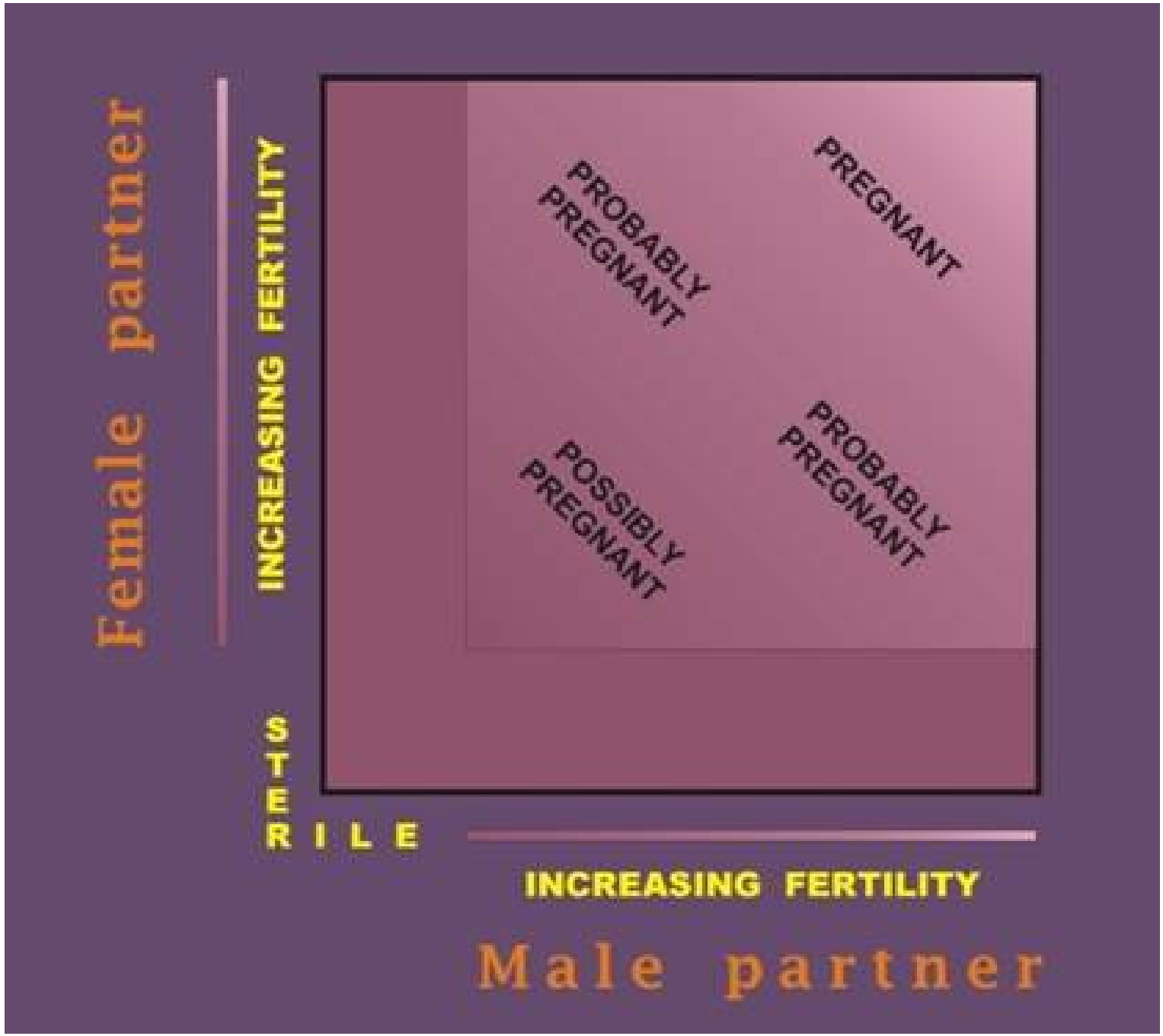
Note: WHO = World Health Organization; FSH = follicle stimulating hormone; LH = luteinizing hormone; PRL= prolactin; US = ultrasound; BMI = body mass index; IVF-ET = in vitro fertilization-embryo transfer; E_2 = estradiol

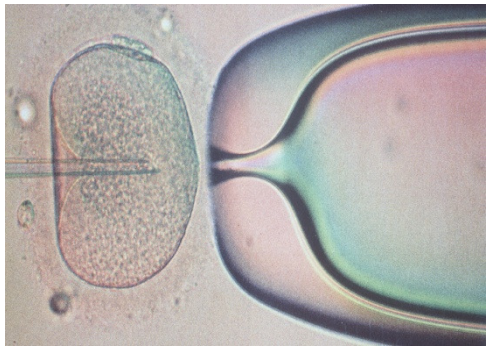
Egon. Poor responders and pregnancy. Fertil Steril 2009.

Male and female contributions to infertility

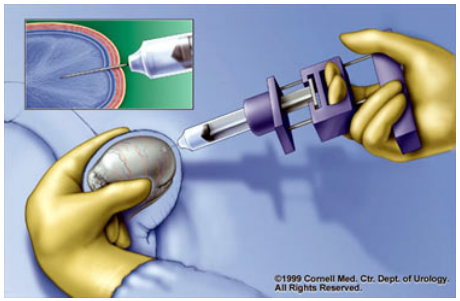


	Female	Male	Female and male	Unexplained
Diagnosis	40	40	65	20
IVF	46	31	13	23
ICSI	16	64	15	20


Female partner
INCREASING FERTILITY
PROBABLY PREGNANT
PREGNANT
POSSIBLY PREGNANT
PROBABLY PREGNANT
INCREASING FERTILITY
Male partner



The success of ISCI has led to a downsizing of clinical care of the male and research into sperm dysfunction



History Taking

- **duration of involuntary infertility**
- **previous partnerships and children**
- **previous infertility investigations**
- **history of diseases with possible adverse effects on fertility (cancer,'flu)**
- **pathology/surgery causing testicular damage**
- **occupational risks**
- **drugs (prescription and recreational)**
- **difficulties with sexual function**

Male Infertility ed TB Hargreave, 1994

How to improve the probability of pregnancy in poor responders undergoing in vitro fertilization: a systematic review and meta-analysis

Dimitra Kyrou, M.D., Efstratios M. Kolibianakis, M.D., M.Sc., Ph.D., Christos A. Venetis, M.D., M.Sc., Evangelos G. Papanikolaou, M.D., M.Sc., Ph.D., John Bontis, M.D., Ph.D., and Basil C. Tarlatzis, M.D., Ph.D.

Insufficient evidence exists to recommend most of the treatments proposed to improve pregnancy rates in poor responders

Physical examination

- **General examination**

  body hair distribution

  gynaecomastia

  Inguinal examination

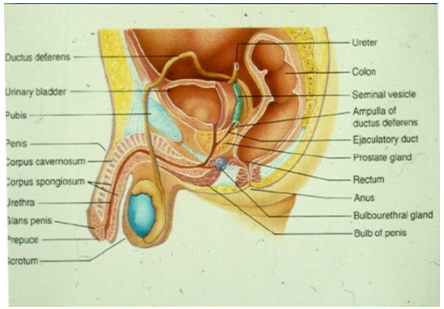
- **Exam of penis**
- **Exam of testis**

  position, axis vol, consistency

- **Exam of epididymis,**

  vasa deferentia,

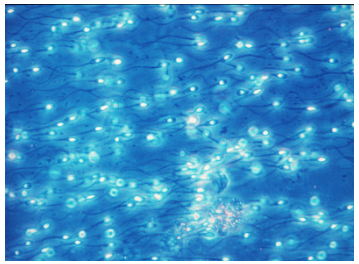
  prostate gland



Lab tests

- Testosterone
- SHBG
- Inhibin
- Inflammatory markers

Conventional Sperm Evaluation



• Recommended Abstinence	• 2-7 days
• Volume	• 1-6mL
• pH, liquefaction, viscosity	• 7.2-8.2, complete, normal
• Presence of leucocytes	• >1 x 10^6 /mL
• Presence of organisms	• none
• Sperm concentration	• >20 x 10^6/mL
• Total and progresssive motility	• >50%, >25%
• Sperm morphology	• >30%, >14% Tygerberg
• Antisperm antibodies (IgG and IgA)	• <50% motile sperm with Ab

criteria recommended by WHO (1999)

Regional and world-wide variation of semen parameters

- **Within USA, New York had highest concentrations (134 x 10^6/mL)**
  Iowa had lowest concentrations (48 x 10^6/mL)
  cf Thailand (52 x 10^6 /mL)
- **In Japan, fertile men had lower semen quality, similar to Norway (20% < WHO)**
- **In Europe, Finland and Denmark's fertile men have markedly different semen profiles**

Fisch et al, 1996, Swan, 2006; Jorgensen et al, 2006; Iwamoto et al, 2006

Variability of semen parameters between and within individuals

- **Marked biological heterogeneity of semen in 243 fertile men**
  Chia et al, 1998

- **Consecutive samples from same individual** (twice a week for 120 weeks)
  WHO, 1990

  (673 samples from 7 men over 324 weeks)
  Mallidis et al,1991

Clinical significance of semen profiles

No single parameter was diagnostic of infertility (n=1461)
Extensive overlap between fertile and infertile ranges
Morphology most powerful
Guzick et al, 2001

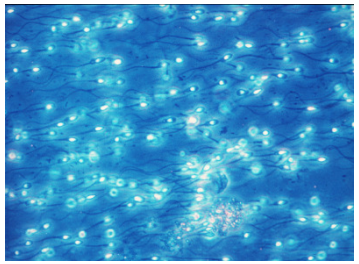
Morphology most powerful but volume and motility of limited value
Concentration <40 x 10^6 /mL no further association (n=430)
Extensive overlap between fertile and infertile ranges
Bonde, Skakkebaek et al, 1998

Concentration and motility were most powerful
Morphology poorest predictive power
- 50% of fertile men had abnormal morphology (n=719)
Nallella, Agarwal et al, 2006

243 fertile men had a mean of only 20% normal morphology by WHO 1992 criteria ***Chia et al, 1998***

Reference values have little diagnostic use

Conventional Sperm Evaluation

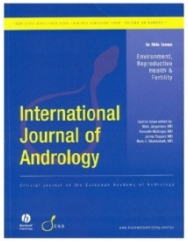


- **Volume** — min 2mL→ 1.5mL
- **Sperm concentration** — >20 x 10^6/mL → 15 x 10^6/mL
- **Motility** — >50%, → > 32%,
- **Sperm morphology** — >14% → 4%
- **Vitality** — 75% → 59%

criteria recommended by WHO (2010)

Fertility rates and future population trends: will Europe's birth rate recover or continue to decline?

Wolfgang Lutz

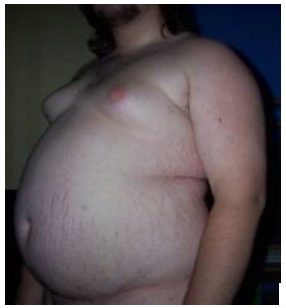


- **After a sustained decline, EU birth rate is now 1.6 children/couple**
- **Why? – choice or reduced fertility?**

Cause of declining semen quality?

environmental pollution

lifestyle factors

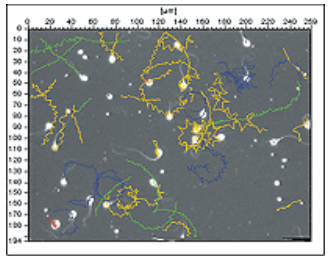


obesity, diabetes

sexually transmitted infections

alcohol, tobacco, recreational drugs

Sperm function tests



- **Quantitative motion (CASA)**

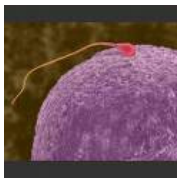
  Donnelly, Lewis et al, 1998;Hirano et al, 2001

- **Hyperactivation (CASA)**

  Sukchareon et al, 1995

- **Cervical mucus penetration**

  Eggert-Kruse et al; 1989 Shara et al, 1995

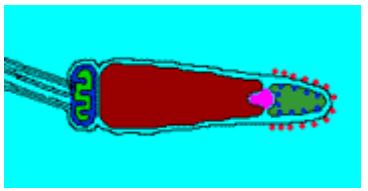


- **Sperm-zona recognition and penetration**

  Liu and Baker, 2004; Cabellero- Capo et al, 2006

- **Acrosome reactions- basal and induced –ARIC**

  Cummins et al, 1991



Oxidative stress tests

- **XS production of ROS, H_2O_2 and $O_2^{\cdot -}$**

  Jones et al, 1979; Aitken and Clarkson, 1987; Aitken et al, 2006

- **Inadequate antioxidant protection**

  Lewis et al, 1995;Agarwal et al, 2003; Aitken, 2005

- **Chemiluminescence tests- Lucigenin and Luminol**

  Donnelly, Lewis et al, 1994; Said et al, 2004

- **Leucocyte contamination - use of anti CD beads**

  Aitken 1996

- **OS measured by lipid peroxidation and nDNA and mtDNA damage**

  Lewis and Aitken, 2005; Aitken, 2006

Sperm DNA damage

Male Infertility

Occupation

Plastics and resins, solvents,
wood processing, metal industry,
Automobile, truck and aircraft mechanics
Sedentary or stressful job

Environment

Endocrine disruptors

xenoestrogens

Anti-androgens

Toxic compounds

Genetic Inheritance

CABVD

Robertsonian translocations

Y-chromosome deletions

Paternal Age

Lifestyle

diet

smoking

alcohol

recreational drugs

STIs

injury

infection

Do Sperm DNA anomalies influence fertility outcomes?

- **Failure of fertilization in IVF**

  Bianchi et al, 1993; Sun et al, 1997

- **Failure to implant in ICSI**

  Sakkas et al, 1996; Lopes et al, 1998

- **Increased time to conception**
- **Poor embryo development**

  Morris et al, 2002; Tomsu et al, 2002

- **Post-implantation loss and malformations**

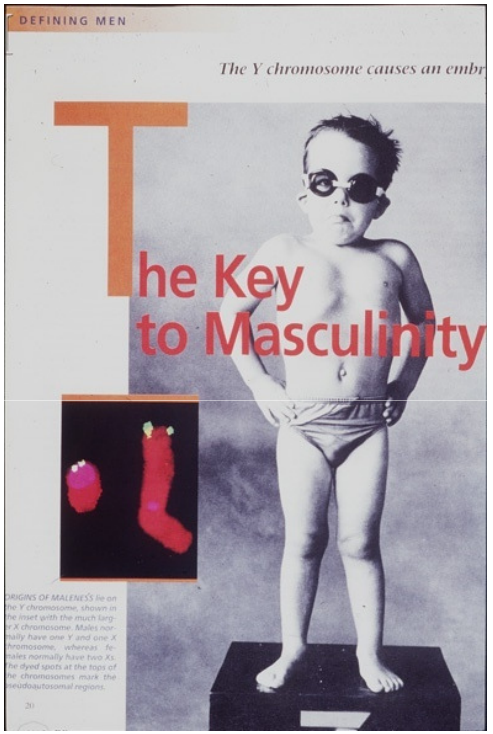
  Robaire et al, 1985

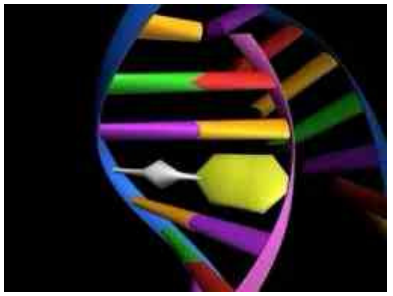
- **Increased miscarriage rate**

  Evenson et al, 1999; Carrell et al, 2003

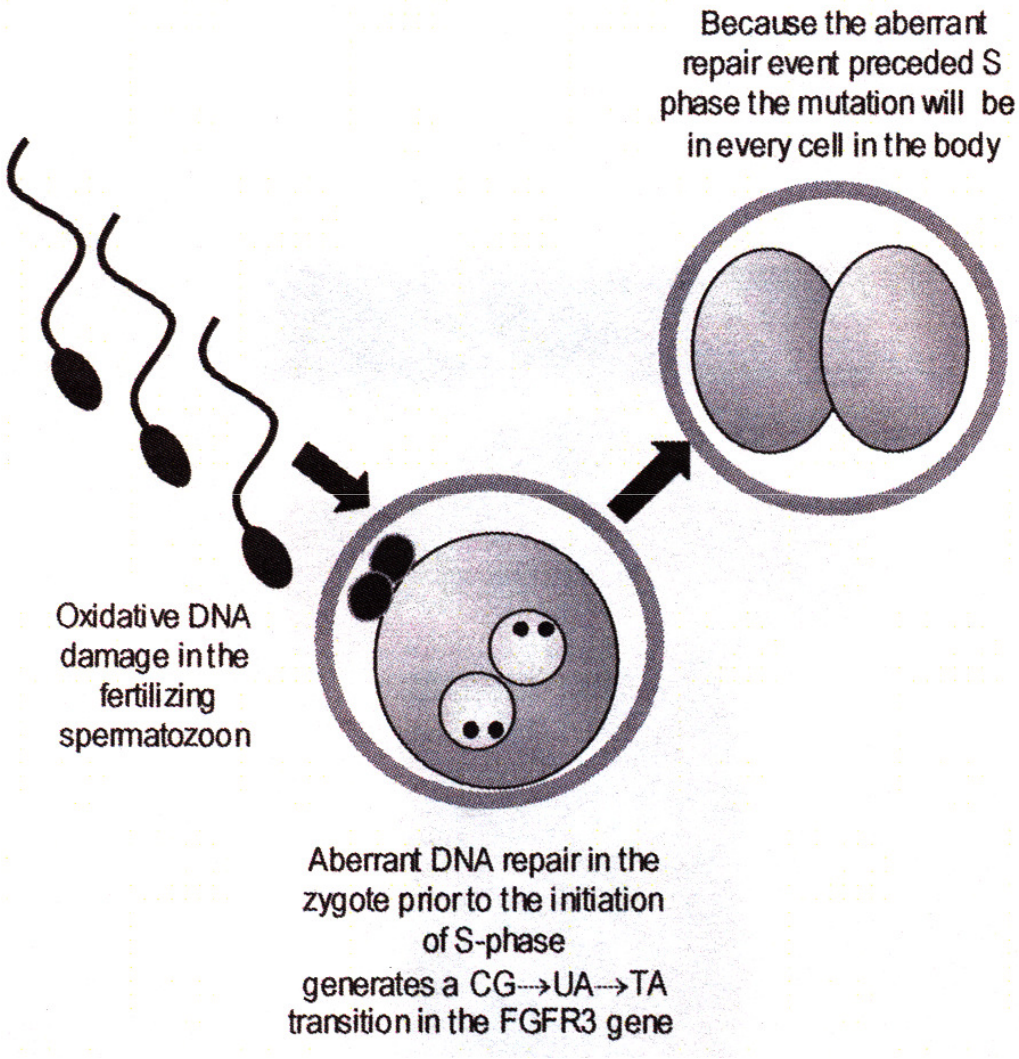
- **Childhood cancers**

  Knight and Marrett, 1997





Ramifications of sperm DNA damage



Aitken and de Iulius, 2007

Risk of Diseases in Offspring from Damaged Sperm DNA

- **Sperm DNA damage increases with ♂ Age**

  Singh et al, 2003; Wyrobek et al, 2006; Aitken and de Iulius, 2007

- **Oxidative damage increases with Age**
- **↑ ♂ age is associated with ↑ incidence of disease**

  -miscarriage *de Rochebrochard and Thonneau, 2002*

- **dominant genetic mutations-Achondroplasia and Apert Syndrome**

  Crow, 2000; Wyrobek et al, 2006

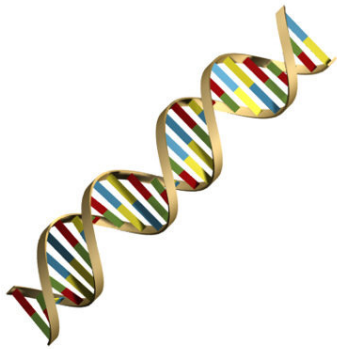
- **neurological Disorders -Schizophrenia, Autism and Bipolar Disease**

  Sipos et al, 2004; Frans et al, 2008

- **Birth defects- neural tube defects and even Downs Syndrome**

  McIntosh et al, 1995

Are sperm DNA tests useful as diagnostic or prognostic clinical tests?



IN VITRO FERTILIZATION

Do sperm DNA integrity tests predict pregnancy with in vitro fertilization?

John A. Collins, M.D.,[a] Kurt T. Barnhart, M.D.,[b] and Peter N. Schlegel, M.D.[c]

Journal of Andrology, Vol. 30, No. 3, May/June 2009

Are Tests of Sperm DNA Damage Clinically Useful? Pros and Cons

Review

ARMAND ZINI* AND MARK SIGMAN

For a DNA test to be useful, it must have strong predictive capacity for pregnancy outcome and little overlap between fertile and infertile samples

IN VITRO FERTILIZATION

Do sperm DNA integrity tests predict pregnancy with in vitro fertilization?

John A. Collins, M.D.,[a] Kurt T. Barnhart, M.D.,[b] and Peter N. Schlegel, M.D.[c]

TABLE 1

Methodological features: studies of the association between sperm DNA fragmentation and pregnancy.

Study	Treatment	Assay	Normal range	Cycles	Pregnancy outcome	Outcome rates (%)
Boe-Hanson et al., 2006 (46)	IVF	SCSA	DFI <27%	139	Clinical	28
	ICSI	SCSA	DFI <27%	47	Clinical	30
Borini et al., 2006 (52)	IVF	TUNEL	<10%	82	Clinical	22
	ICSI	TUNEL	<10%	50	Clinical	24
Bungum et al., 2007 (27)	IVF	SCSA	DFI <30%	388	Delivery	28
	ICSI	SCSA	DFI <30%	223	Delivery	38
Check et al., 2005 (47)	IVF	SCSA	DFI <30%	106	Ongoing	17
Gandini et al., 2004 (48)	ICSI	SCSA	DFI <30%	22	Full term	41
Host et al., 2000 (53)	IVF	TUNEL	≤4%	175	Biochemical	29
	ICSI	TUNEL	≤4%	61	Biochemical	34
Huang et al., 2005 (54)	IVF	TUNEL	≤4%	217	Pregnancy	55
	ICSI	TUNEL	≤4%	86	Pregnancy	51
Larson et al., 2000 (24)	IVF, ICSI	SCSA	DFI <27%	24	Pregnancy	29
Larson-Cook et al., 2003 (25)	IVF, ICSI	SCSA	DFI <27%	89	Clinical	31
Payne et al., 2005 (49)	IVF, ICSI	SCSA	DFI <27%	94	Clinical	33
Seli et al., 2004 (14)	IVF, ICSI	TUNEL	<20%	49	Clinical	47
Virro et al., 2004 (50)	IVF, ICSI	SCSA	DFI <30%	249	Ongoing	41
Zini et al., 2005 (51)	ICSI	SCSA	DD ≤30%	60	Clinical	52

Note: DD, sperm DNA denaturation; DFI, DNA fragmentation index; SCSA, sperm chromatin structure assay; TUNEL, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling assay.

Collins. Sperm DNA integrity tests. Fertil Steril 2008.

- 22 studies
- 13 studies with 2161 cycles
- SCSA or TUNEL
- biochem preg. to delivery
- female age uncontrolled
- DFI : 27% or 30%
- overall preg rates 17-55%

(Diagnostic) Odds Ratios

An Odds Ratio gives us the chance of a pregnancy occurring if the test result is above our specified threshold

Odds ratios need to be > 2.0
to be useful
If CIs include 1.0,
relationship is usually NS

TABLE 2

Diagnostic test properties: studies of the association between sperm DNA fragmentation and pregnancy.

Study	Treatment	Sens	Spec	Sens + Spec	Abnormal tests (%)	DOR	(95% CI)
Boe-Hansen et al., 2006 (46)	IVF	0.06	0.97	1.03	5	2.04	(0.38, 11.0)
	ICSI	0.36	0.57	0.94	38	0.76	(0.21, 2.73)
Borini et al., 2006 (52)	IVF	0.17	0.89	1.06	16	1.57	(0.38, 6.51)
	ICSI	0.71	0.75	1.46	60	6.55	(1.77, 24.3)
Bungum et al., 2004 (26)	IVF	0.17	0.85	1.02	16	1.16	(0.64, 2.12)
	ICSI	0.30	0.63	0.93	33	0.74	(0.42, 1.31)
Check et al., 2005 (47)	IVF	0.30	0.83	1.13	27	1.90	(0.61, 5.89)
Gandini et al., 2004 (48)	ICSI	0.38	0.44	0.83	45	0.52	(0.10, 2.74)
Host et al., 2000 (53)	IVF	0.34	0.80	1.14	30	1.91	(0.93, 3.91)
	ICSI	0.58	0.38	0.96	59	0.84	(0.29, 2.43)
Huang et al., 2005 (54)	IVF	0.22	0.83	1.04	19	1.30	(0.66, 2.56)
	ICSI	0.64	0.50	1.14	57	1.78	(0.76, 4.16)
Larson et al., 2000 (24)	IVF, ICSI	0.58	0.94	1.59	42	10.17	(1.77, 58.4)
Larson-Cook et al., 2003 (25)	IVF, ICSI	0.17	0.98	1.16	11	5.08	(1.24, 20.8)
Payne et al., 2005 (49)	IVF, ICSI	0.16	0.71	0.87	20	0.44	(0.15, 1.27)
Seli et al., 2004 (14)	IVF, ICSI	0.46	0.61	1.07	43	1.32	(0.43, 4.07)
Virro et al., 2004 (50)	IVF, ICSI	0.35	0.81	1.17	29	2.27	(1.30, 3.96)
Zini et al., 2005 (51)	ICSI	0.17	0.81	0.98	18	0.87	(0.24, 3.19)

Note: CI, confidence interval; DOR, diagnostic odds ratio; Sens, sensitivity; Spec, specificity.

Collins. Sperm DNA integrity tests. Fertil Steril 2008.

Small and significant risk of failed pregnancy
(diagnostic OR 1.44, CI:1.03-2.03)
but
Current tests not strong enough yet to warrant clinical use

To improve diagnostic accuracy

- **identify vulnerable subgroups**
- **control for female age**
- **make end point live birth not pregnancy**
- **consecutive accrual**
- **standardise protocols, blinded testing**
- **develop more sensitive markers**

My question to you-

is it not more predictive than a semen analysis?

Journal of Andrology, Vol. 30, No. 3, May/June 2009

Are Tests of Sperm DNA Damage Clinically Useful? Pros and Cons

Review

ARMAND ZINI* AND MARK SIGMAN

Sperm DNA Damage and IVF Outcomes

Author	n	design	Female sel	Assay	Threshold (%)	< Preg (%)	> Preg (%)	Fert	Preg	OR	CI
Filatove ’99	176	-	none	Chromatin compaction	50	23	6	0	↓	6.33	1.82,22.08
Host ’00	175	Pro	none	TUNEL	4	NA	NA	↓	↓	1.92	0.92,4.04
Tomlinson ’01	140	-	none	ISNT	-	NA	NA	0	↓		
Tomsu ’02	40	Pro	<40	COMET	-	NA	NA	0	↓		
Morris ’02	20	Retro	<40	COMET	-	NA	NA	0	0		
Henkel ’03	208	Pro	None	TUNEL	37	34.7	18.7	0	0	2.24	1.09,4.58
Gandini ’04	12	Pro	None	SCSA	27	25	0	0	0		
Huang ’05	217	Retro	None	TUNEL	10	56.8	51.7	↓	0	1.30	0.66,2.56
Boe- Hansen ’06	139	Pro		SCSA	27	29	14.3		↓	2.43	0.28,20.83
Borini ’06	83	-	None	TUNEL	10	23.2	15.4	↓	↓	1.66	0.33,8.28
Bakos ‘07	45	-	None	TUNEL	-	NA	NA	↓	↓		
Benchaib ’07	84	pro	<40	SCSA	15	29	25	0	↓	0.46	0.11,2.00
Bungum ‘07	388	pro	<40	SCSA	30	33.7	29	0	↓	1.24	0.69,2.26
Frydman ‘07	117	pro	<40	TUNEL	35	57.8	23.5	0	↓	2.97	1.39,6.32
Lin ‘07	117	pro	<40	SCSA	27	51.3	54.4	0	↓	0.88	0.35,2.19

So is DNA damage a useful test for IVF?

- **Combined odds ratio 1.67 (1.27-2.20) p<0.01**
- **Positive predictive value 74% no PR (with high DNA damage)**

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Sperm DNA Damage and ICSI Outcomes

Author	n	design	assay	Threshold (%)	< Preg (%)	> Preg (%)	Fert	Preg	OR	CI
Hammadeh ’96	61	Pro	A-Blue	29	18.5	35.3	0	↓	2.40	0.72,7.96
Host ’00	61	Pro	TUNEL	4	NA	NA	0	0	0.79	0.28,2.25
Virant-Klun ’02	183	Pro	AO	56	--	--	↓	0		
Morris ’02	40	Pro	COMET	-	NA	NA	0	0		
Henkel ’03	54	Retro	TUNEL	24	48	22.2	0	0	3.67	1.12,12.0
Gandini ’04	22	Pro	SCSA	30	44.4	55.6	0	0	0.36	0.06,2.08
Huang ’05	86	Retro	TUNEL	4	59.5	33.3	↓	0	1.80	0.76,4.27
Check ’05	104	-	SCSA	30	--	--	-	0	1.34	0.52,3.43
Zini ‘05	60	Pro	SCSA	30	51	55	0	0	0.87	0.23,3.22
Boe-Hansen ’06	47	Pro	SCSA	27	27.6	33.3		0	0.76	0.21,2.72
Borini ’06	50	-	TUNEL	10	45	10	0	↓	7.36	1.67,32.4
Muriel ’06	85	Pro	SCD	-	NA	NA	↓	0		
Benchaib ’07	218	pro	TUNEL	15	37.4	27.8	0	↓	1.55	0.70,3.41
Bungum ’07	223	Pro, consec	SCSA	30	37.3	47.9	0	0	0.65	0.37,1.14
Lin ’07	86	pro	SCSA	27	52.3	47.6	0	0	1.21	0.45,3.23
Bakos ‘07	68	-	TUNEL	35	NA	NA	0	↓		

Combined Odds ratio=1.20 (0.91,1.59)
p>0.05

so there is no clinical application as sperm DNA damage does not affect pregnancy rates after ICSI

- ISCI appears to bypass poor sperm DNA too

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Sperm DNA Damage and Pregnancy Loss after IVF and/or ICSI

Author	ART	n	Threshold	< Preg loss (%)	> Preg loss (%)	Preg loss (%)	Risk	OR	CI
Virro '04	IVF and ICSI		30%	NA	NA				
Check '05	ISCI	104		--	--	47	↑	2.27	0.45,1.59
Zini '05	ISCI	60	30%	12	33	16	↑	3.67	0.46,29.42
Borini '06	IVF	82	10%	15.8	50	6	↑	32.0	0.62,1663
Borini '06	ICSI	50	10%	0	62.5	25	↑	108.0	1.73,6729
Benchaib '07	IVF	84	30%	2.6	25	13	↑	10.0	0.87,114.8
Benchaib '07	ICSI	218	30%	2.8	8.3	13	↑	3.51	0.89,23.28
Lin '07	ISCI	137	27%	11.8	40	12	↑	2.56	0.44,15.03
Lin '07	IVF	86	27%	8.5	16.7	12	↑	5.00	0.97,25.77
Frydman '07	ISCI	117	35%	10	36.8	19	↑	5.25	1.31,21.11
Bungum '07	IVF	388	30%	24.4	19	22	0	0.73	0.23,233
Bungum '07	ICSI	223	30%	15.6	23.8	22	↑	1.69	0.63,4.49

So is DNA damage a useful test for predicting pregnancy loss?

- **Combined odds ratio 2.48 (1.52-4.04) p<0.0001**
- **Rate of pregnancy loss is 37% with high DNA damage and only 10% with low DNA damage**
- **Clinically valuable information but**
- **will this information affect clinical practice?**

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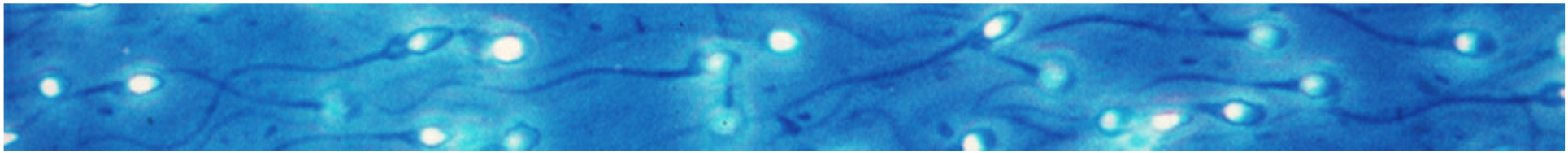
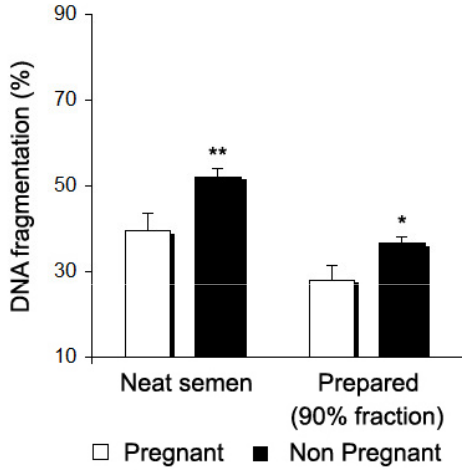
Early clinical pregnancy loss rate in poor responder patients does not change compared to age-matched normoresponders

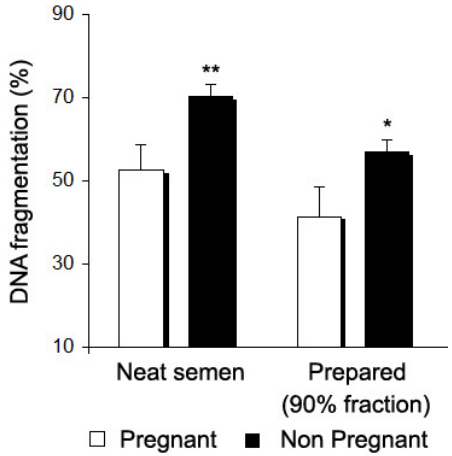
Banu Kumbak, M.D.,[a] Ulun Ulug, M.D.,[b] Burcak Erzik, M.D.,[b] Hande Akbas, M.D.,[b] and Mustafa Bahceci, M.D.[b]

- All fresh ART cycles (n=1300, IVF and ICSI)
- Only exclusion –testicular sperm
- lower probability of clinical pregnancy
- But no increase in ECPRL



Relationship between sperm DNA fragmentation and pregnancy rates in IVF





Assay	Sample	n	ROC	CI	P
Comet	Native	219	0.648	0.56-0.74	0.006
	DCG	219	0.629	0.54-0.72	0.016
Comet + FPG	Native	64	0.776	0.64-0.91	0.004
	DCG	64	0.693	0.52-0.86	0.005

- **Native semen – 39.5 v 51.7 %**
- **DGC sperm – 26.9 v 36.8%**
- **Potential breaks constitute additional 12 – 20 %**
- **Adducts present in both native and DGC sperm**

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Only couples presenting with abnormal semen parameters i.e male infertility according to WHO criteria were included

Table 1: Demographic data on IVF treatment

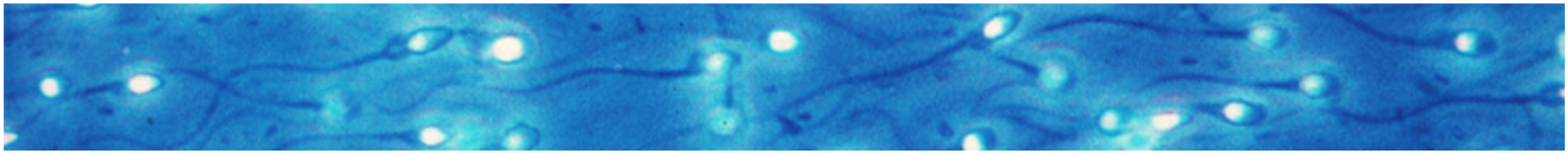
	IVF			
	Pregnant	Non-Pregnant	CI	P value
Couples included (n)	20	50	--	--
Female age (years)	33.4 ± 0.9	34.4 ± 0.5	-3.0 – 1.0	NS
Male age, (years)	35.9 ± 1.1	37.6 ± 0.6	-4.3 – 0.9	NS
Sperm concentration (10^6ml^{-1})	52.6 ± 7.1	51.4 ± 5.2	-17.8 – 20.3	NS
Progressive motility (%)	46.8 ± 4.2	44.2 ± 2.1	-6.1 – 11.4	NS
Normal morphology (%)	32.7 ± 4.3	26.3 ± 1.4	-0.7 - 13.5	NS
DNA fragmentation in native semen (%)	33.8 ± 3.6	68.5 ± 2.3	-43.3 - -26.0	<0.001
DNA fragmentation in DGC sperm (%)	23.2 ± 2.8	50.3 ± 2.3	-35.5 - -18.7	<0.001

Values expressed as mean & SD, NS – P > 0.05, CI – 95% Confidence interval

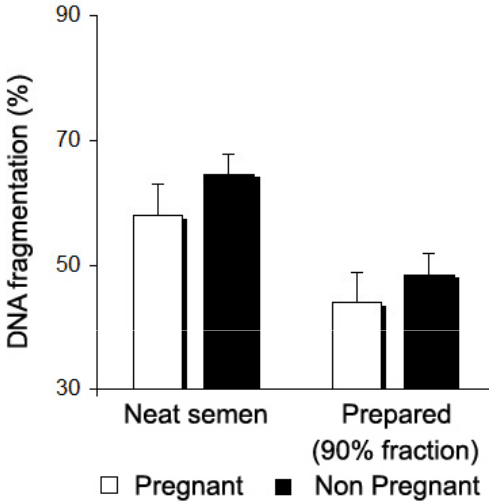
Prognostic value of sperm DNA fragmentation in diagnosing male infertility and predicting clinical pregnancy after IVF

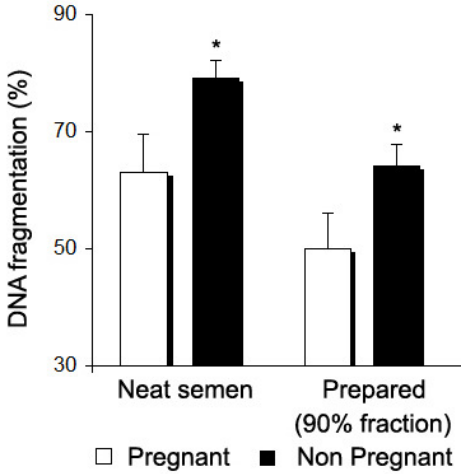
	Male Infertility	IVF	
		Native semen	DGC sperm
	25	52	42
Odds Ratio (95% CI)	117.25 (12.73-2731.83)	76.00 (8.69-1714.44)	24.18 (2.89-522.34)
Sensitivity (%)	63.64	95.00	95.00
Specificity (%)	98.53	80.00	56.00
PPV (%)	93.33	65.52	46.34
NPV (%)	89.33	97.76	96.55
RR (95% CI)	8.75 (4.48-17.08)	4.75 (2.70-8.34)	2.16 (1.55-3.00)
ROC curve (95% CI)	0.970 (0.94-1.0)	0.905 (0.81-0.99)	0.879 (0.78-0.97)

PPV - Positive Predictive Value; NPV - Negative Predictive Value; RR - Relative Risk, ROC - Receiver Operator Characteristic



Relationship between sperm DNA fragmentation and pregnancy rates in ISCI





Assay	Sample	n	ROC	CI	P
Comet	Native	116	0.601	0.49-0.71	0.117
	DCG	116	0.572	0.46-0.68	0.271
Comet + FPG	Native	51	0.704	0.54-0.87	0.015
	DCG	51	0.717	0.56-0.88	0.005

- **No relationship between Comet alone and pregnancy**
- **Significant relationship between Comet plus adducts and pregnancy**

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Recommendations from Consensus Document

1. **Fundamental research is urgently required**
2. **Standardization of clinical assays**
3. **Animal Models**
4. **High quality clinical data is urgently required**
5. **Long term follow up of ART children**

Sperm DNA: organization, protection and vulnerability: from basic science to clinical applications
edited by Chris Barratt,
ESHRE Campus symposium, Stockholm, Sweden , 21-22 May 2009

The role of ART is finally recognised

Human Reproduction Update, Vol.14, No.6 pp. 583–592, 2008 doi:10.1093/humupd/dmn038
Advance Access publication September 11, 2008

Assisted reproductive technologies are an integrated part of national strategies addressing demographic and reproductive challenges

Søren Ziebe[1,3] and Paul Devroey[2] on behalf of the State of the ART 2007 Workshop Group

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In 2008, European Parliament acknowledged for the first time that falling birth rates were a major cause of its demographic decline. Over mortality and migration, infertility is the major determinant of the future size and population composition in Europe

Europe performs 60% of world ART
1-6% of births in Europe are by ART

The European Parliament (resolution adopted by parliament on 21 February 2008) 'calls on the member states to ensure the right of couples to universal access to infertility treatment.

Improving diagnosis and success rates is essential

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