An ICSI strategy too far?

Testicular or ejaculated sperm (when both are available) in Oligozoospermia and ICSI failure

Sandero Esteves MD., PhD.
ANDROFERT & University of Campinas (UNICAMP) Campinas, BRAZIL

Aqeel Morris

Clinical Reproductive Biologist, PhD Candidate

Cape Town, South Africa

Merck

Importance of Sperm DNA damage

- Higher prevalence of Sperm DNA damage in infertile men
- Sperm DNA damage associated with lower Pregnancy rate and higher pregnancy loss
- Concern of sperm genetic defect transferred to offspring via ICSI

WHY Testicular Sperm over Ejaculated Sperm for ICSI

(when both are available)

Experimental evidence

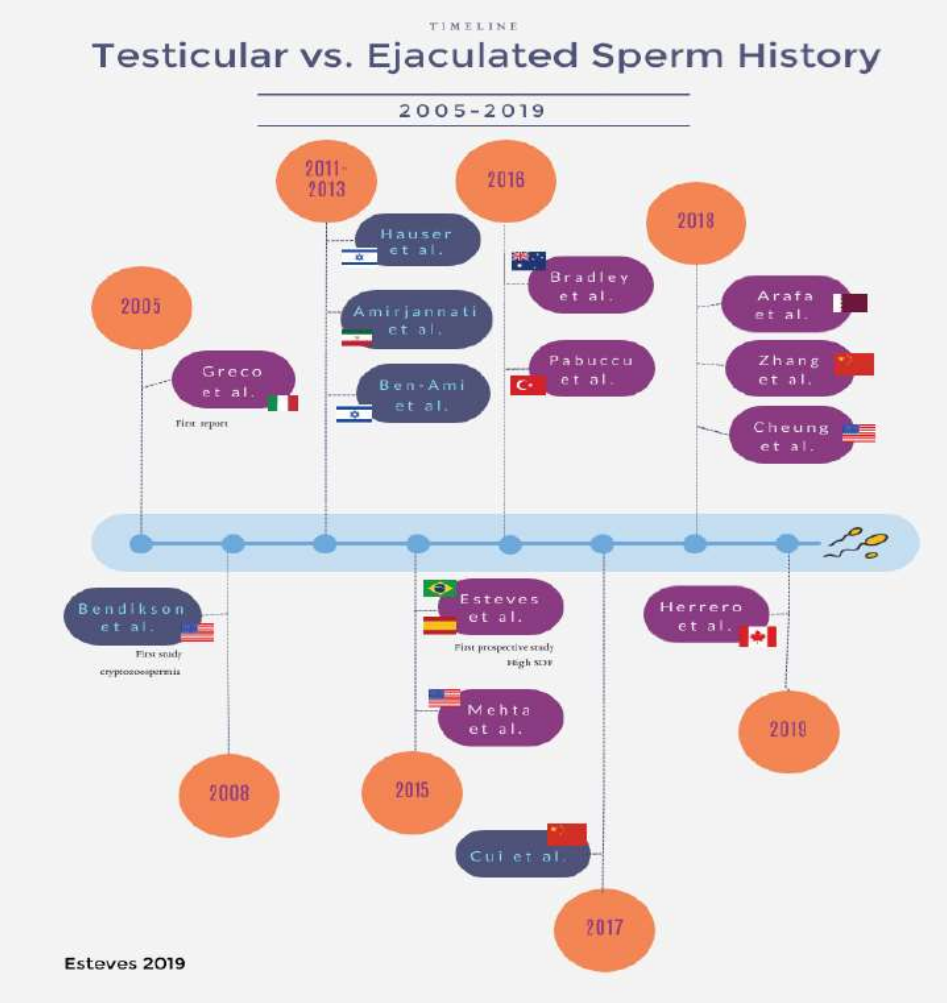
- Suganuma et al, 2005
  - Sperm DNA damage increase during transit through epididymis
  - Decline in fertility with abnormal chromatin during epididymal passage

Greco et al, 2005

- No specific treatment for SDF
  - Less SDF in testicular vs ejaculated sperm
  - Use of testicular sperm improved ICSI clinical outcomes

Testicular sperm should be offered to ICSI candidates with high Sperm DNA Fragmentation (SDF) in semen

1. SDF negatively impacts ART outcomes
2. SDF is lower in testicular than ejaculated sperm of non-azoospermic infertile men with high SDF in neat semen
3. Testicular sperm (therefore with lower SDF than ejaculated sperm) improves ICSI pregnancy outcomes in couples whose male partners have high SDF in semen



Premise # 1

Sperm DNA Fragmentation (SDF) negatively impacts ART outcomes

Best Practice & Research Clinical Obstetrics and Gynaecology xxx (2017) 1–19

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

5

Review: Diagnosis and impact of sperm DNA alterations in assisted reproduction

Luke Simon [a], Benjamin R. Emery [a, *], Douglas T. Carrell [a, b, c]

[a] Department of Surgery (Urology), University of Utah School of Medicine, Salt Lake City, UT, USA
[b] Department of Human Genetics, University of Utah School of Medicine, Salt Lake City, UT, USA
[c] Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT, USA

70 studies; 9363 IVF; 6260 ICSI; 2121 mixed IVF/ICSI

- **By fertilization method**
  - IVF studies: OR 1.15 (95% CI 1.05-1.27); P=0.003
  - ICSI studies: OR 1.12 (95% CI 1.01-1.25); P=0.025
- **By SDF assay type**
  - TUNEL: OR 1.85 (95% CI 1.52-2.26); P<0.0001
  - SCD: OR 1.16 (95% CI 1.02-1.32); P=0.023
  - Comet: OR 4.15 (95% CI 3.04-5.68); P<0.0001
  - SCSA: OR 1.14 (95% CI 1.04-1.25); P=0.004
- **Female infertility factors excluded**
  - 1704 cycles: OR 1.37 (95% CI 1.11-1.68); P=0.003 (irrespective of method)

Translating the impact of SDF to Clinical Practice

IVF/ICSI Miscarriage :

RR: 2.2 16 studies; 2969 couples (95% CI: 1.54–3.03); P<0.00001
Robinson et al, *Hum Reprod 2012*
Simon et al. *Best Pract Res Clin Obstet Gynaecol 2017*

OR~2.3 14 studies; 2756 couples (95% CI: 1.55–3.35; P<0.001)

ICSI only: OR 2.7 (95% CI: 1.40–5.14; P=0.003)
Zhao et al, *Fertil Steril 2014*

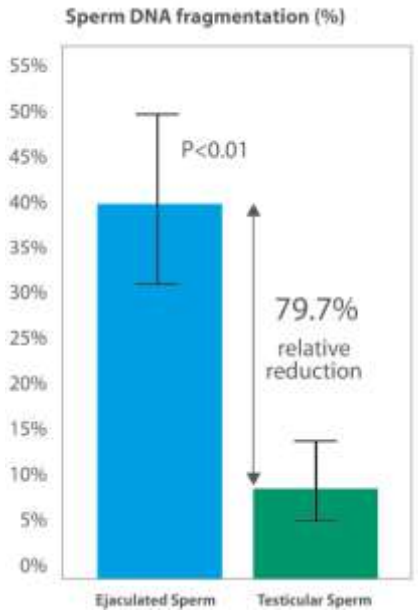
Premise #2:

SDF is lower in testicular than ejaculated sperm of non azoospermic infertile men with high SDF in neat semen

Comparison of reproductive outcome in oligozoospermic men with high sperm DNA fragmentation undergoing intracytoplasmic sperm injection with ejaculated and testicular sperm

Sandro C. Esteves, M.D., Ph.D.,[a] Fernando Sánchez-Martín, M.D.,[b] Pascual Sánchez-Martín, M.D.,[b] Danielle T. Schneider, M.Sc.,[a] and Jaime Gosálvez, Ph.D.[c]

[a] Androfert, Andrology and Human Reproduction Clinic, Campinas, Brazil; [b] Ginemed, Seville, Spain; and [c] Unit of Genetics, Department of Biology, Universidad Autónoma de Madrid, Madrid, Spain



Greco 2005: 4.8% (T) vs. 23.6% (E)

Moskovtsev 2010: 13.3% (T) vs. 39.7% (E)

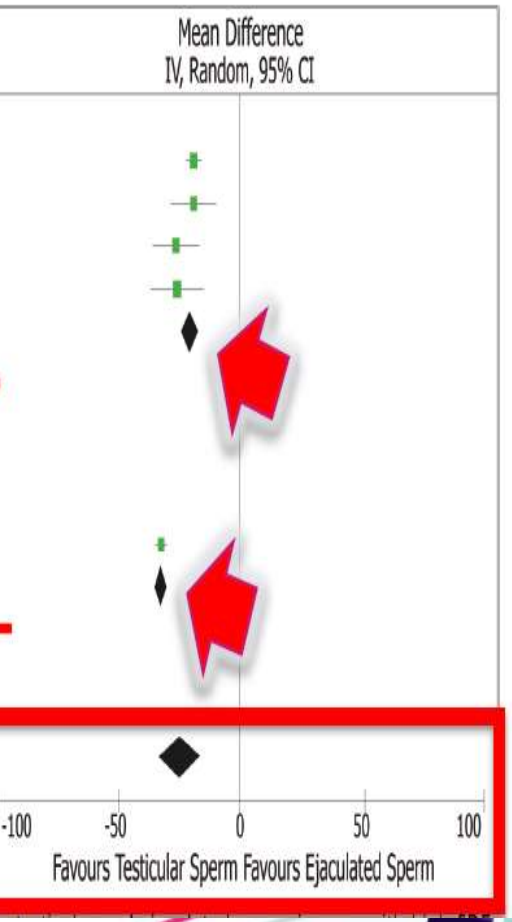
Moskovtsev 2012: 14.9% (T) vs. 40.6% (E)

Mehta 2015: 4.7% (T) vs. 24.0% (E)

Esteves 2015: 5.3% (T) vs. 40.7% (E)

5 studies; 143 men serving as own controls

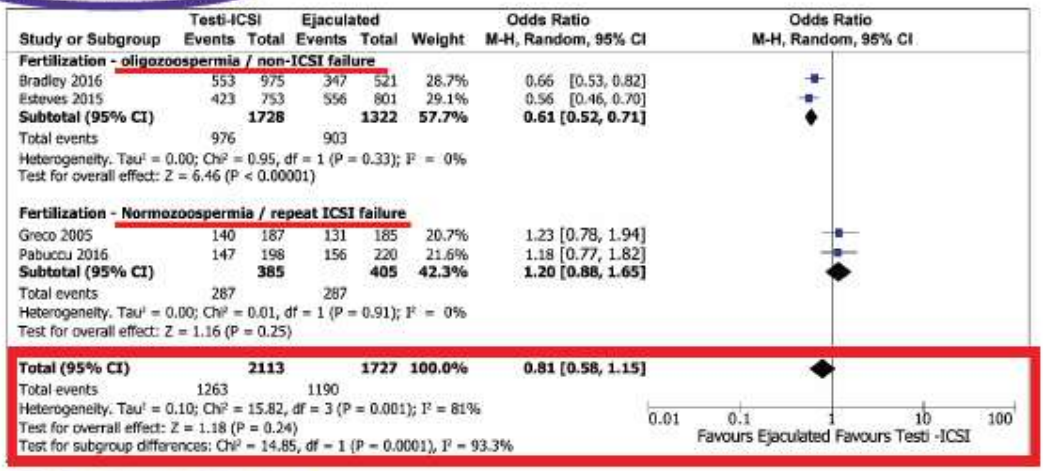
Study of Subgroup	Testicular sperm Mean	SD	Total	Ejaculated sperm Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TUNEL								
Greco 2005	4.8	3.6	18	23.6	5.1	18	23.4%	-18.80 [-21.68, -15.92]
Mehta 2015	5	4.7	24	24	23	24	18.1%	-19.00 [-28.39, -9.61]
Moskovtsev 2010	13.3	7.3	12	39.7	14.8	12	18.1%	-26.40 [-35.74, -17.06]
Moskovtsev 2012	14.9	5	8	40.6	14.8	8	16.7%	-25.70 [-36.53, -14.87]
Subtotal (95% CI)			**62**			**62**	**76.4%**	**-20.43 [-23.92, -16.95]**
Heterogeneity. $Tau^2 = 2.65$; $Chi^2 = 3.55$, df = 3 ($P < 0.31$); $I^2 = 15\%$								
Test for overall effect: Z = 11.49 ($P < 0.00001$)								
SCD								
Esteves 2015	8.3	5.3	81	40.7	9.9	81	23.6%	-32.40 [-34.85, -29.95]
Subtotal (95% CI)			**81**			**81**	**23.6%**	**-32.40 [-34.85, -29.95]**
Heterogeneity. Not applicable								
Test for overall effect: Z = 25.97 ($P < 0.00001$)								
Total (95% CI)			**143**			**143**	**100.0%**	**-24.58 [-32.53, -16.64]**
Heterogeneity. $Tau^2 = 67.94$; $Chi^2 = 52.20$, df = 4 ($P < 0.00001$); $I^2 = 92\%$								
Test for overall effect: Z = 6.06 ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 30.36$, df = 1 ($P < 0.00001$), $I^2 = 96.7\%$								



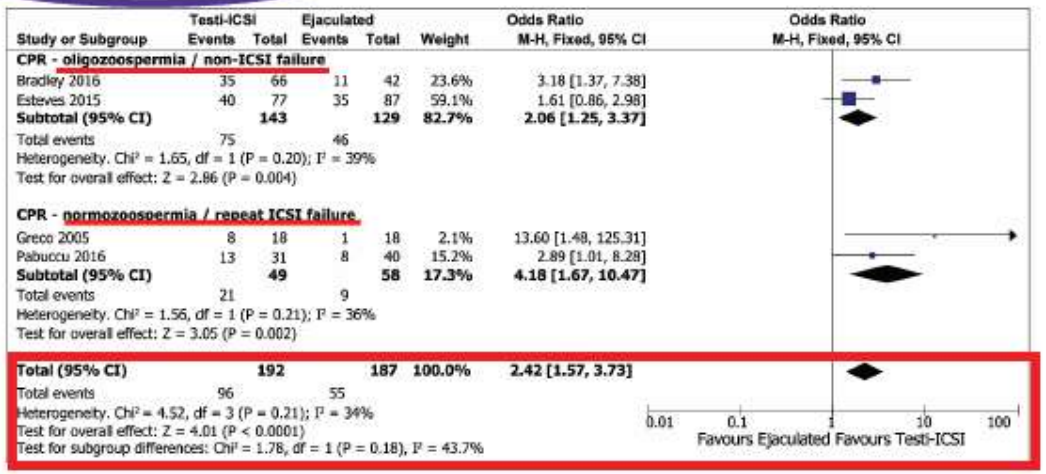
Premise #3:

Testicular sperm improves ICSI pregnancy outcomes in couples whose male partners have high SDF in semen

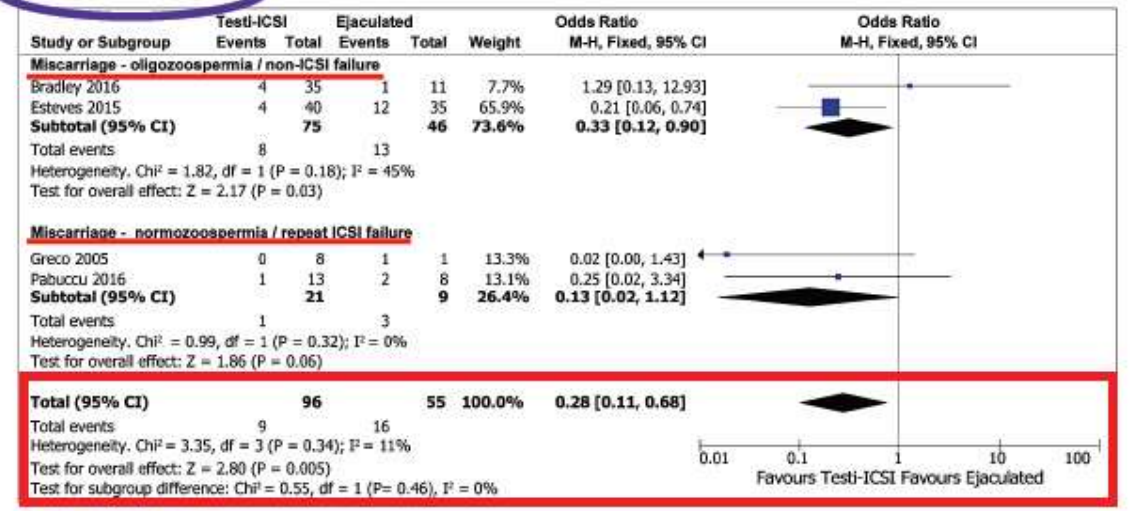
A. Fertilization rate



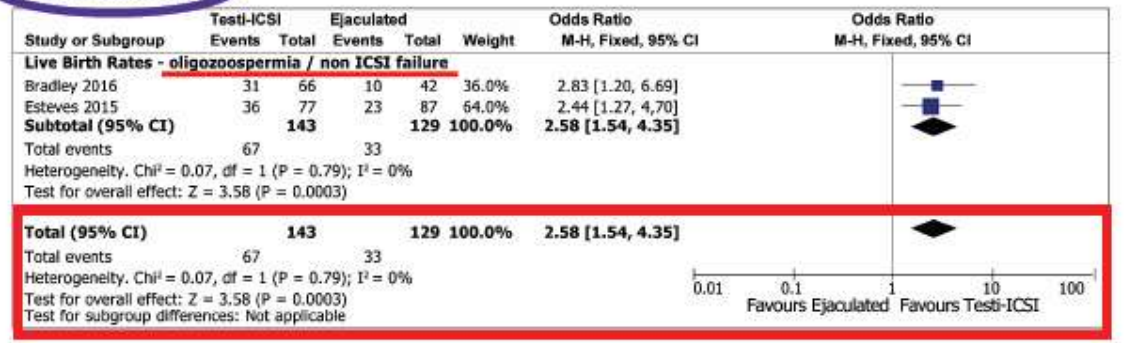
B. Clinical pregnancy rate



C. Miscarriage rate

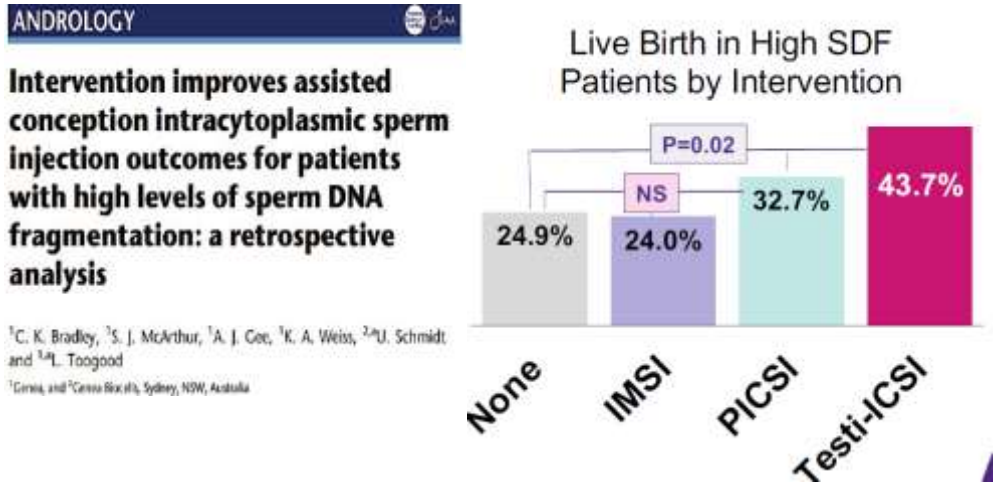


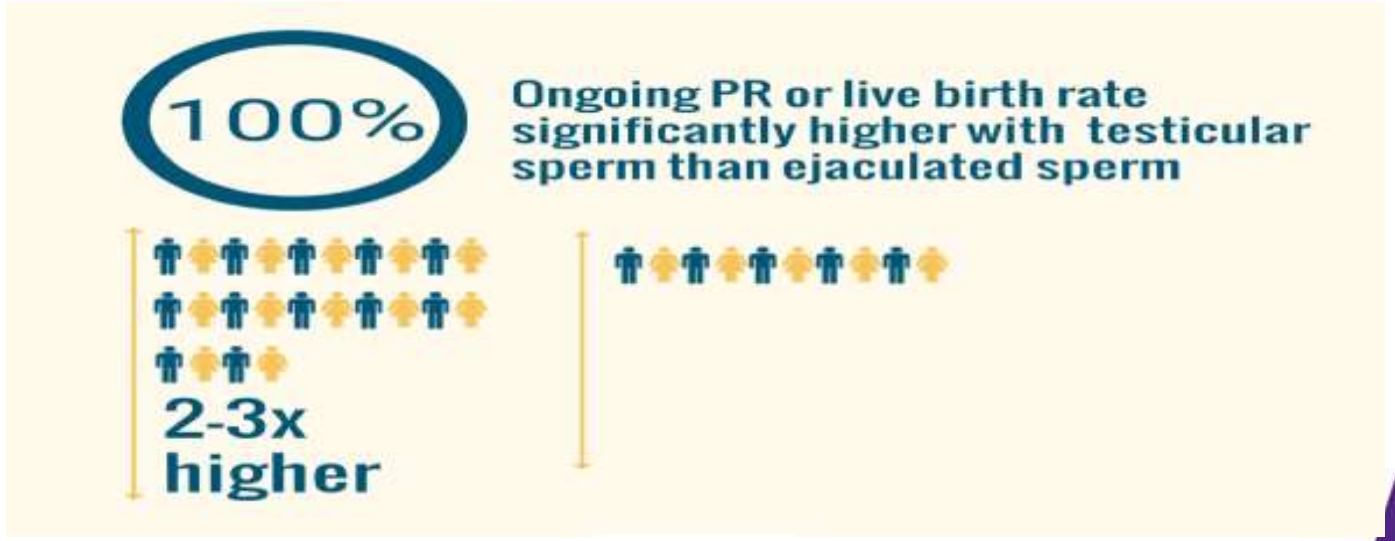
D. Live birth rate



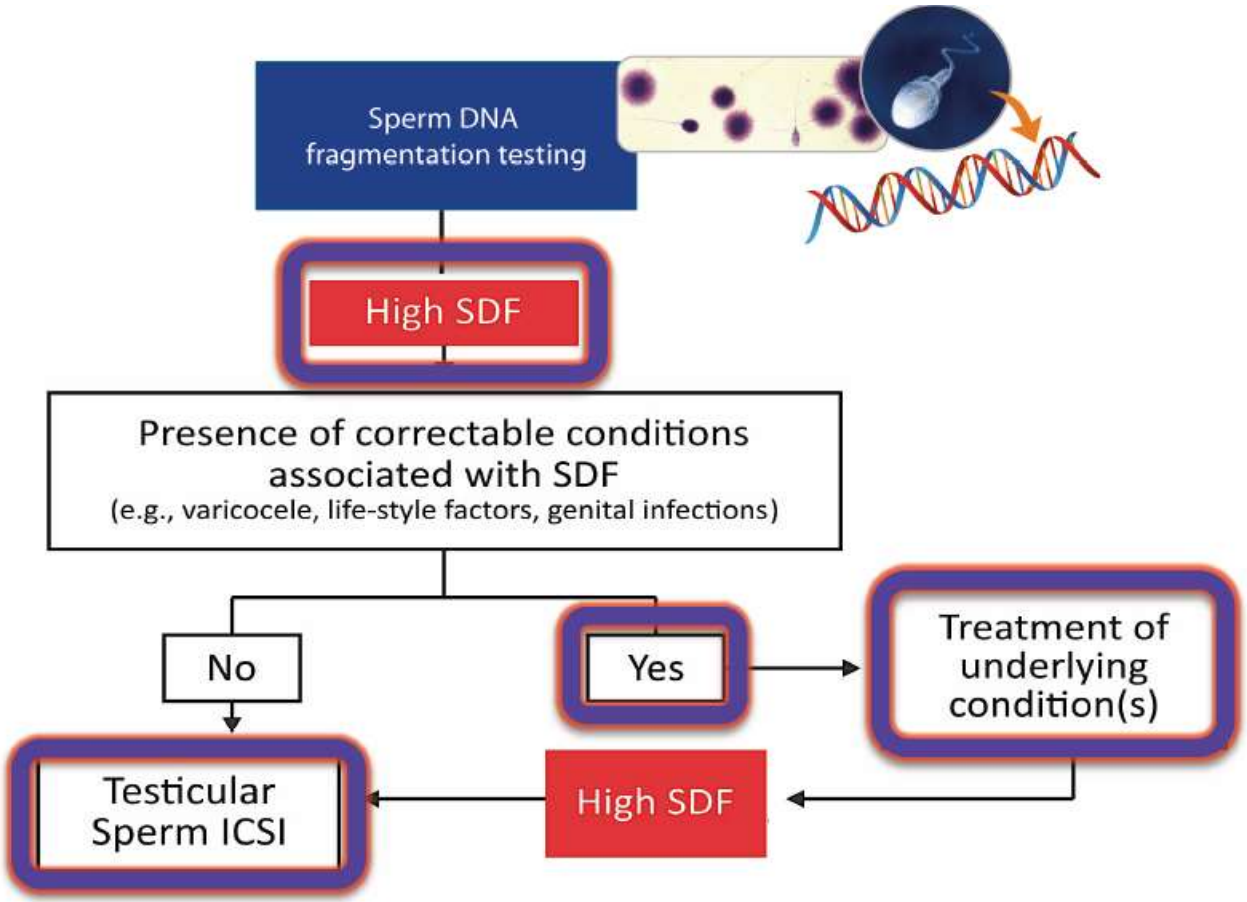
Evidence to date

Arafa 2018	Prospective	36 oligozoospermic and normozoospermic men with history of ICSI failure	SCD (30%)	LBR 39% (T) vs. 8% (E) (P<0.0001)
Zhang 2018	Prospective	102 oligozoospermic and normozoospermic men; No history of ICSI failure	SCSA (30%)	LBR 36% (T) vs. 10% (E) (P=0.001)
Herrero 2019	Retrospective	145 couples with ICSI failure	SCSA (25%) TUNEL (36%)	• CLBR 22% (T) vs. 9% (E) (P<0.01; SCSA); • CLBR 20% (T) vs. 0% (E) (P<0.02; TUNEL)





Conclusion



WHERE DO WE GO FROM HERE?

Need more Basic Research & Good Clinical Studies (RCT)

- **To Determine if Testi-ICSI is**
  1. A valid approach (superior to Ejac-ICSI)
  2. A safe approach (late complications)
- **To Establish Clinical Indications**
  1. Sperm profile (eg. High SDF)
  2. Clinical profile (e.g. prior ICSI failure, all ICSI candidates)