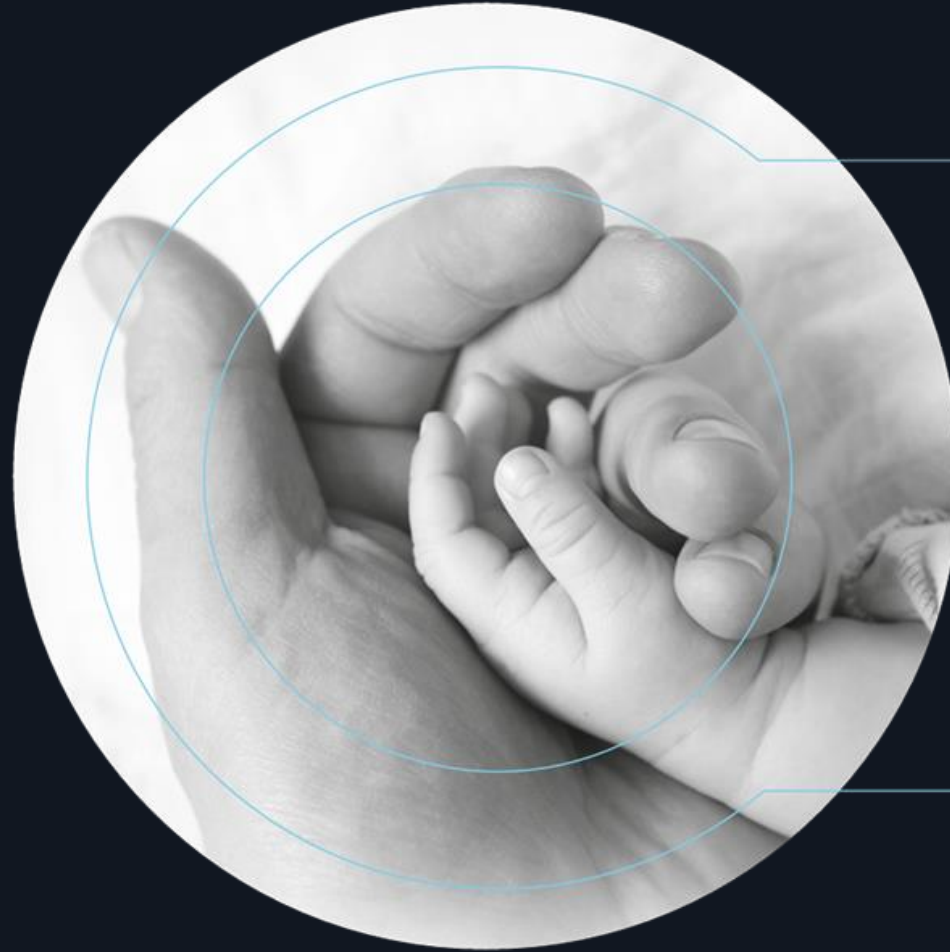


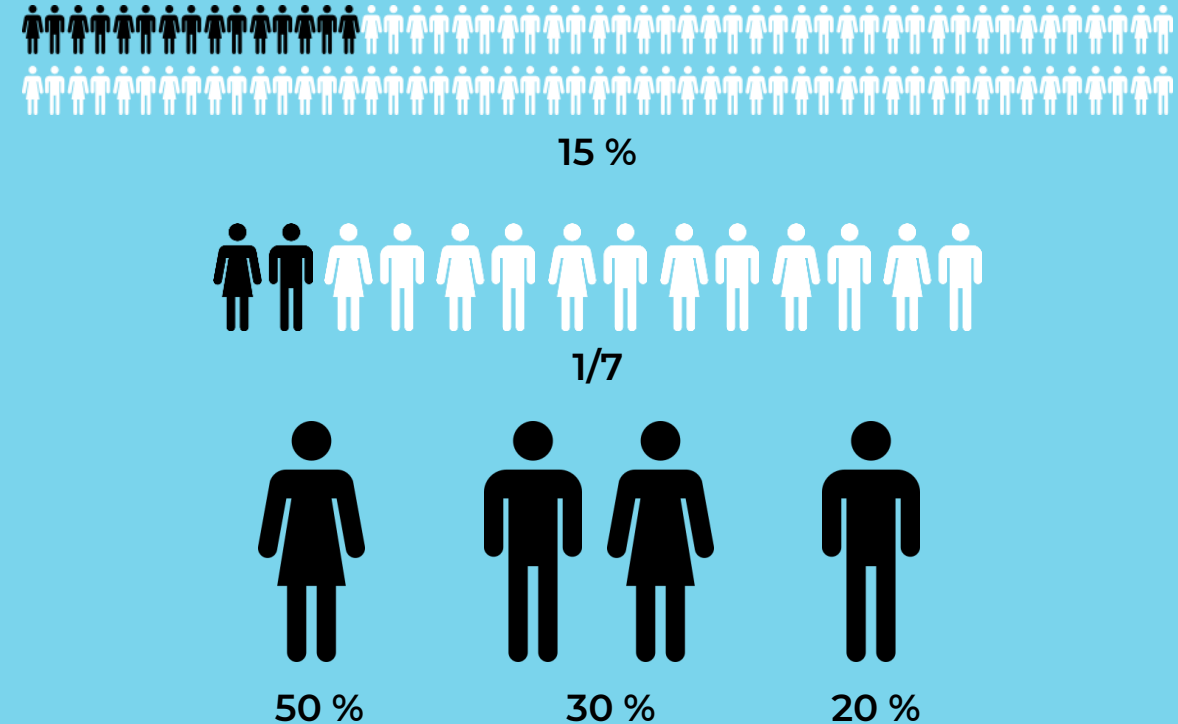
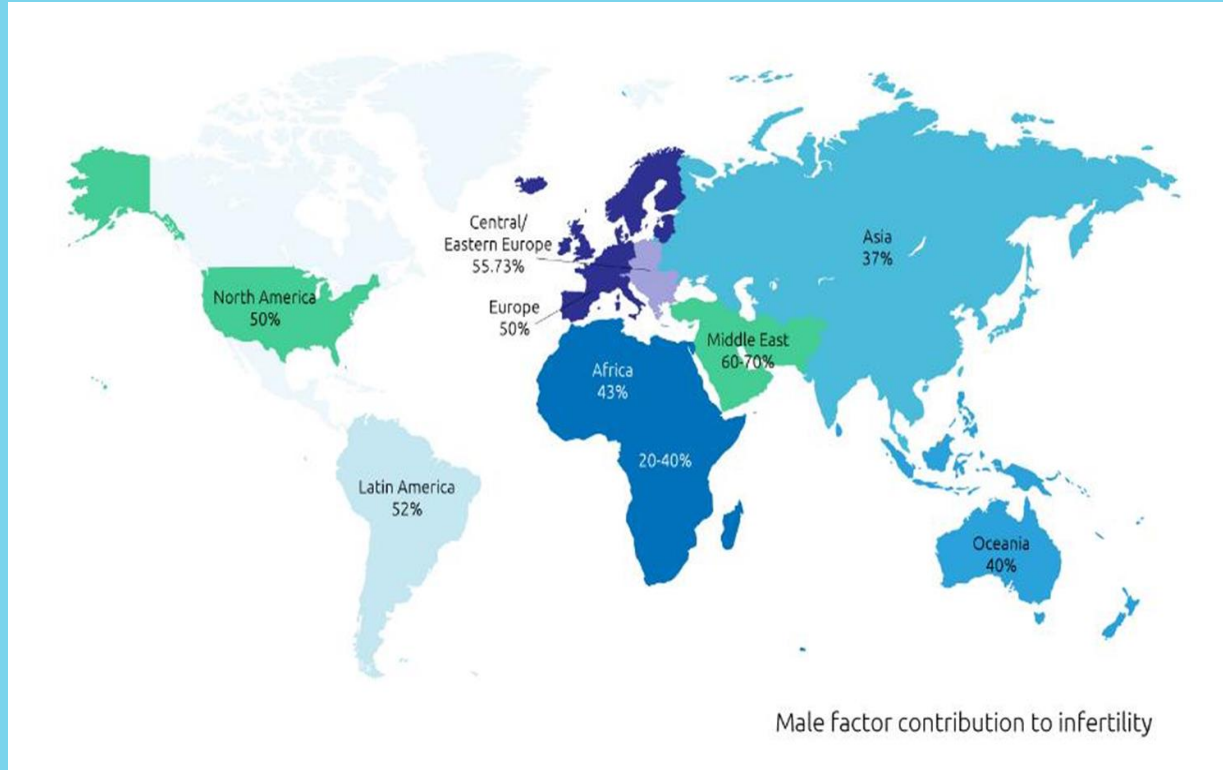
MiOXSYS[®]

MALE INFERTILITY OXIDATIVE SYSTEM

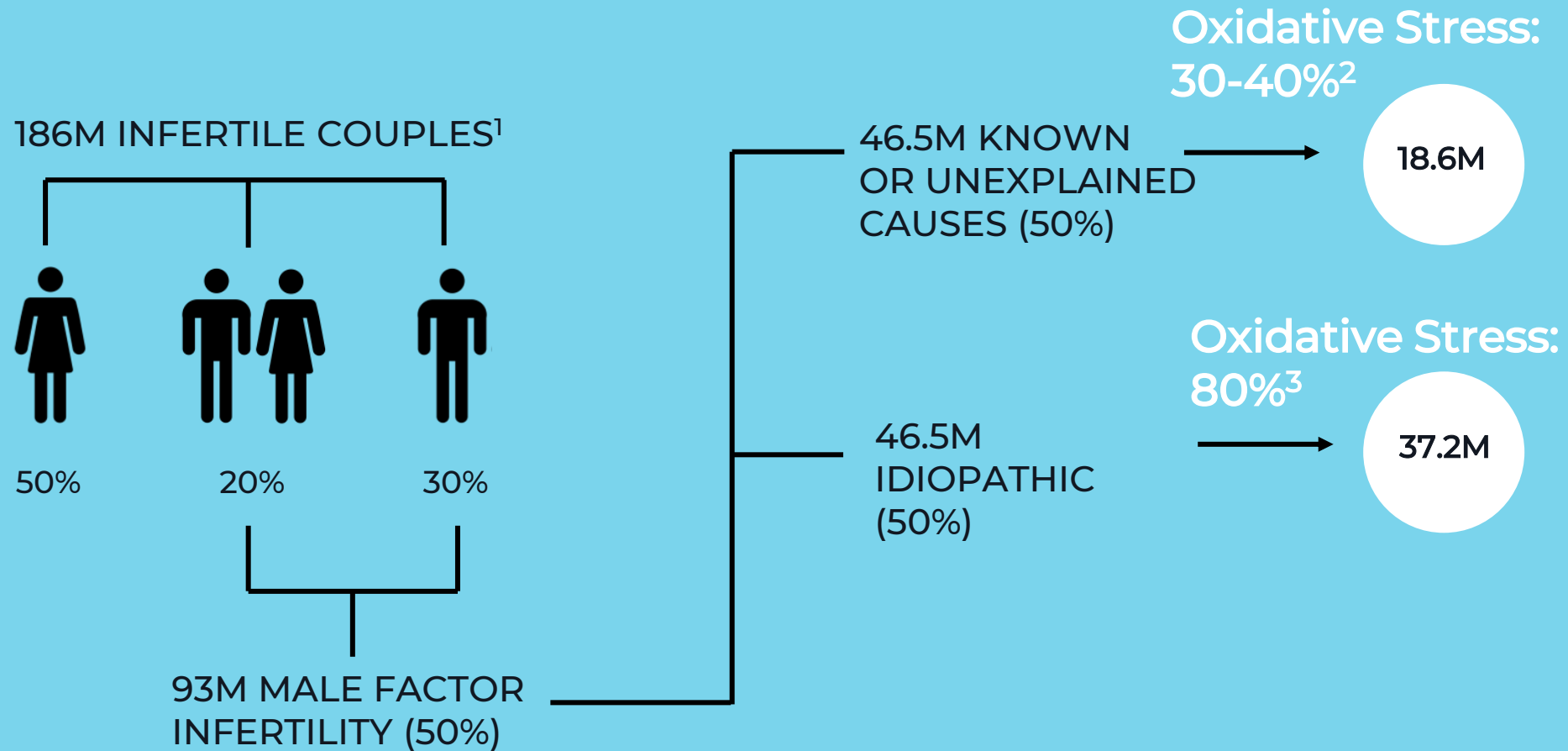
Complete, accurate and rapid oxidative
stress diagnostic



Male factor contributes to around 50% of all causes of infertility



30% of infertile couples worldwide are affected by Male Oxidative Stress Infertility



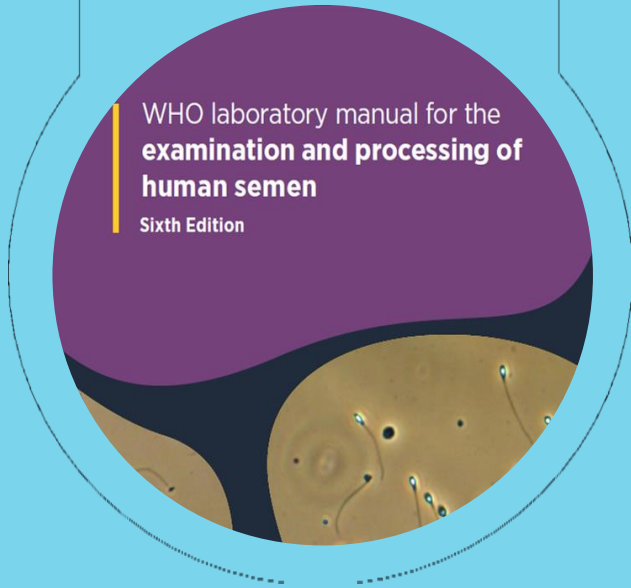
Source: [https://www.auanet.org/guidelines/male-infertility-optimal-evaluation-\(reviewed-and-validity-confirmed-2011\)](https://www.auanet.org/guidelines/male-infertility-optimal-evaluation-(reviewed-and-validity-confirmed-2011)) (Accessed 20 March 2019; Agarwal et. Al, 2015, RB&E, Cleveland Clinic 2019)

1- Rutstein and Shah (World Health Organization, 2004)

2- Agarwal et. al., 2014, WJMH

3- Ko et al., 2014, F&S, Wagner et. Al, 2018 AJU

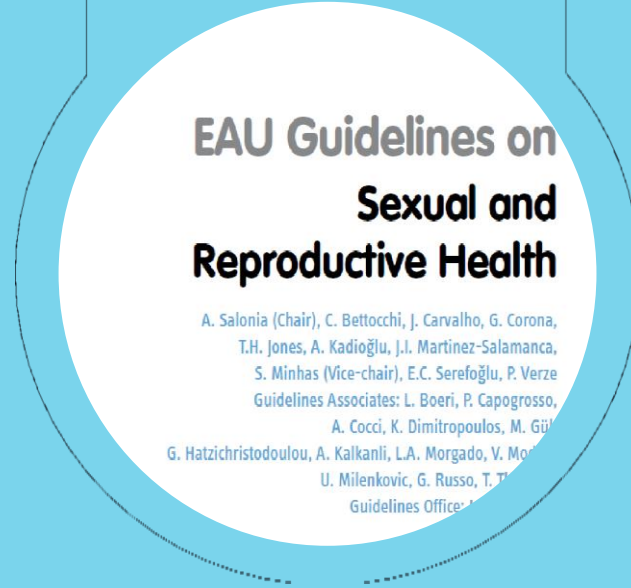
Caerus Biotechnologies, 2022



WORLD HEALTH ORGANIZATION:

“oxidative stress is a key factor for reproductive outcomes”

Oxidative stress is likely to be an important modulator of human sperm function and conception outcomes.



EUROPEAN ASSOCIATION OF UROLOGY:

“oxidative stress negatively affect reproductive outcomes”

Oxidative stress is considered to be central in male infertility by affecting sperm quality, function, as well as the integrity of sperm.



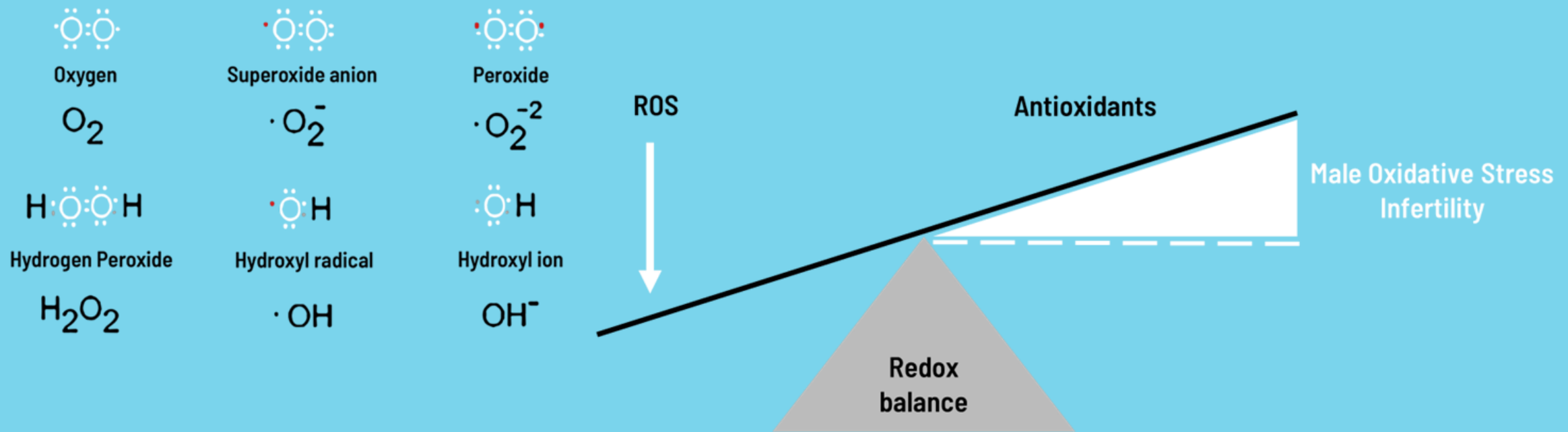
ESHRE:

“the main cause of DNA damage is oxidative stress”

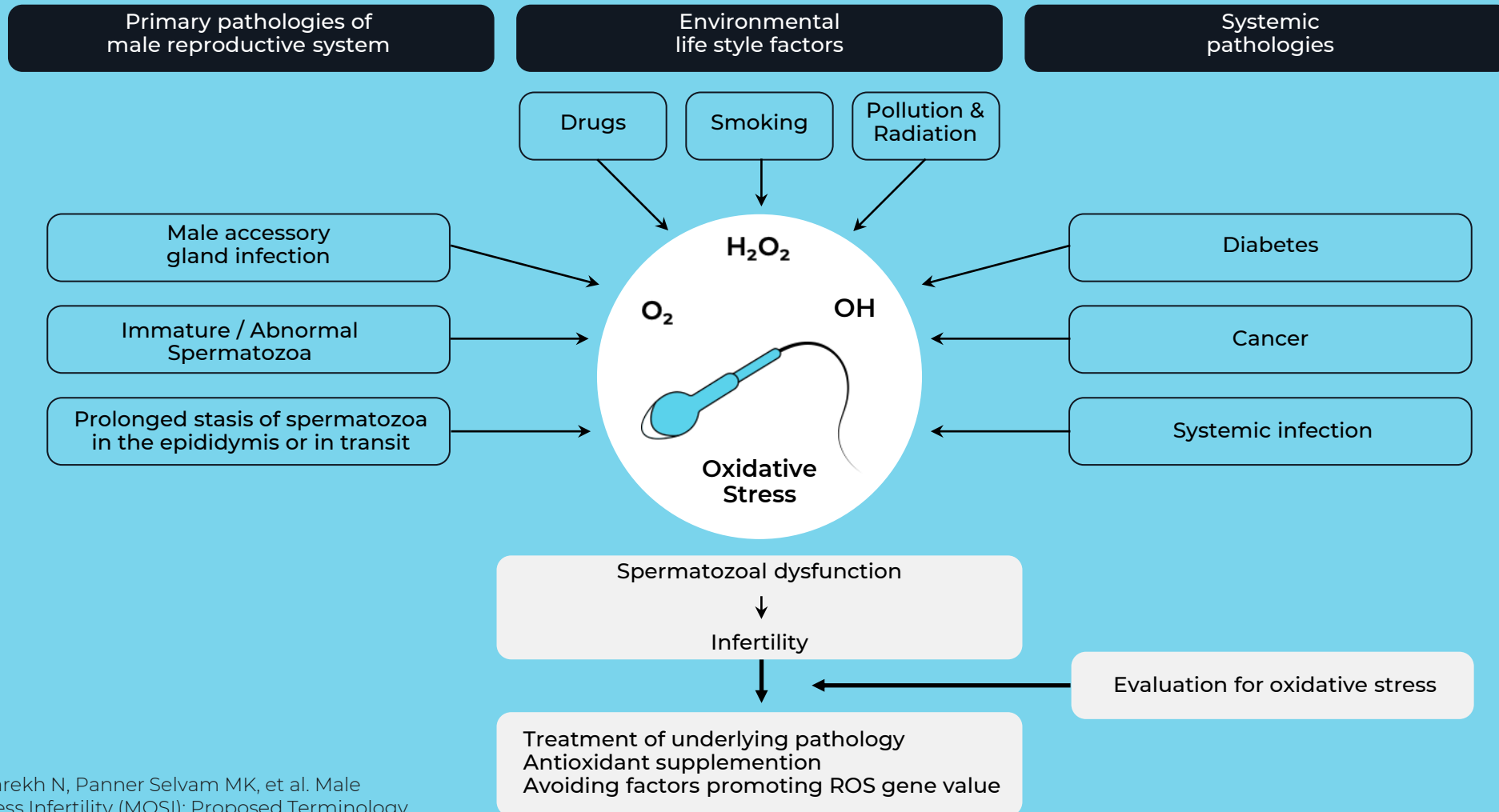
A significant increase in miscarriage rates in men with high sperm DNA damage is demonstrated.

Oxidative Stress Introduction

Oxidative stress is caused by the imbalance between the production reactive oxygen species (ROS) and the body's antioxidant system responsible for their neutralization and removal.



Causes of Oxidative Stress

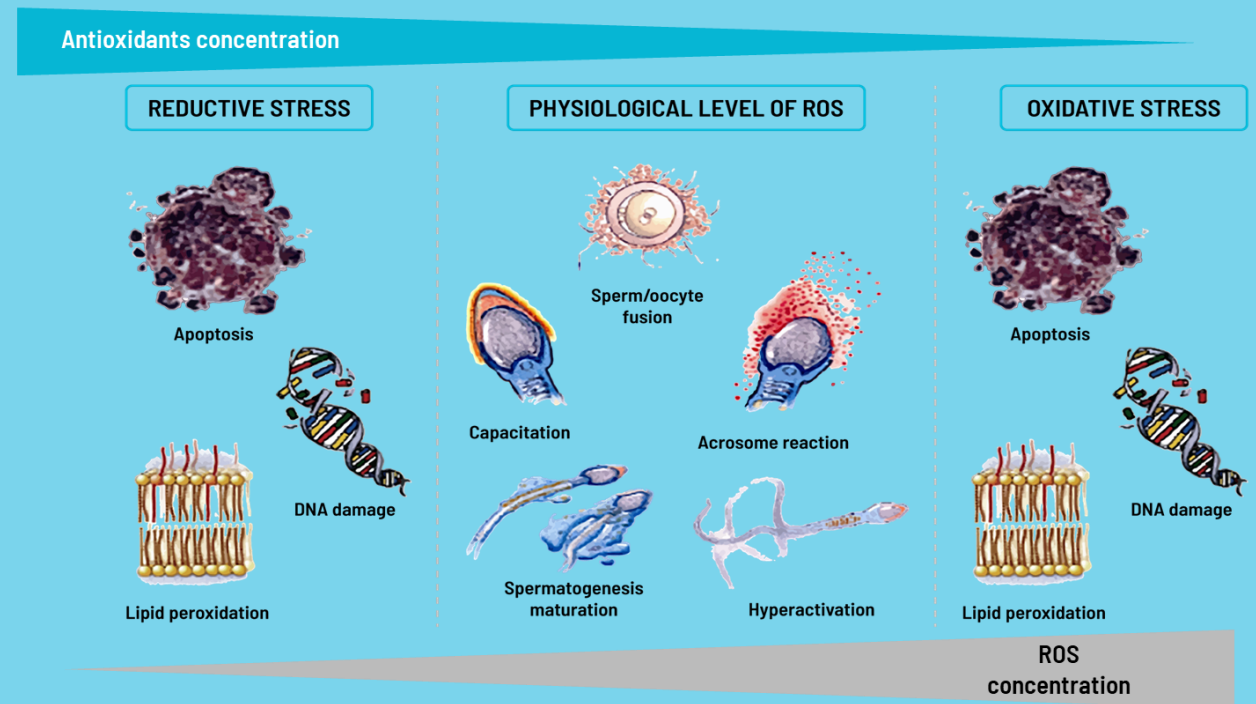


Physiological level of ROS is a prerequisite for normal sperm function

While small amounts of ROS are required for normal sperm functioning, disproportionate levels can negatively impact the quality of spermatozoa and impair their overall fertilizing capacity.

Excessive ROS production or decreased concentration of available antioxidants result in a state of oxidative stress (OS).

On the other hand, the reduced ROS production or shift in the redox balance towards a more reductive status results in reductive stress (RS), which is as harmful as OS.



Agarwal A, Virk G, Ong C, du Plessis SS. Effect of oxidative stress on male reproduction. World J Mens Health. 2014 Apr;32(1):1-17. doi: 10.5534/wjmh.2014.32.1.1. Epub2014 Apr 25. PMID: 24872947; PMCID: PMC4026229.

Panner Selvam MK, Agarwal A, Henkel R, et al. The effect of oxidative and reductive stress on semen parameters and functions of physiologically normal human spermatozoa. Free Radic Biol Med. 2020;152:375-385. doi:10.1016/j.freeradbiomed.2020.03.008

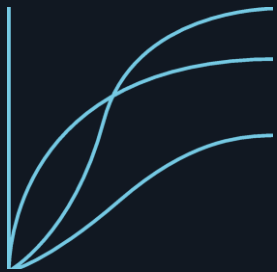
Caerus Biotechnologies, 2022

MIOXSYS[®]

NOVEL
METHOD
MEASURING
ORP



www.mioxsys.com



WELL RESEARCHED

WHO recognized,
150+ scientific
publications



COMPLETE

Measures the balance
between all oxidants
and antioxidants



CLINICALLY VALIDATED

Established cut-off
value



EASY TO USE

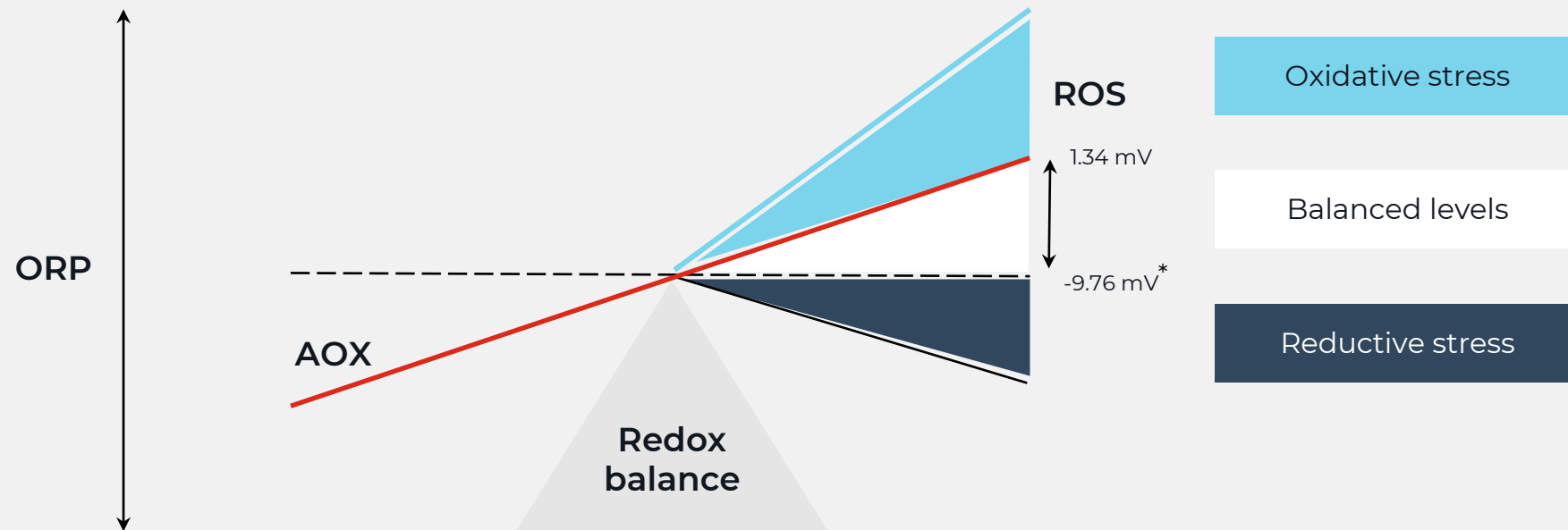
Test takes 5 min



Oxidative Reductive Potential (ORP) - the most complete measure of Oxidative Stress

MiOXSYS® ORP measure is based upon the principle of oxidation-reduction potential which measures the giving and taking of electrons.

It is a measure of the balance between total oxidant to total reductant activity in sperm.



* Actual level can be less than -9.76 mV



Diagnostic application of oxidation-reduction potential assay for measurement of oxidative stress: clinical utility in male factor infertility; A.Argval, 2016. Infertile Men Have A Redox Imbalance That Distinguishes Them From Fertile Men; A.Ayaz, K>B. Bjugstad, D. Bar-Or, A.Armagan. ASRM 2016 Poster. Panner Selvam MK, Agarwal A, Henkel R, et al. The effect of oxidative and reductive stress on semen parameters and functions of physiologically normal human spermatozoa. Free Radic Biol Med. 2020;152:375-385. doi:10.1016/j.freeradbiomed.2020.03.008

Caerus Biotechnologies, 2022

MiOXSYS[®] : the only complete male oxidative stress measurement system

MiOXSYS[®] measurement represents an integrated measure of all oxidants and all antioxidants, making it a **clinically valuable measure**.

MiOXSYS[®] rapidly provides ORP (oxidative-reductive potential) values that are predictive of male fertility potential with PPV of >95%.¹

The only one such machine on the market with **extensive clinical research** and **patent protection**.



1. Arafa M, Agarwal A, Al Said S, Majzoub A, Sharma R, Bjugstad KB, AlRumaihi K, Elbardisi H. Semen quality and infertility status can be identified through measures of oxidation-reduction potential. *Andrologia*. 2018 Mar;50(2). doi: 10.1111/and.12881. Epub 2017 Aug 3. PMID: 28771782.

MiOXSYS® : a compact system for a lab of any size

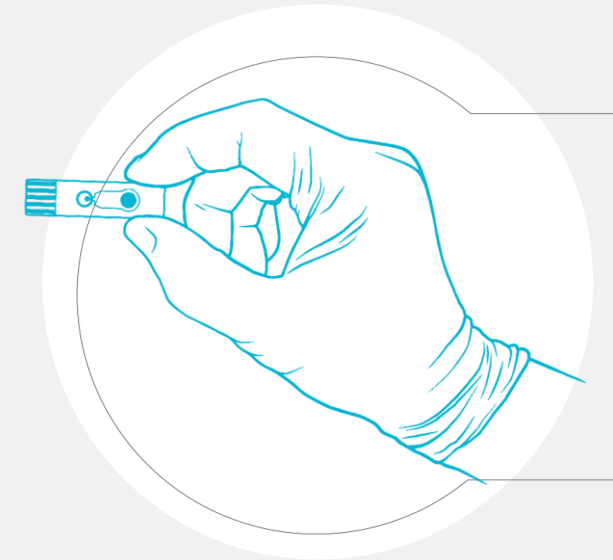
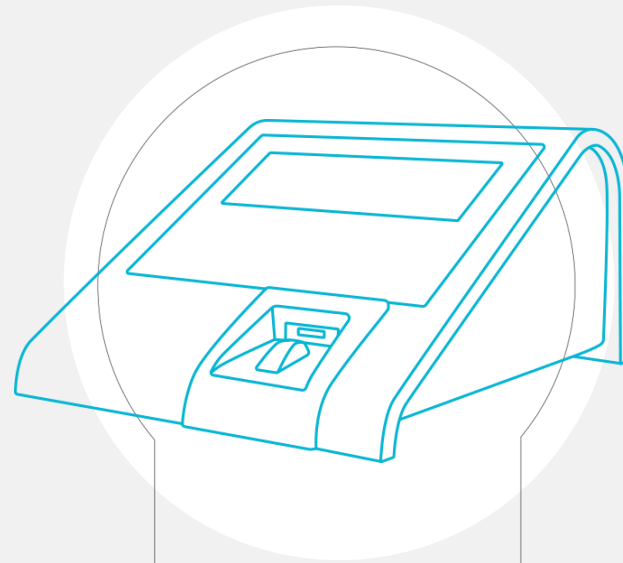
MiOXSYS® analyzer

MiOXSYS® single-use sensors

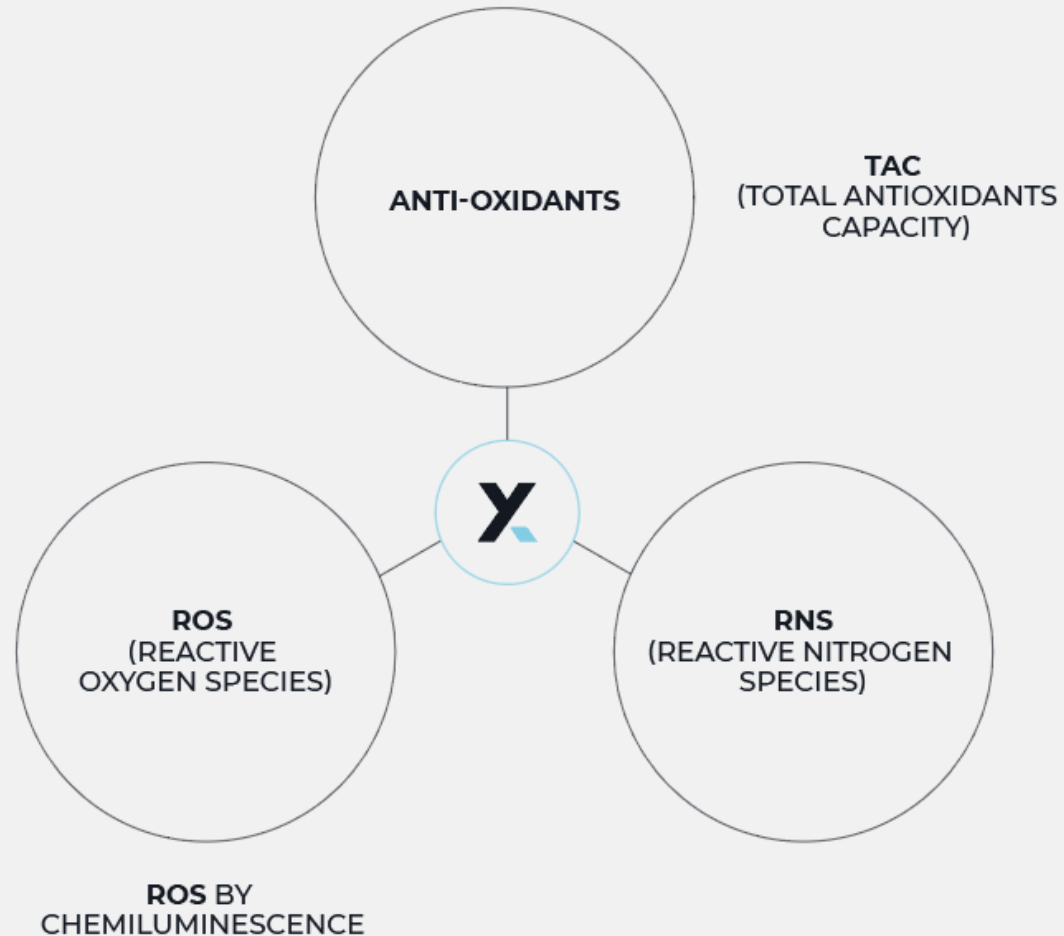
MiOXSYS® calibration key

MiOXSYS® desktop software

MiOXSYS® external control solutions

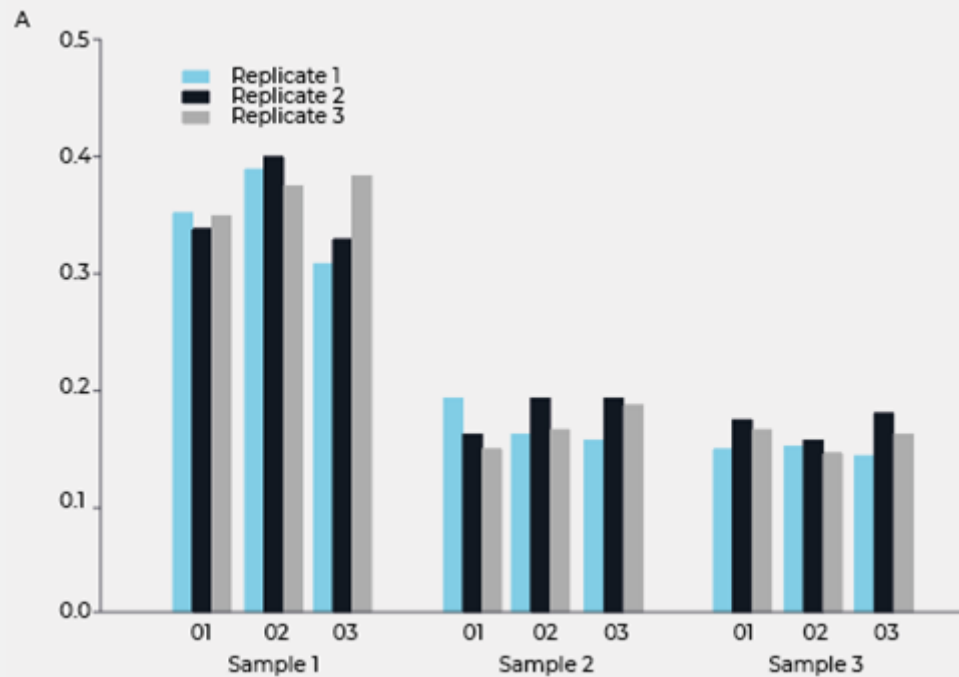


MiOXSYS[®] is the only device that provides full picture of redox balance in semen



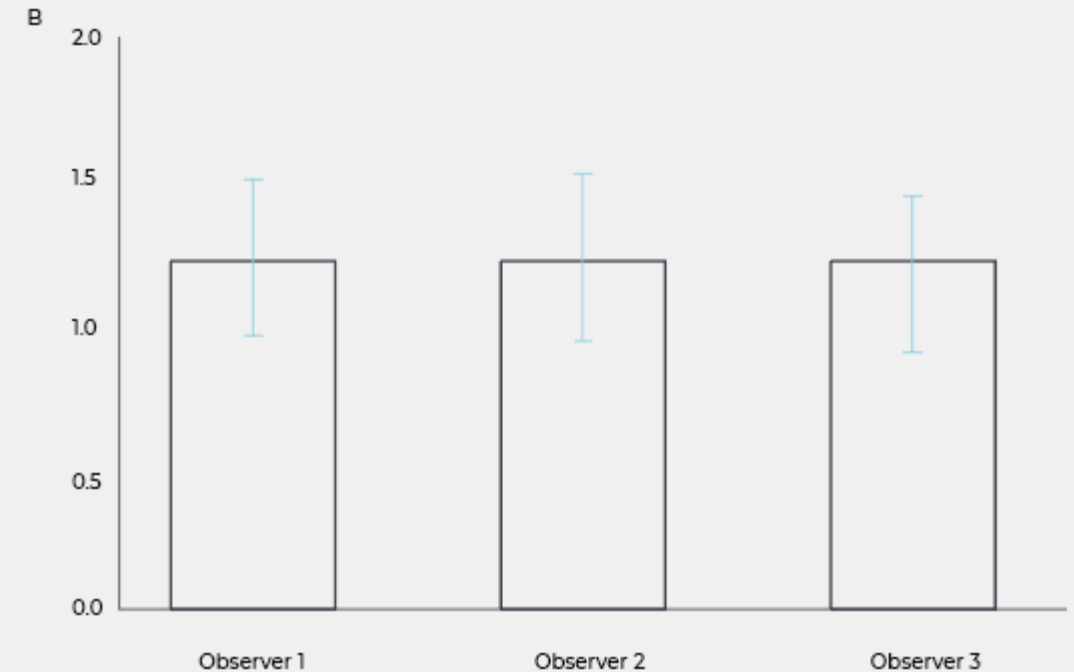
MiOXSYS[®] complete and accurate oxidative stress diagnostic

MiOXSYS[®] – demonstrates low technical variability



Graph shows that 3 different laborants performed the test 3 times and got results with no significant difference.

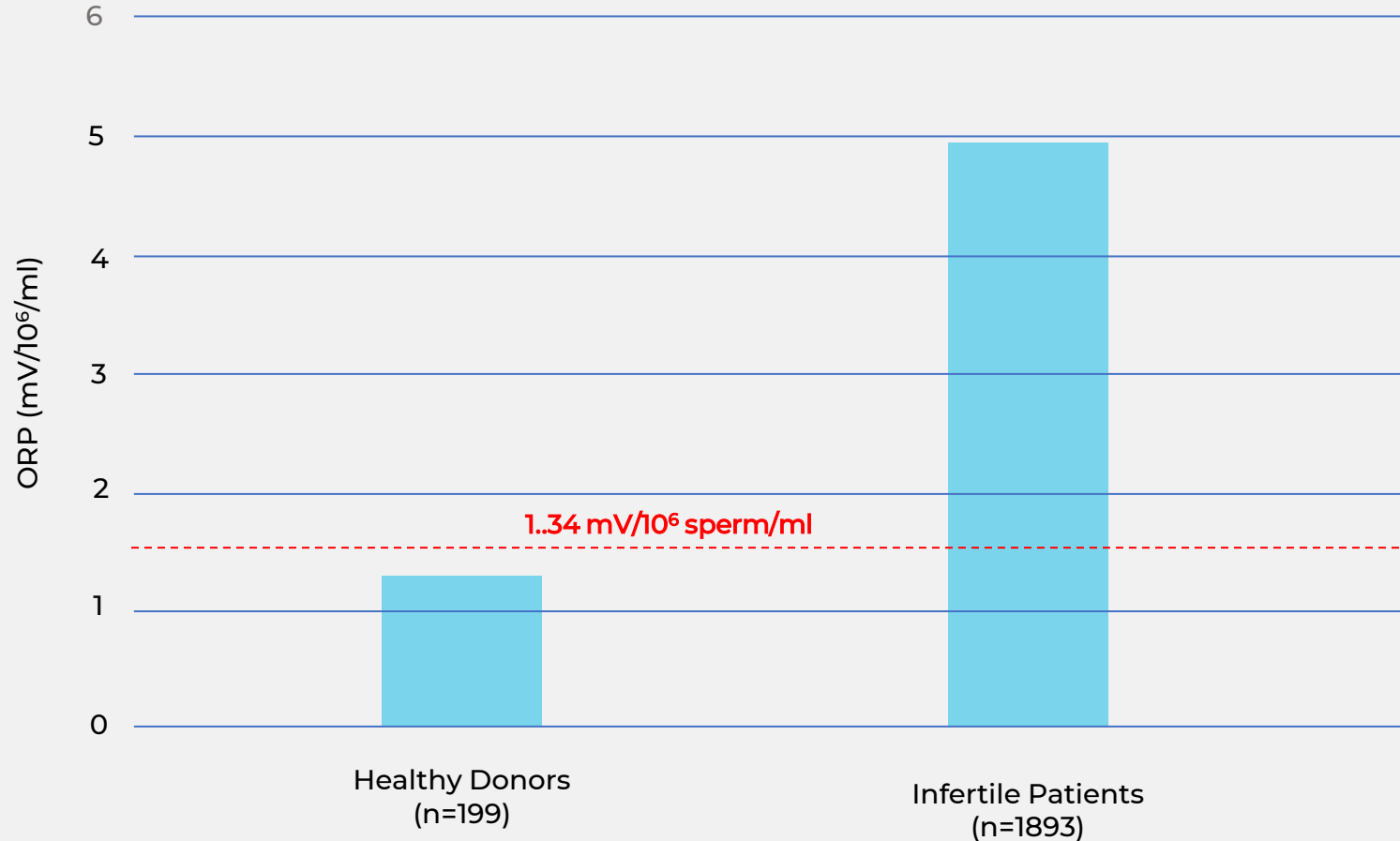
MiOXSYS[®] demonstrates low intra-observer (CV 8.39%) and inter-observer variability (correlations >0.97)



Graph shows 3 different observers testing the same sample.



MiOXSYS[®] has a clinically established cut- off value to determine the male fertility potential



International multi-center study

2092 participants

9 countries

A cut-off value of **1.34 mV/10⁶ sperm/ml** for ORP provides the greatest predictability when identifying abnormal/normal semen quality.



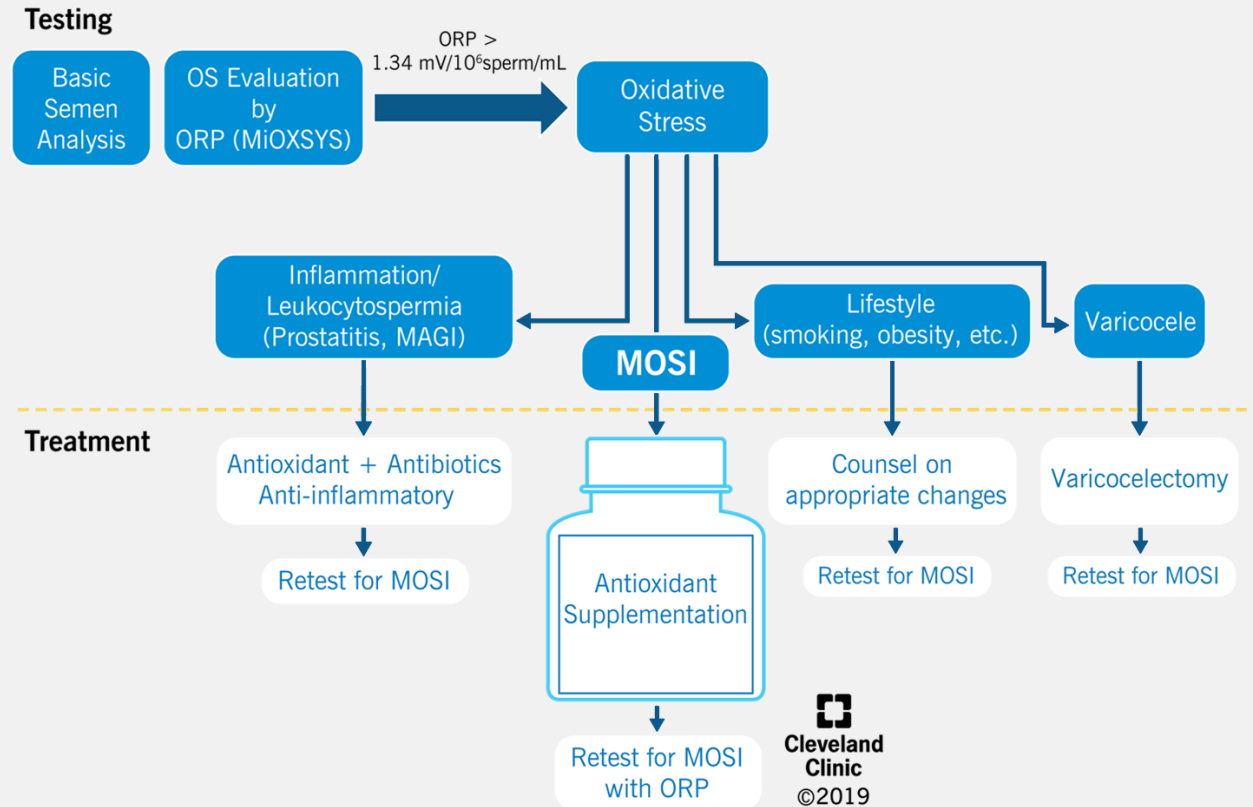
Argawal A., Selvam M.K.P., Arafa M, Okada H, Homa S, Killeen A, et. al. Multi-center evaluation of oxidation – reduction potential by the MiOXSYS in males with abnormal semen. Asian J Androl. 2019 Nov-Dec; 21 (6): 565-569.

MiOXSYS® is the cornerstone of Male Oxidative Stress Infertility (MOSI) diagnostics and management

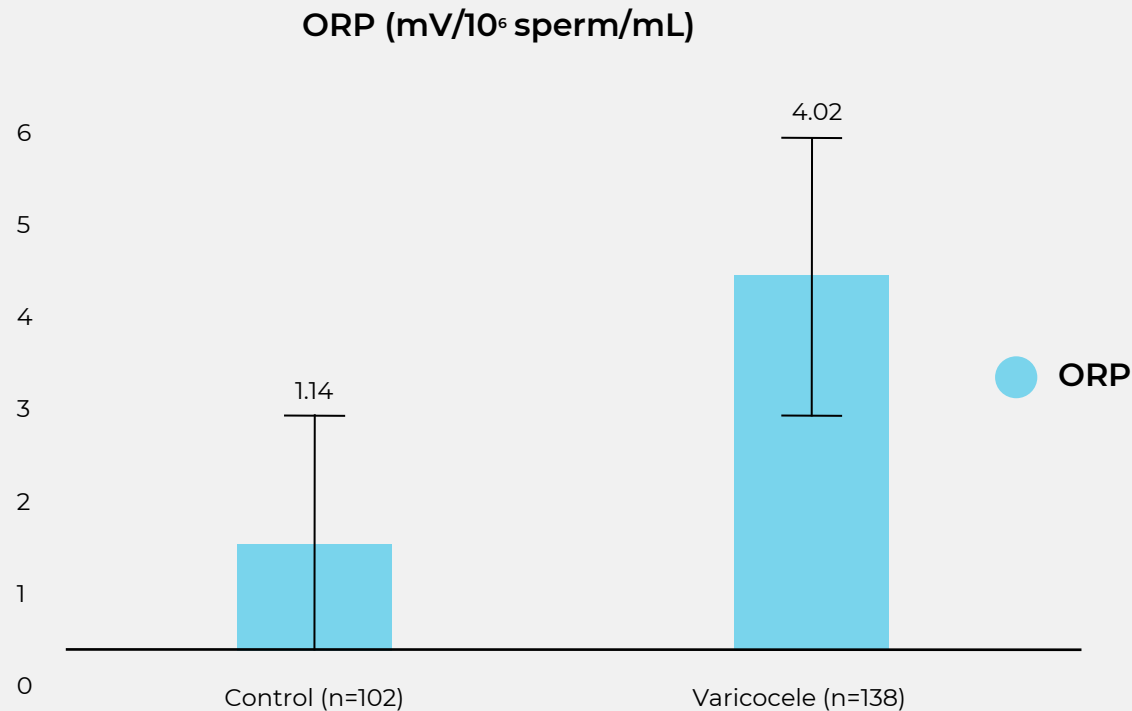
Key Points:

The authors propose the term Male Oxidative Stress Infertility, or MOSI, as a novel descriptor for infertile men with abnormal semen characteristics and OS, including many patients who were previously classified as having idiopathic male infertility.

The authors recommend that men with idiopathic infertility should be screened for MOSI using an efficient, inexpensive, high sensitivity/specificity test for ORP such as MiOXSYS, which has practical advantages over alternative techniques.



The mean ORP of the infertile men with a varicocele might be ~3.5x higher than that of the normozoospermia controls



138 infertile men with varicocele (Grade 1, 24 cases; Grade 2, 47 cases; Grade 3, 67 cases) and 102 men with normozoospermia without varicocele were evaluated.

The mean ORP of the infertile men with a varicocele was three times higher than that of the normozoospermia controls ($p < 0.01$).



Varicocele repair improves ORP



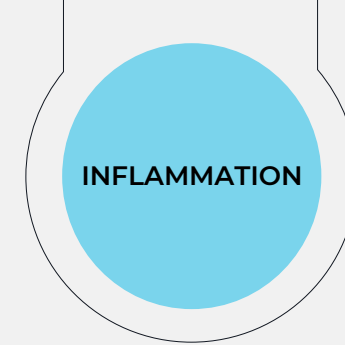
SEMEN PARAMETERS	MEANS		P VALUE	95% CI
	PRE-VARICOCELE	POST-VARICOCELE		
sORP (mV/10 ⁶ sperm/mL)	4.73	2.03	0.001	-1.38 - -2.68
Progressive Motility (%)	19.98	27.98	0.001	24.69-30.20
Total Motility (%)	45.88	54.85	0.01	49.60-59.09
Morphology (%)	3.82	4.27	NS	3.44-5.21
Sperm Concentration (10 ⁶)	28.11	37.85	.05	2.77-15.78
Total Sperm (10 ⁶)	85.21	111.96	NS	2.66-48.08

Post varicocele repair compared to pre varicocele repair revealed significant improvement in ORP (P<0.001), SDF (P<0.001) total motility (P<0.01), and progressive motility (P<.0.001). Although there was an improvement in morphology, it was not statistically significant.

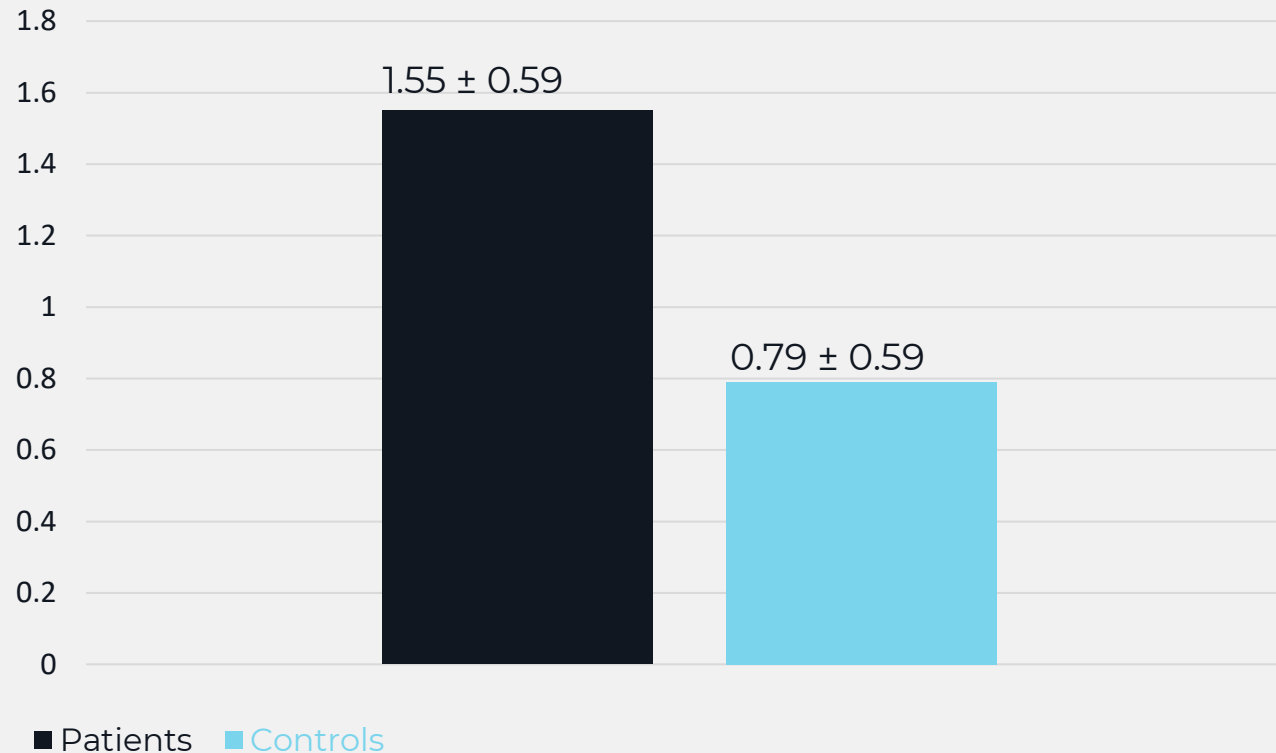
This study validates previous data that varicocele repair improves bulk semen parameter values and SDF, but is **the first to demonstrate it improves ORP.**



Chronic inflammation increases ORP levels and impairs male fertility



ORP levels



Males diagnosed with inflammatory bowel diseases have worse basic sperm parameters compared to those who are healthy

Regarding the sperm of males ill with inflammatory bowel diseases, the phenomenon of oxidative stress is intensified, which may be the cause of the deterioration of semen parameters, as well as an intensified DNA fragmentation

An asymptomatic carrier state of bacteria may contribute to the intensification of oxidative stress



ORP increases with paternal age

Study Objective:

To investigate the relationship between the ORP and paternal age with the goal of using the ORP as an indicator of semen oxidative stress.

Study Location:

Yokohama University Medical Center, Japan

Results:

The semen ORP level was positively correlated with age ($p < 0.05$). The rate of ORP positivity was significantly increased in men ≥ 34 years of age compared with that in men < 34 years of age (33% compared with 12%, respectively; $p < 0.01$).

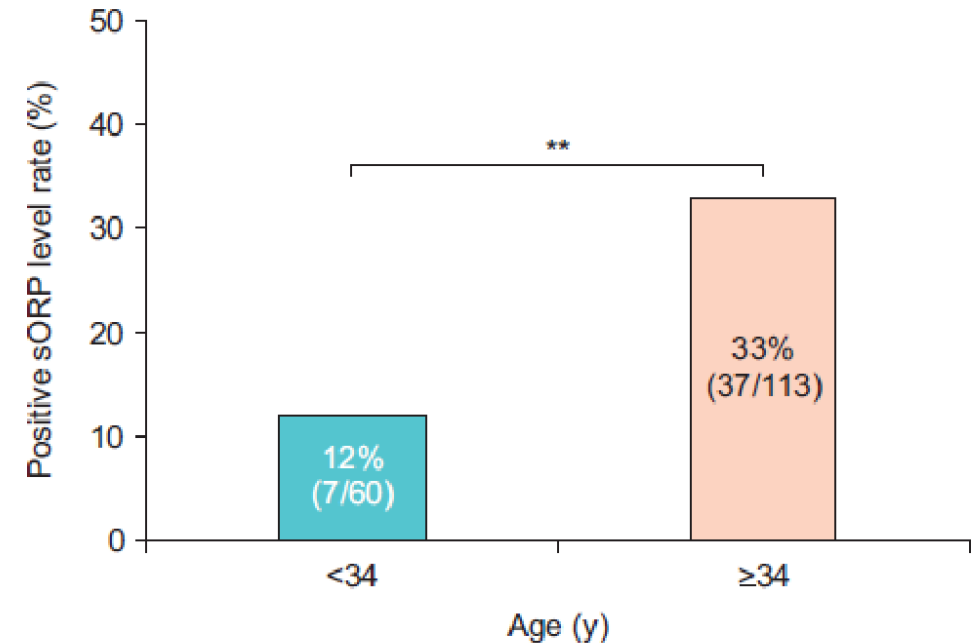
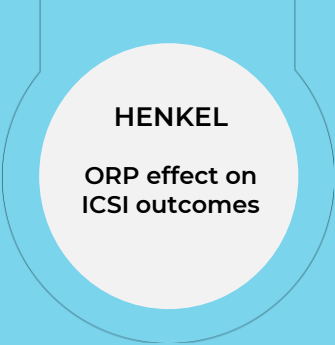
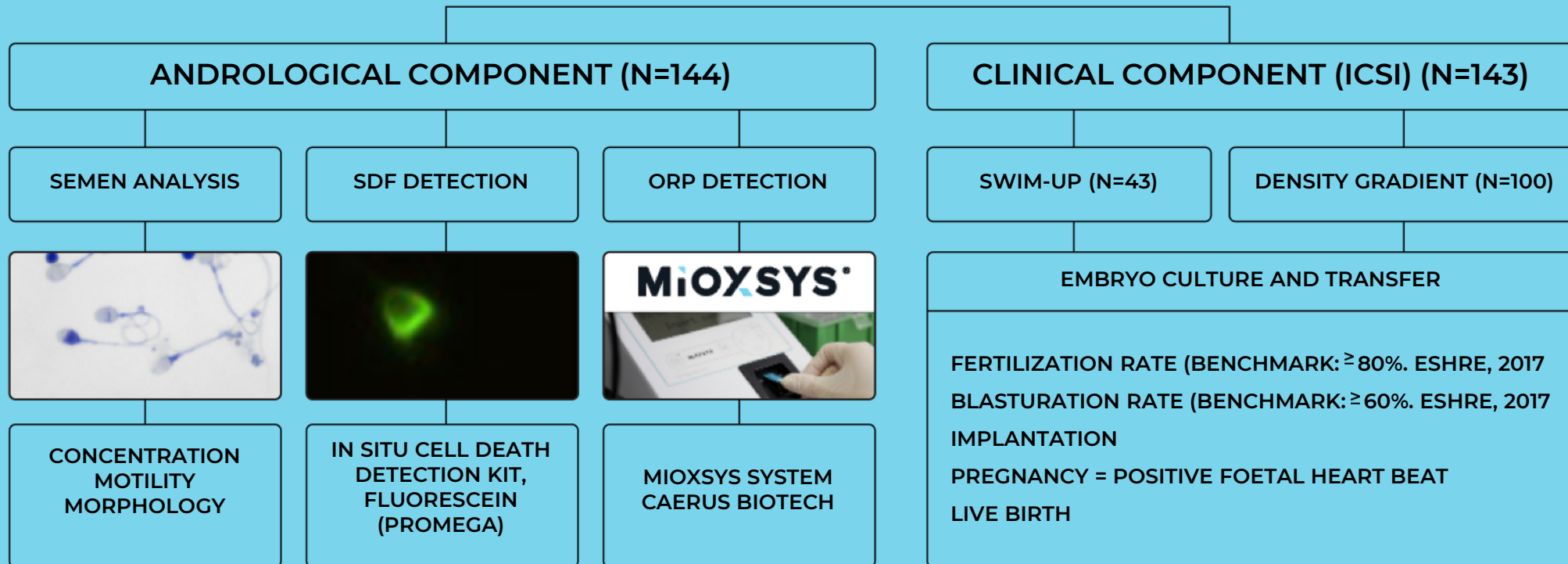


Fig. 4. Comparisons of the rate of static oxidation reduction potential (sORP) positivity between men aged < 34 and ≥ 34 years. The vertical axis shows the rate of positive sORP, with the horizontal axis showing age. sORP ≥ 1.38 was defined as a positive level. ****** $p < 0.01$.

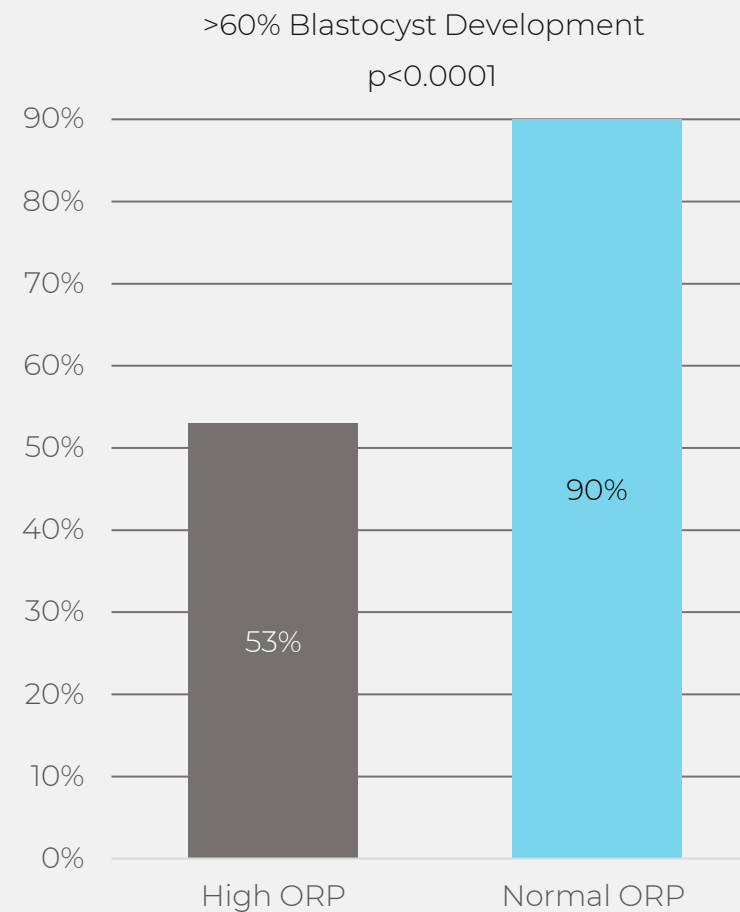
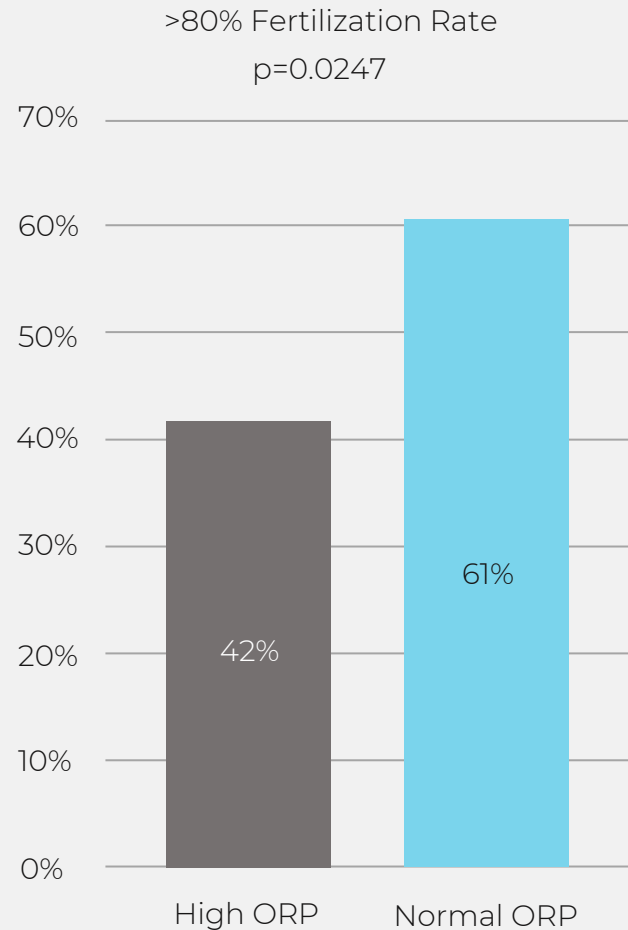
Predictive value of seminal ORP analysis for reproductive outcomes of ICSI cycles



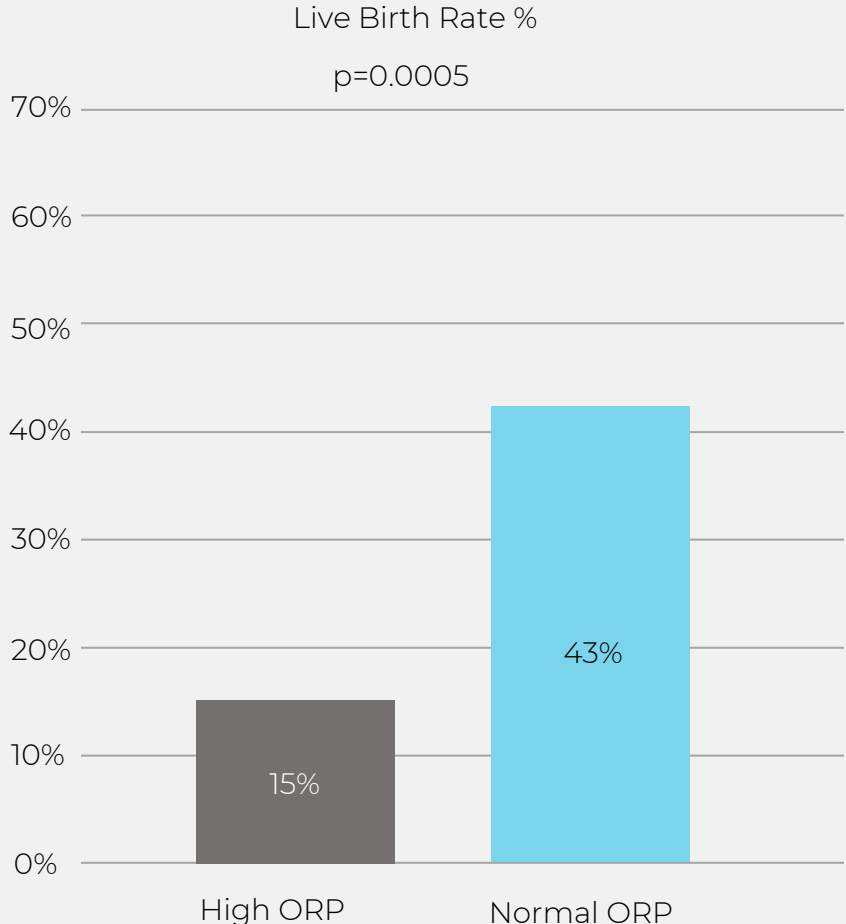
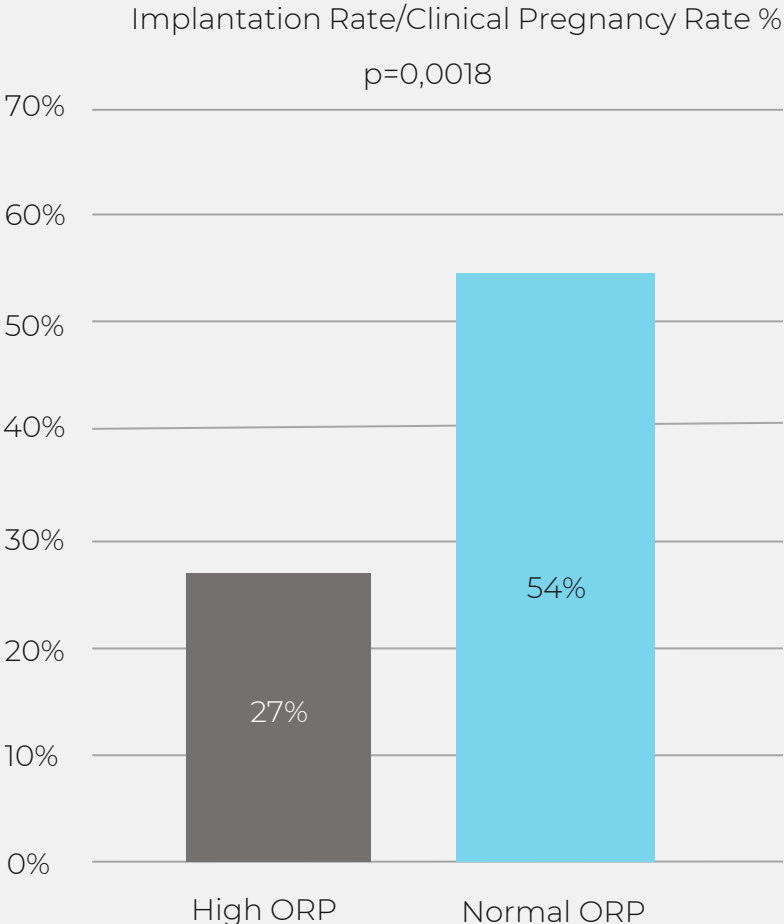
EJACULATED SEMEN SAMPLE (N=144)



High ORP negatively affects reproductive outcomes after ICSI



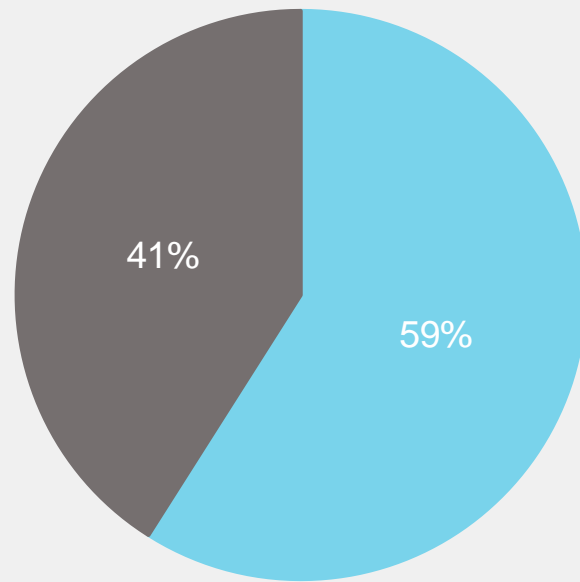
High ORP negatively affects reproductive outcomes after ICSI



Ralf Henkel, et al, Predictive value of seminal oxidation-reduction potential (ORP) analysis for reproductive outcomes of intracytoplasmic sperm injection (ICSI) cycles, Reproductive BioMedicine Online, 2022

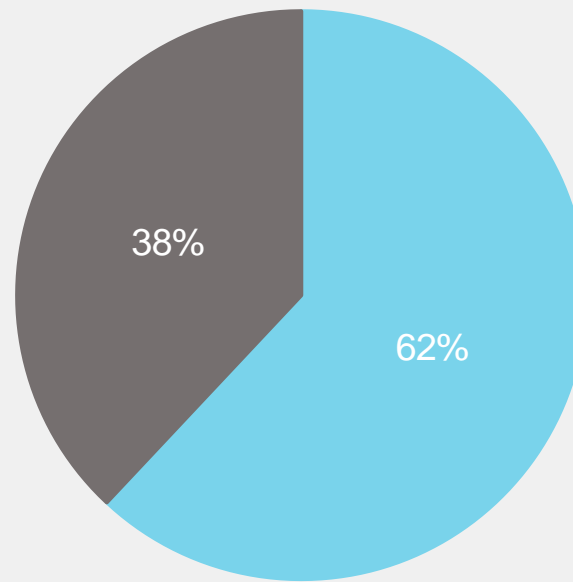
High ORP negatively affects reproductive outcomes after ICSI

Fertilization Rate 96.5%



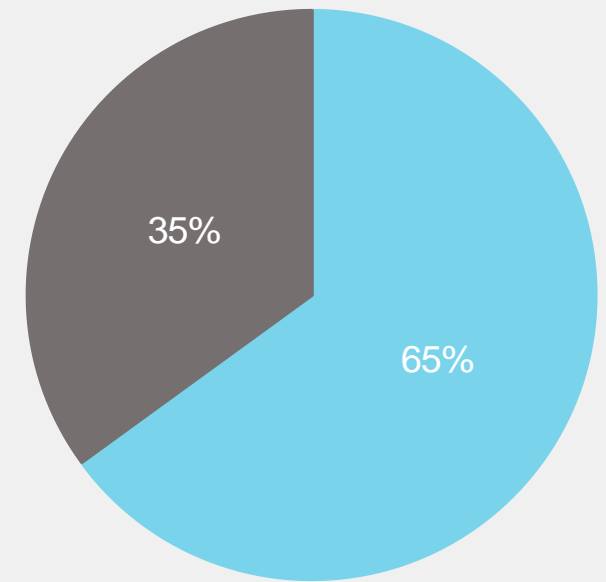
■ Normal ORP ■ High ORP

Blastocyst Development Rate 68.5%



■ Normal ORP ■ High ORP

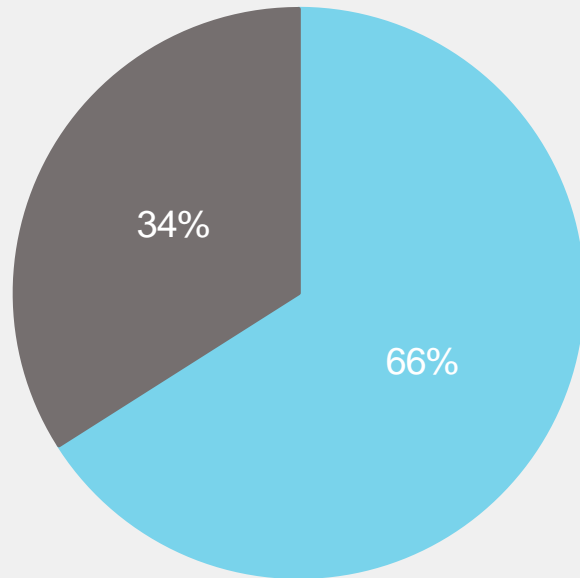
Implantation Rate 40.3%



■ Normal ORP ■ High ORP

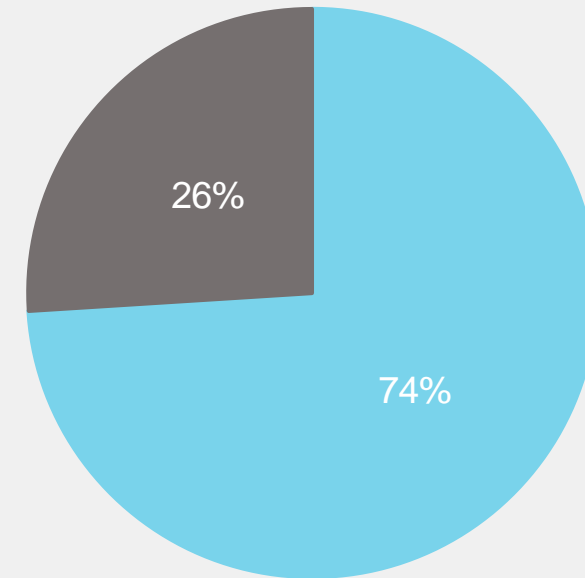
High ORP negatively affects reproductive outcomes after ICSI

Clinical Pregnancy Rate 39.6%



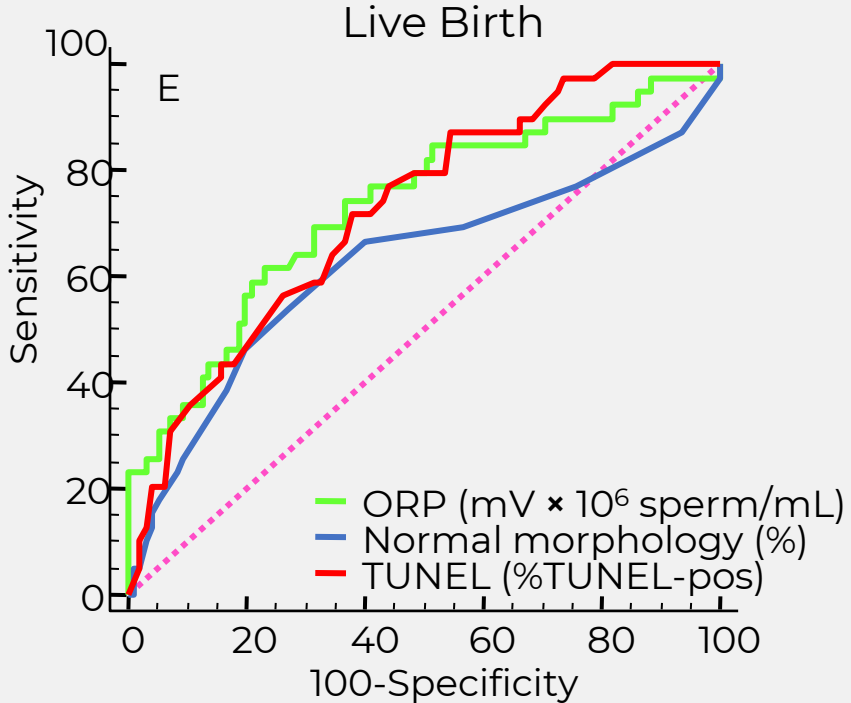
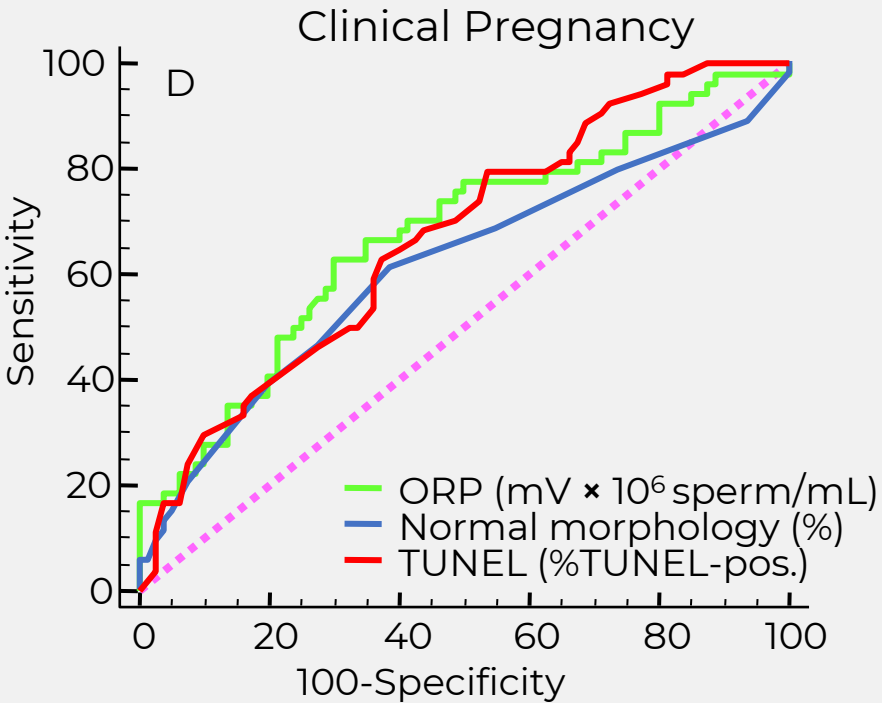
■ Normal ORP ■ High ORP

Live Birth Rate 29.1%



■ Normal ORP ■ High ORP

ORP is strongly predictive for success rates in Clinical Pregnancy and Live Birth



**Average cut-off for ORP:
0.51 mV/10⁶ sperm/mL**

Variable	AUC	Cut-off	Sens. (%)	Spec. (%)	+PV (%)	-PV (%)	P-value
ORP	0.680	≤0.465	62.7	71.3	59.6	74.0	0.0002
Morphology	0.614	>4	61.1	62.5	52.4	70.4	0.0278
TUNEL	0.665	≤19	63.0	62.5	53.1	71.4	0.0005
Comp. of AUC	ORP versus TUNEL:						0.7332
	ORP versus Morphology:						0.2376
	TUNEL versus Morphology:						0.3856

Variable	AUC	Cut-off	Sens. (%)	Spec. (%)	+PV (%)	-PV (%)	P-value
ORP	0.728	≤0.393	61.5	76.8	52.2	83.00	<0.0001
Morphology	0.621	>4	66.7	60.0	40.6	81.4	0.0420
TUNEL	0.723	≤19	71.8	62.1	43.8	84.3	<0.0001
Comp. of AUC	ORP – TUNEL:						0.9100
	ORP – Morpho:						0.1183
	TUNEL – Morpho:						0.1504

ORP measurement can be used to determine the successful embryo development during IVF

Study Objective:

Investigate whether ORP in semen of men undergoing ART affects embryo quality during IVF and plays any role in predictive value for clinical pregnancy.

Study Location:

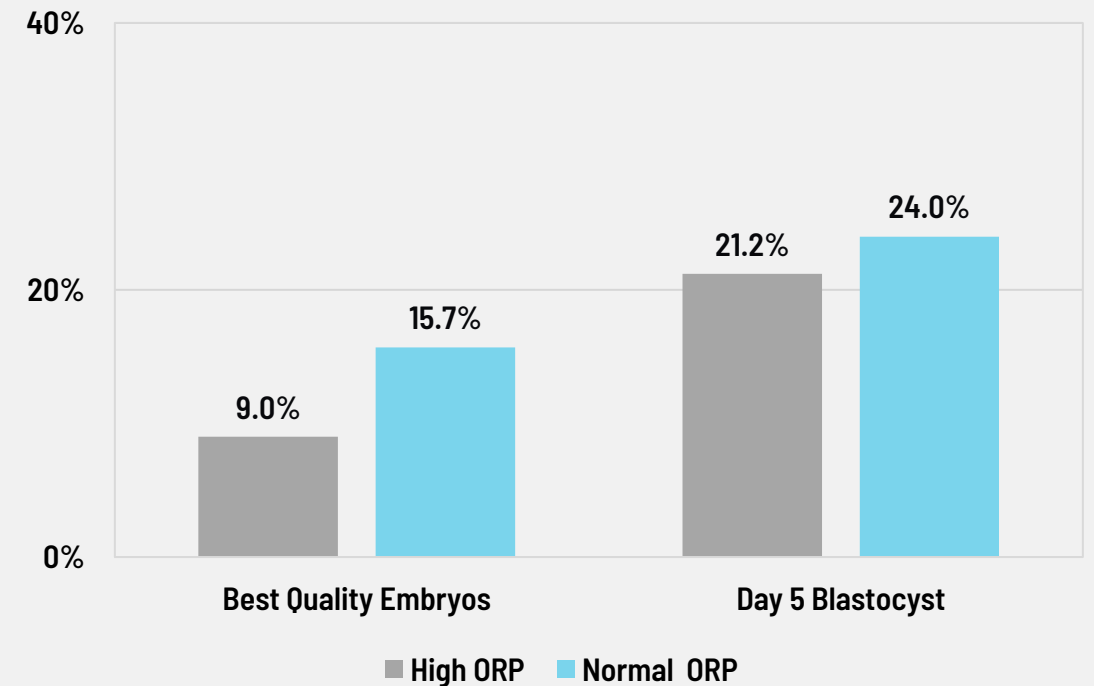
Tulane University, USA

KF American Hospital, Turkey

Results:

Positive correlation was demonstrated in High ORP group with decreased clinical pregnancy rate. High seminal ORP values had negative effect on embryo and blastocyst quality.

Embryo/Blastocyst Development



ASRM 2018: Determination Of ORP In Follicular Fluid (FF) And Culture Media Used For Washing And Oocyte Culture After Egg Collection

Redox potential of washing and culture media is significantly higher than the redox potential of follicular fluid from infertile patients and oocyte donors.

	FF- infertile Patients	FF-oocyte donors	Culture medium	Wash medium
ORP (mV)	100.8±17.5	86.0±14.8	225.1±3.1	275.0±2.9
	p<0.0001		p<0.0001	

Low ORP values in the culture medium compared to the wash media, may be due to the complex composition of the culture media.

ORP in culture media may need adjustment to increase success rates in ART.



ESHRE 2019: The Supraphysiological Levels Of ORP In The Human Culture Media Affects Blastocysts Formation And Ongoing Pregnancies In IVF Cycles

140 Patients undergoing an in vitro fertilization (IVF) cycle, 732 Zygotes obtained

GROUP 1: 360 zygotes cultured in 1 mL of culture media adjusting the ORP levels at 80 mV every of 12h

GROUP 2: 372 zygotes cultured in 1mL of embryo culture media without adjusting the ORP levels

Figure 1: **Blastocyst formation** rate of embryos cultured in natural (adjusted) ORP culture media vs supraphysiological

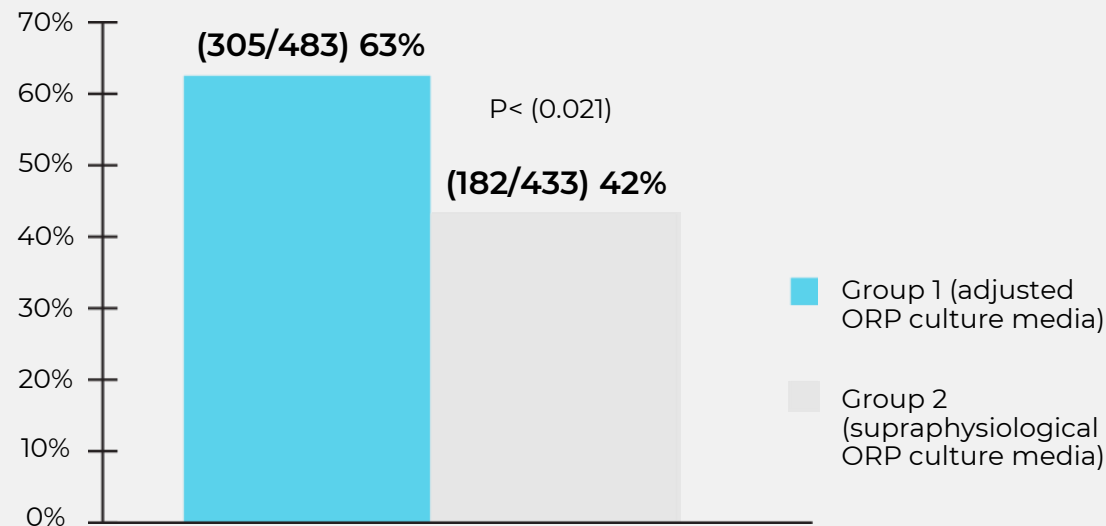
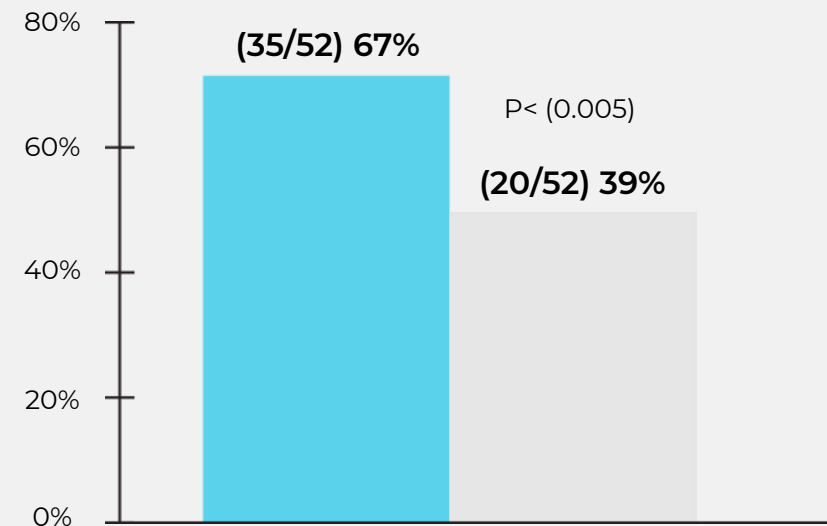
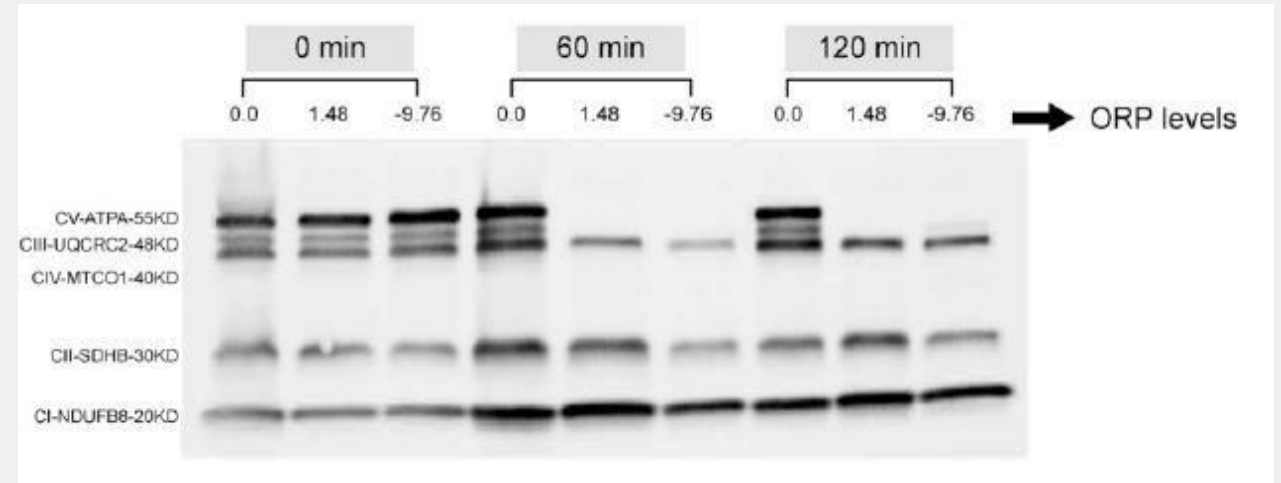


Figure 2: **Ongoing pregnancy** rate from embryos cultured in natural (adjusted) ORP culture media vs supraphysiological



Reductive stress has negative effect on sperm functions

- Until recently, scientific studies only focused on OS as a major factor contributing to male infertility, but lacked clinical awareness about RS.
- Incorrect usage of antioxidants may scavenge the physiologically necessary ROS resulting in sperm not being able to undergo capacitation and acrosome reaction
- Therefore, it is essential to not only understand this redox balance but also know the physiological ORP range in which sperm are able to fulfill their normal physiological functions..
- Establishment of a reductive environment due to high antioxidant concentration has a deleterious impact on sperm motility, vitality and mitochondrial activity.



Expression profile of OXPHOS complex proteins at time points 0, 60 and 120 min after sperm exposure to oxidative stress with ORP level 1.48 mV/10⁶ sperm/mL and reductive stress with ORP level -9.76 mV/10⁶ sperm/mL.

Reductive stress has negative effect on sperm functions

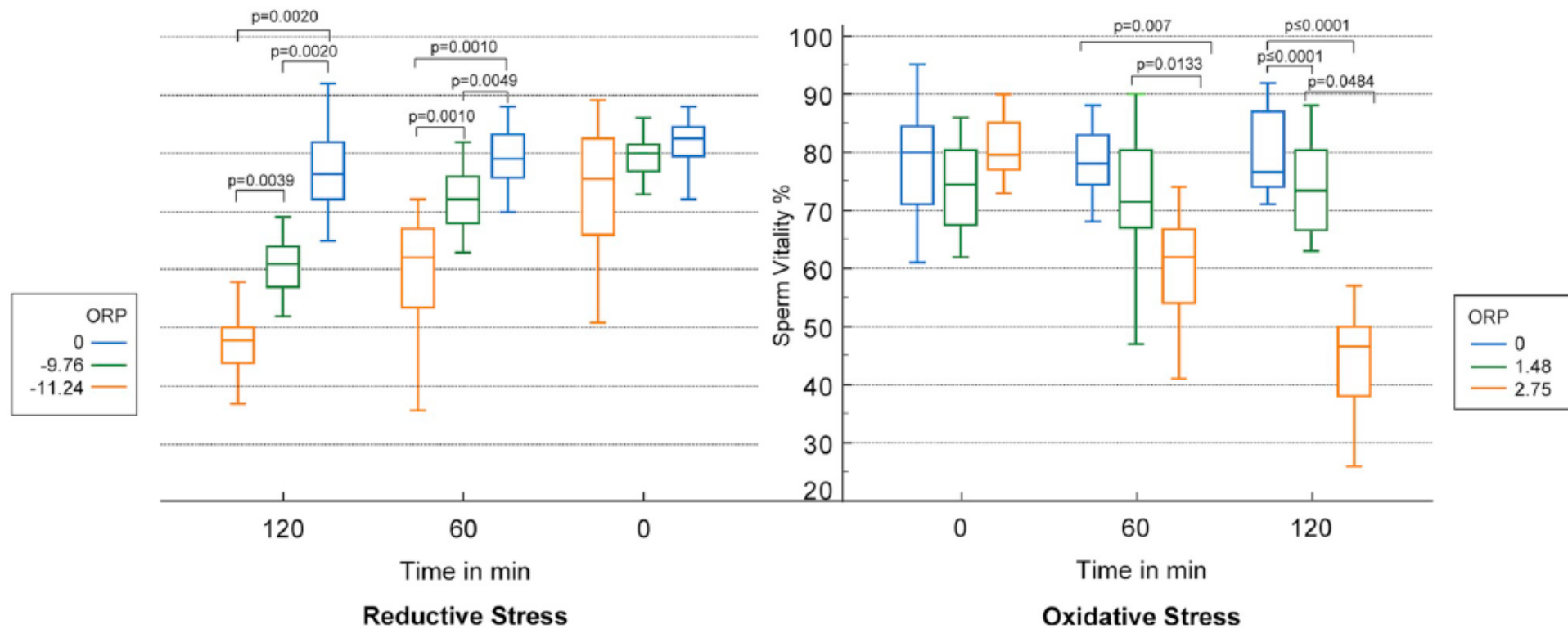


Fig. 4. Vitality of sperm at time points 0, 60 and 120 min after exposure to oxidative stress with ORP levels 1.48 and 2.75 mV/10⁶ sperm/mL and reductive stress with ORP levels -9.76 and -11.24 mV/10⁶ sperm/mL. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography© 2020. All Rights Reserved.



Trust and Advocacy Of The Scientific Community

MiOXSYS® scientific symposium
ESHRE 2022, Milan, Italy



Prof. Ashok Agarwal

President, Global Andrology Solutions
Professor, Case Western Reserve University, Cleveland
Assistant Professor, Harvard Medical School
Director of Research, Global Andrology Forum
Moreland Hills, Ohio, United States



Israel Maldonado Rosas MS

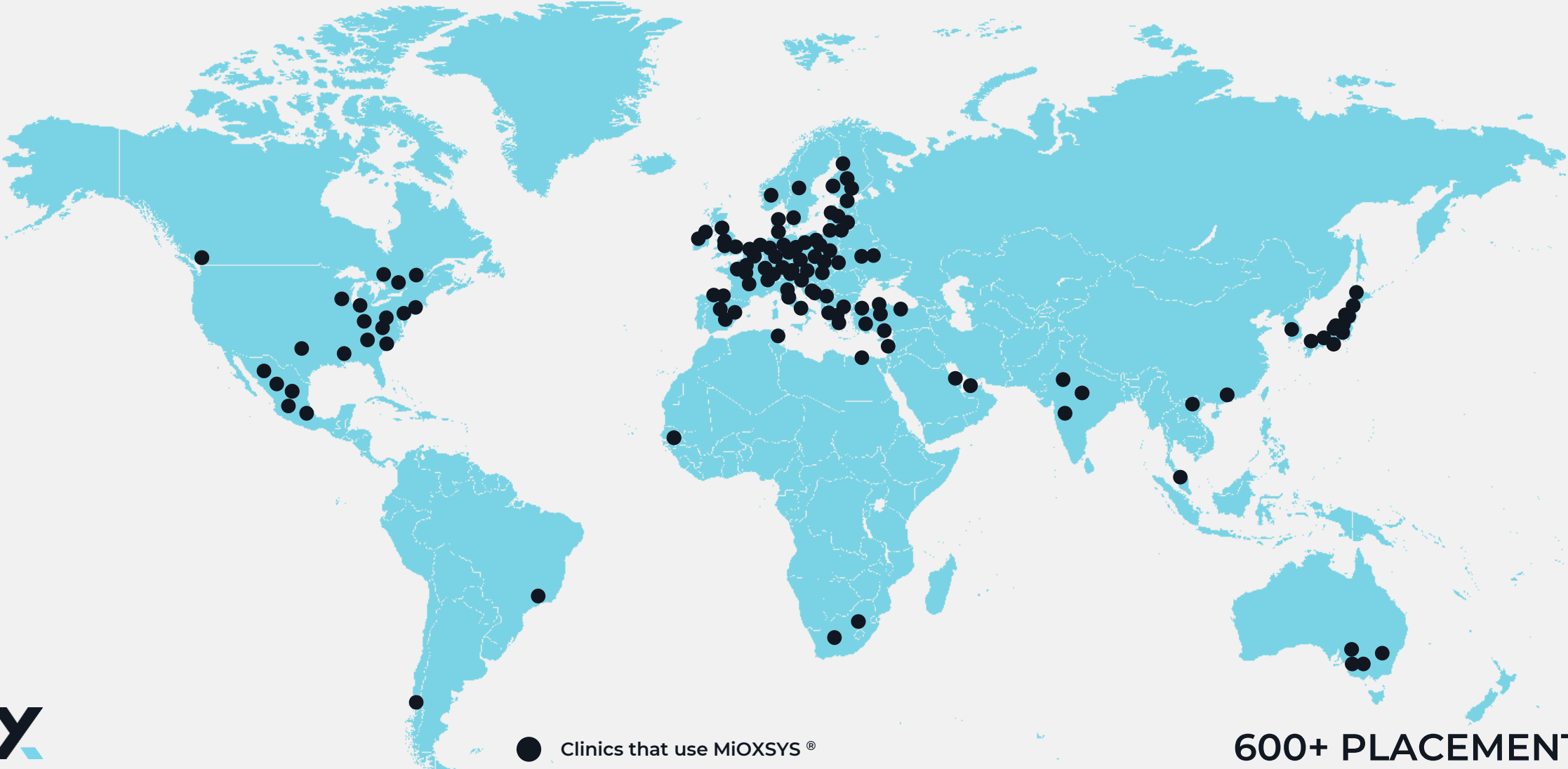
Clinical Embryologist
IVF Lab Director, Center of Technological Innovation
and Reproductive Medicine (CITMER)
REDLARA Certified Embryologist
Mexico City, Mexico



Prof. Ralf Henkel

Chief Scientific Advisor: LogixX Pharma, Reading, UK
Visiting Reader: Department of Metabolism, Digestion and
Reproduction, Imperial College London, London, UK
Extraordinary Professor: Department of Medical Bioscience,
University of the Western Cape, Bellville, South Africa,
Honorary Professor: Universidad Peruana Cayetano Heredia,
Lima, Peru

Recognized and used by clinics worldwide



● Clinics that use MiOXSYS®

600+ PLACEMENTS



MiOXSYS[®] – complete, accurate and rapid oxidative stress diagnostic

OXIDATIVE STRESS

30% of couples worldwide are affected by male oxidative stress infertility

ORP

Complete, well researched, clinically validated and easy to use measure of seminal oxidative stress

ELEVATED ORP LEVELS

Have impact on reproductive outcomes

MiOXSYS[®]

The cornerstone of MOSI diagnostics and management

