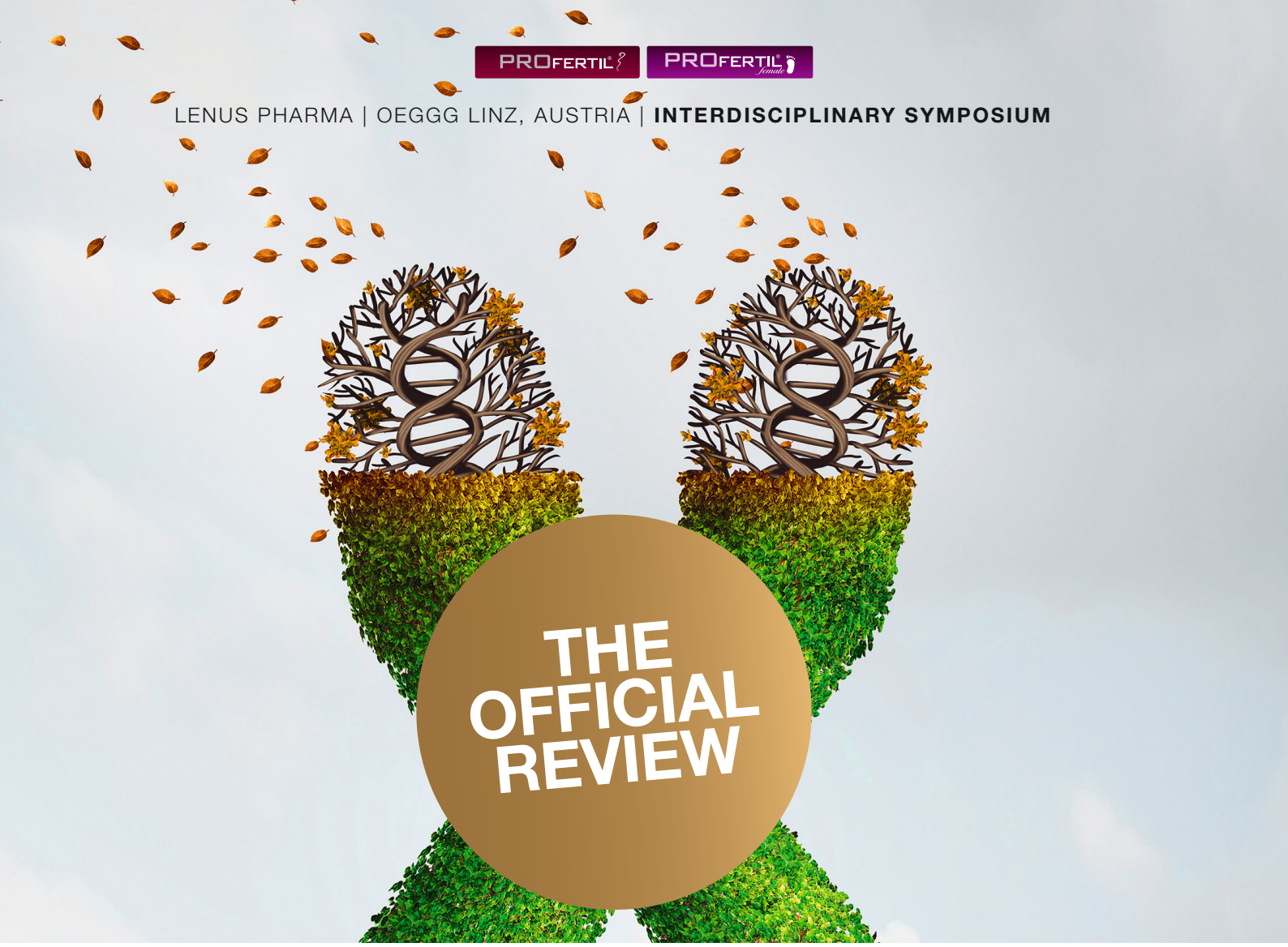


»Late Parenthood and Fertility«

When procreation is part of our genetic program, but delayed parenthood is part of the modern way of life, the question of fertility comes with a health warning. Both men´s and women´s fertility decreases with age. Lenus Pharma presents: updates on ovarian aging, sperm DNA fragmentation and the challenges created by oxidative stress.

»Spermageddon« – the word is part of the vocabulary of experts on male sexual and reproductive health in order to highlight one of the facts of modern life: The sperm quality of men is not what it used to be. As a highly acclaimed study by Hebrew University Jerusalem showed, the sperm counts in the West plunged by 60% in 40 years.[1)] A recent update from the same research team showed that sperm count is declining at an accelerated pace globally.[2)]

And that is not the only reason why urologists have increasingly become partners in support of fertility issues. ”Today it is also clear that the age of the father-to-be is an important risk factor for male infertility“, says urologist Dr. Claus Riedl. Fertility declines with age. The keyword to the problem is ”sperm DNA fragmentation“, and a worldwide trend makes it a crucial one: Both women and men tend to postpone parenting a child until later in life. It is well known that ovarian aging starts earlier than the aging of other organs. But sperm also have a ticking biological clock that impacts fertility as well. “Infertility”, says gynecologist Prof. Dr. Martin Imhof, ”is not just a female problem, nor is the loss of fertility.“ From the 35th year of age, the problems start to accelerate. As it happens, this is also more often the moment in time, when the desire to have children becomes focal for both women and men.

In a recent interdisciplinary symposium, with about 150 attendees, Prof. Dr. Martin Imhof, Assoc. Prof. Dr. Johannes Ott (gynecologic endocrinology) and urologist Dr. Claus Riedl provided updates on the problems of fertility in late parenthood and discussed the benefits of a regimen with antioxidants.

The review at a glance ▶

Oxidative Stress and Ovarian aging. What can we do?

Assoc. Prof. Dr. Johannes Ott[3]

There is a dream that seems to be deeply humane, says Assoc. Prof. Dr. Johannes Ott. »We dream that we can live and procreate forever. The problem is that the reproductive phase ends early. And ovarian aging starts earlier than the aging of other organs.« But how does ovarian aging develop?

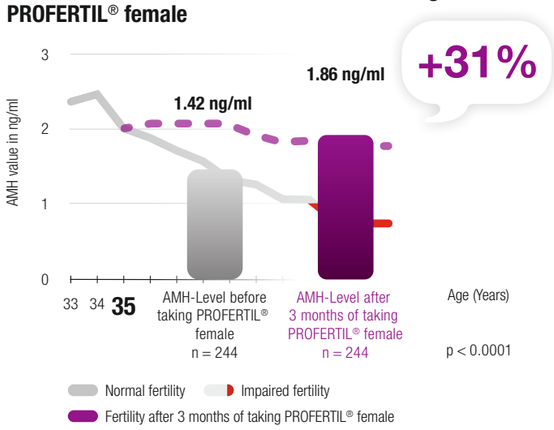
There are a number of hypothesis, says Ott, but the most important is the Free-Radical Theory. Reactive oxygen species (ROS), which are byproducts of the normal metabolism of oxygen, are permanently formed in our bodies, and they perform important functions in the ovaries, particularly during ovulation after the LH-peak. But there has to be a balance. And as soon as the anti-oxidative capacities, which regulate the process, are overloaded, a harmful imbalance occurs.

There is increased oxidative stress in the ovaries, the sources of which are various: Antioxidative systems decline with age; there is the possibility of mitochondrial dysfunction; repeated ovulation after the LH-peak leads to inflammatory reactions, to name a few. The consequences of too much ROS in the ovaries are bad news for fertility. So, what can we do?

Quite a few studies have shown the efficacy of antioxidants. PROFERTIL® female is a combination of several antioxidants with rather positive effects on the female reproductive system. Several studies have shown positive immunological and anti-inflammatory effects, results courtesy of the antioxidant-mix.

To highlight a recent study on women aged 35+, whose level of Anti-Müllerian Hormone (AMH) was decreased, indicating a reduced functional ovarian reserve, results showed that PROFERTIL® female increases the AMH level when it is too low in women 35+.

AMH value before and after 3 months of taking PROFERTIL® female



In another study among women with PCOS (whose AMH-level is often too high) PROFERTIL® female decreased the AMH level only after a three-month-intake. The antioxidant-mix creates hormonal balance.

ROS, concludes Assoc. Prof. Dr. Ott," are an important factor in ovarian aging, as the antioxidant capacities in the follicle liquid decline with age. And studies have shown that antioxidant regimens are a good way to slow-down ovarian aging. Plus, they are an option for women with PCOS, which is strongly connected with elevated levels of oxidative stress."

Intra-ovarian OS increases with age

Lipovac M. et al., Gynecol Endocrinol. 2022 Apr;38(4):310-313.

Late Parenthood and Fertility
INTERDISCIPLINARY SYMPOSIUM

Update on Sperm DNA Fragmentation and non-invasive Treatment options for Male Infertility.

Dr. Claus Riedl[4]

»The concern about a worldwide decline of sperm quality is the base for increasing andologic-gynecologic efforts to improve male fertility.«, says Dr. Claus Riedl. »This is also reflected by a new recommendation from the European Association of Urology (EAU)[5]: Since routine sperm analysis cannot differentiate between fertile and infertile men in all cases, it is essential to implement sperm DNA fragmentation tests. In contrast to mere numeric sperm analysis, these tests shed light on disorders of the genetic material, the DNA.«

The reasons for male infertility are numerous, but in 20-30% of couples, the routine spermiogram does not detect a disorder. In these men with unexplained infertility, a sperm DNA fragmentation test is mandatory to assess a damage at the level of the DNA.

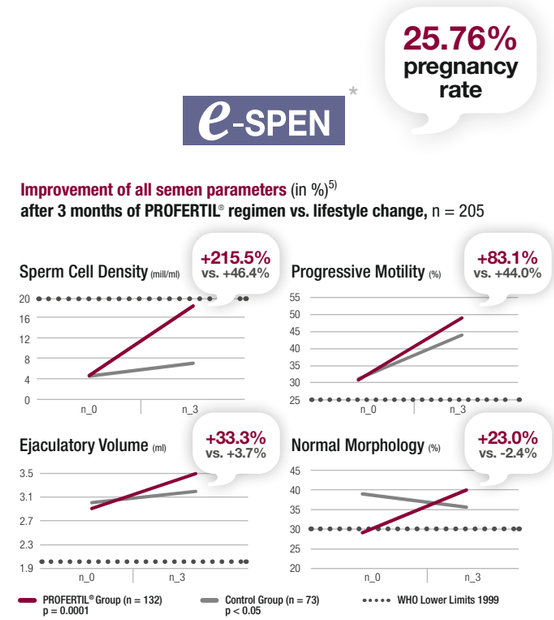
We are aware of multiple causes for DNA damage: endocrine disruption consequent to environmental pollution, smoking, unhealthy diet, heat and cell-phone radiation. Oxidative stress, triggered by those drivers, lies at the root of the problem. Beside that, sperm DNA fragmentation also increases with age, and demographic data show that today more fatherhoods in the industrialized world occur after age 35.

Thus, the urologist strongly recommends sperm DNA fragmentation tests for infertile couples in case of multiple spontaneous miscarriages, as also included in the EAU Guidelines Panel on Male Sexual and Reproductive Health.

However, what can be done against sperm DNA fragmentation? The closest is to change individual lifestyle to eliminate reasons for damage. This is always harder than it sounds. In addition, there is also the option of using antioxidants to reduce oxidative stress.

"Free reactive oxygen species (ROS) is the key player in effecting DNA damage. A Cochrane review has shown the efficacy of antioxidant therapy in cases of male infertility in 34 randomized studies covering 3,000 couples, with significant positive effects on life birth and pregnancy rates for subfertile couples. There were also several studies with single antioxidants", says Dr. Riedl, "but the best results were achieved by a combination of several antioxidants, because they effectively influence all parts of the sperm maturation process."

A frequently quoted study of PROFERTIL® male (an antioxidant micronutrient combination) versus the mono substance L-Carnitine showed a significant improvement of sperm number, motility and morphology, and proved superiority to the mono substance.



* Controlled study 2012; Improvement of sperm quality after micronutrient supplementation; Imhof M. et al.; published in e-SPEN , Volume 7, Issue 1, February 2012; patients (n = 205): PROFERTIL® group: n = 132, control group: n = 73; inclusion criteria: ≥ 1 year of subfertility and ≥ 2 pathological semen analyses; exclusion criteria: aspermia, varicocele, azoospermia, urogenital infections. Pregnancy rate control group = 15.07%.

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Late Parenthood and Fertility
INTERDISCIPLINARY SYMPOSIUM

The Importance of DNA Fragmentation in Sperm: Spontaneous Miscarriages and Implantation Failure.

Prof. Dr. Martin Imhof[6]

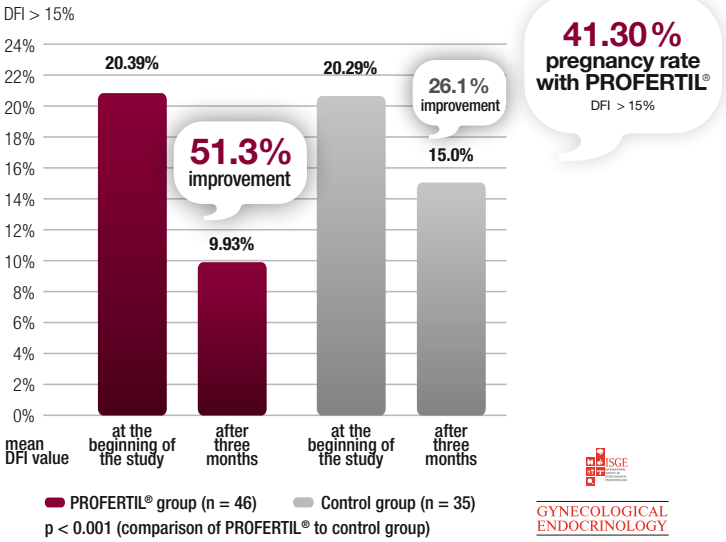
Repeated implantation failure, says Prof. Dr. Imhof, means no achievement of clinical pregnancy after transfer of at least 4 good-quality embryos in a minimum of 3 fresh or frozen cycles in a woman under the age of 40 years. And habitual miscarriages refer to »recurrent« pregnancy loss, defined as the loss of two or more pregnancies before viability. Which has been traditionally considered to be a »woman problem«.

Unfortunately, says Prof. Dr. Imhof, any activity of "influencing the sperm quality as a way of improving the success rate has not been considered for too long." But the great share of unexplained male infertility, the importance of DNA fragmentation, The Male Factor needs consideration: "A significant increase in DNA damage can be found in sperm from infertile men with normal standard semen parameters." (Imhof) But what is DNA fragmentation? Prof. Dr. Imhof: "Think Railway. Consider a train that works properly, this train is on its way – but on the track there is a bit missing. The damage is considerable, because the ride ends there." If a single or double DNA strand is fragmented, the rest of the functioning structure – the healthy ovum, the healthy genitals and the seemingly healthy sperm are compromised. The transfer of the gene-pool won´t take place. And, as we have learned by now: "DNA fragmentation is age-dependent and increases from the 35th year of age." (Imhof) And as to unexplained habitual miscarriages, there is a previously unconsidered correlation: "High levels of sperm DNA fragmentation are positively associated with miscarriage. Meaning, that male partners of women with recurrent pregnancy loss (RPL) have a significantly higher rate of sperm DNA fragmentation." (Imhof) Accordingly, DNA fragmentation should be considered in couples with unexplained RPL. Results in poor ART outcome, impaired embryo development, miscarriage and birth defects are more often due to damaged sperm than men would like to accept.

As mentioned by the experts above, oxidative stress is responsible for bad news. And yes, "change of lifestyle in order to reduce DNA fragmentation is important", says Prof. Dr. Imhof, but undeniably, "PROFERTIL® regimen is superior to lifestyle changes in order to achieve the desired result. The pregnancy rate improves significantly."

Which is, what everybody involved wants in the end – a successful pregnancy. As to miscarriages, Prof. Dr. Imhof insists, "men have to accept that their part in those tragedies is bigger than previously anticipated. And treatment of subfertile couples should never go ahead without a DNA fragmentation test, especially with couples aged 35+."

Reduction of sperm DNA fragmentation (DFI in %) after 3 months of PROFERTIL® regimen, n = 339



*DNA-Study 2021; The effect of micronutrient supplementation on spermatozoa DNA integrity in subfertile men and subsequent pregnancy rate; Riedl C. et al.; published in Gynecological Endocrinology 2021 Jun; 37(6); patients (n = 339): PROFERTIL® group: n = 162, control group n = 177.

Watch the full presentation video here!

GERMAN VERSION

[1] Levine H. et al.; Temporal trends in sperm count: a systematic review and meta-regression analysis, Hum Reprod Update 2017 Nov 1;23(6):646-659.
[2] Levine H. et al.; Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries, Hum Reprod Update, 2022 Nov 15; Online ahead of print.
[3] Assoc. Prof. Dr. Johannes Ott, Deputy Head of Depart. of Gyn Endo and Repro Medicine, University of Vienna.
[4] Prim. Univ. Doz. Dr. Claus Riedl, Dept. Head of Urology at Hospital Baden-Moedling.
[5] Tharakan T. et al.; European Association of Urology Guidelines Panel on Male Sexual and Reproductive Health, Eur Urol Focus 2022 Jan;8(1):339-350.
[6] Prof. Dr. Martin Imhof, Dept. Head of Gynecology and Obstetrics at Hospital Korneuburg, Austria.