'Andrological Ignorance' and 'ICSI Paradox': Is Men's Reproductive Health at Stake?

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Summary

Male infertility undeniably is a serious global issue affecting one in every 20 men and about 50% of overall infertility cases are contributed by male factor(s). Despite the declining trend of male fecundity and overwhelming prevalence of men infertility, there are very subtle efforts made to address the yet unknown underlying causatives for the deteriorating reproductive health of men. Development of assisted reproductive technologies (ARTs) seems to deviate the research and clinical attention, from the male reproductive health, towards achieving successful pregnancy with developed techniques of sperm retrieval and manipulations, as well as interventions to ameliorate the female reproductive functions to improve the ARTs outcome. The time ahead for male reproductive health does not lit any hope for betterment if male infertility problems are kept ignored, the underlying causatives of male infertility remain elusive and extensive research interventions are not made. Andrology research plays a massive role in understanding the core mechanisms of male infertility which needs to be accelerated in order to lay light upon better perception, diagnosis and management of male factor infertility and thereby strive towards future generations who no more experience the global declining trend in male fertility.

Keywords: Andrology, assisted reproductive techniques, male infertility, reproductive health

1. Background

For the past few decades, men's reproductive health issues have become a prime concern in reproductive biology research. Numerous reports have been published describing the declining trend in semen quality as well as other aspects of reproductive health (Carlsen et al, 1992; Nelson & Bunge, 1974; Swan et al, 1997). In 1992, Carlsen et al. had reported an alarming trend in decreasing semen quality since 1938. His group had reported a global diminution in sperm counts by about 50% between 1938 and 1990 (Carlsen et al, 1992). Since then several research works have reported regional or global trends in declining semen quality (Rolland et al, 2013; Van Waeleghem et al, 1996; Younglai et al, 1998). Our group has also reported a diminishing trend in semen quality in different continents (Sengupta, 2015; Sengupta et al, 2018a; Sengupta et al, 2017a; Sengupta et al, 2018b; Sengupta et al, 2017b). Numerous confounding factors have been identified to contribute to this diminishing reproductive health status in men, involving environmental and occupational factors (Sengupta, 2013), climate change (Jegasothy et al, 2020), lifestyle factors (Leisegang & Dutta, 2021), obesity (Leisegang et al, 2021) and other systemic diseases (Omolaoye & Du Plessis, 2018), reproductive tract infections (Sengupta et al, 2020) and so on. As a consequence of this declining trend in men's reproductive health, an alarming fall in the global fertility rate has also been noticed. About 15% of the couples of reproductive ages are infertile (Jarow et al, 2002). According to Sharlip et al. (2002), males are found to be solely responsible for 20%–30% of infertility cases and contribute to 50% of cases overall. This overall indicates a threat to our future generations (Jarow et al, 2002).

However, to mitigate these infertility issues, several assisted reproductive technologies (ART) have been introduced, including *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), physiological ICSI (PICSI), intracytoplasmic morphologically selected sperm injection (IMSI) so on (Nayan et al, 2018), which is showing some light to the infertile couples of reproductive age.

2. 'Andrological Ignorance' and 'ICSI Paradox'

Male infertility seems to be mostly addressed bypassing men's reproductive health and focusing on various ARTs to achieve a successful pregnancy with developed techniques of sperm retrieval and *in vitro* gamete manipulations, as well as interventions to ameliorate the female reproductive functions to improve the ARTs outcome. ART is an innovative multibillion-dollar enterprise. The year 1992 marked the birth of the first ICSI-conceived baby and henceforth this technology has rapidly spread all over the world, so much so that couples,

with or without male-factor fertility issues, are pursuing ICSI aiming for better and more reliable outcome (Boulet et al, 2015; De Geyter et al, 2018). The paradox lies here. The Clinicians, Researchers and the couples who are seeking ARTs, are likely to embrace any new technology, regardless of expenses, to achieve a successful pregnancy, without paying heed to the understanding and/or treatment of the reproductive health of the infertile male partners. ICSI does not address the male fertility status but manipulates the gametes and treats the female partner which mainly includes ovarian stimulation, egg recovery and embryo transfer. This technology indeed diverts science from solving the actual health issue towards finding technical shortcuts to achieve success. The future of men's reproductive health sees no improvement if male infertility problems are kept ignored and if the underlying causatives of male infertility are not elucidated by extensive research interventions. For the last three decades, ICSI seems to roadblock the global scientific advancement in andrology (Skakkebaek, 2017). Andrology research plays a massive role in understanding the core mechanisms of male infertility which needs to be accelerated for better understanding, diagnosis and treatment of male infertility or subfertility. To add to the temptation of skipping the extensive process of evaluation and treatment of male reproductive issues, "artificial human sperm" may soon be invented in the near future world of technology as *in vitro* fertile mouse sperm can already be produced (Saitou & Miyauchi, 2016). Moreover, sperm DNA can already be edited using "Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein-9 nuclease: CrispR-Cas9" (Vassena et al, 2016). With these robust scientific advancements, the main fear is, the future generation will experience a steeper declining trend in male fertility worldwide. It is not yet too late to address the fundamental andrology problems in order to ameliorate men's reproductive health and spare the technology only for real need.

3. Conclusion and future perspectives

Male reproductive health is facing a global crisis. Despite a colossal advancement in reproductive technology, most of the male infertility cases remain idiopathic. Extensive research in the field of Andrology should be encouraged to reveal the yet unknown core underlying mechanisms of male infertility. The regulatory bodies must encourage and highlight the emerging and concerning information on male reproductive health at the national strata. There should be more studies on the association of male reproductive health with somatic health, the causative factors and the mechanisms that pave the way to male reproductive disruptions and the kinds of heritable defects that paternal gamete can pass to the next generation. Finally, there is a need to advocate and revitalize the national policies from time to

time, as per the changing global scenario of male fertility status, to direct and support research in this field.

Conflict of interest

The authors declare that they have no conflict of interests

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