Editorial

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The role of clinical trials in advancing reproductive medicine: a comprehensive overview

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Reproductive health encompasses the entire spectrum of reproductive processes and functions throughout a person's life, playing a vital role in the harmonious development of populations, economies, and societies. This critical aspect has garnered increasing global attention. Ensuring sexual and reproductive health stands as a fundamental step toward achieving the United Nations Sustainable Development Goal (SDG) by 2030 [1]. Despite extensive efforts, both China and the world at large confront a multitude of reproductive challenges. These challenges encompass declining fertility rates [2, 3], high prevalence of birth defects, and the presence of various reproductive diseases that threaten fetal development. These issues contribute to emotional distress, relationship problems, social stigmatization, and an increased risk of adult-onset diseases, imposing a significant burden on individuals and society [2].

In the realm of human reproductive health research, epidemiological approaches have played a pivotal role. When compared to other research methods in epidemiology, clinical trials offer several advantages, particularly in establishing causality between an intervention and its effects. Well-designed randomized controlled trials (RCT) are widely regarded as the gold standard in scientific research, thanks to their prospective, randomized, and parallel-controlled design. Clinical trials have revolutionized the field of reproductive medicine and have played a crucial role in evaluating reproductive-health-related interventions, thus improving the effectiveness and safety of reproductive medicine.

Clinical trials and infertility treatment

Assisted reproductive technology (ART), encompassing techniques like *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), has emerged as the most effective treatment for infertility. However, the rationale for the use of IVF and ICSI in specific populations has been controversial. In 2021, a research team from Vietnam conducted the largest randomized trial by involving 1,064 couples with non-male factor infertility. Their data showed that ICSI did not improve the rates of livebirth over conventional IVF, providing robust evidence to question the routine use of ICSI for infertility when the male partner has a normal total sperm count and motility [4]. Furthermore, our research team embarked on a groundbreaking endeavor, conducting the first RCT involving 2,346 couples across 10 centers in China with non-severe male infertility including mild and moderate oligospermia with or without asthenospermia. We aimed to compare the ICSI and conventional IVF to provide comprehensive evidence regarding which method, ICSI or conventional IVF, offers superior outcomes in terms of live births for couples facing non-severe male infertility [5].

Beyond comparing the effects of IVF/ICSI, clinical trials are extensively employed to assess the effectiveness and safety of various phases within infertility treatment. Between 2010 and 2020, a total of 505 trials were registered in the ClinicalTrials.gov database, the largest and most comprehensive source of information on active and completed clinical studies worldwide. Most clinical trials on

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ClinicalTrials.gov studied drug interventions, followed by procedures and laboratory techniques. When examining trial topics, ovarian stimulation emerged as the most frequently studied area. In terms of geographical distribution, Europe hosted the highest number of clinical trials, with North America, Asia, Africa, and South America following in that order. It's noteworthy that, despite its significance for patients, live birth was a relatively infrequent outcome in RCTs. Conversely, pregnancy and implantation outcomes were more frequently observed [6]. The current landscape of clinical trials related to infertility treatment provides valuable insights that should be taken into full consideration for future research endeavors.

Clinical trials and genetic screening/pre-implantation genetic diagnosis

In addition to infertility, numerous pregnancy-related diseases, abortion, stillbirth, can cause serious harm to maternal and infant health. These issues often stem from irregularities during embryo implantation and subsequent embryonic and fetal development. Preimplantation genetic testing (PGT), preimplantation genetic diagnosis (PDG), preimplantation genetic screening (PGS), and other technical platforms are important technical solutions for selecting embryos with implantation and fertility potential or embryos without genetic material abnormalities, thus improving pregnancy outcomes and preventing birth defects.

As an emerging technology, the impact of PGT has been controversial. To shed light on this matter, a lot of RCTs were performed. Recently, a large multicenter, randomized, controlled, non-inferiority clinical trial including 14 academic fertility centers throughout China was performed. The primary focus of this study was to evaluate the cumulative live birth rate resulting from up to three embryo transfers conducted within one year. This extensive RCT furnishes high-quality evidence, demonstrating that among women with three or more high-quality blastocysts, conventional IVF yielded a cumulative live birth rate that was on par with the rate achieved with PGT-A [7]. In the PGT process, embryos are biopsied and subjected to chromosomal ploidy testing before they are transferred into the uterus. However, this biopsy procedure is invasive and raises concerns about potential, yet unknown, health risks that may impact the long-term development of the embryos. As a result, non-invasive PGT, involving the assessment of cell-free DNA (cfDNA-based ni-PGT) in spent culture media, has been explored in preliminary studies as an alternative. To further investigate this approach, our research team conducted a multicenter, randomized, controlled trial aimed at comparing the ongoing pregnancy rates between the ni-PGT and conventional morphology groups. This trial involved 1,148 couples at 13 hospitals in China undergoing ICSI [8].

Clinical trials and prevention of birth defects

Birth defects, also known as congenital anomalies, are structural or functional abnormalities present at birth that can affect a child's physical, mental, or developmental health. The etiology of birth defects is intricate, involving genetic, environmental, and genetic-environmental factors. Early detection and intervention are paramount for both managing and preventing birth defects. The application of folic acid (FA) supplementation to prevent the most severe birth defect, neural tube defects, represents a significant milestone in the field of birth defect prevention, showcasing the profound impact of clinical research in the field of reproductive medicine. From 1993 to 1995, the China–U.S. Collaborative Project for Neural Tube Defects (NTDs) Prevention performed a large non-randomized trial in China. The campaign included 130,142 women who took FA and 117,689 women who had not taken FA, and evaluated pregnancy outcomes among the two populations. The study found that a periconceptional intake of 400 μg of FA daily can reduce the risk of NTDs, thus providing strong evidence for preconception FA supplementation in China and the mandatory flour fortification with FA in several countries [9]. Nowadays, more trials are conducted to determine the optimal dosage of FA, the combination of FA with vitamins and minerals, and other nutrients like inositol and vitamins for the prevention of neural tube defects, providing refined guidance for birth defect prevention.

Clinical trials and personalized/precision reproductive medicine

Reproductive medicine increasingly emphasizes individualized treatment to meet the unique needs of each patient. In personalized reproductive medicine, the genetics biomarkers, environmental exposures, developmental phenomena, epigenetic changes, and behaviors

all need to be taken into account to determine the most effective approach for treating each patient. Personalized treatments have gained widespread use in ART, including the development of controlled ovarian stimulation plans, identifying the implantation window, and managing early pregnancy.

The rapid advancement of personalized medicine has introduced challenges to traditional RCT designs. Traditional RCTs involve randomly assigning participants to treatment or control groups to ensure that both known and unknown factors that may influence individual responses to treatment are equally distributed across all study arms. Consequently, RCT outcomes are typically reported as average treatment effects. However, most patients do not experience treatment effects on average. As diseases are increasingly subdivided into smaller categories based on biomarker findings, and rare biomarkers associated with the pathophysiology of specific conditions are discovered, it may become impractical to achieve adequate sample sizes for standard RCTs. Therefore, alternative clinical trial designs, such as N-of-1 clinical trials, intervention matching trials, adaptive clinical trials, and basket trials, are assuming significant roles in the evaluation of targeted therapies within the context of precision medicine [10].

Prospects

Clinical trials hold significant promise for the future of reproductive medicine. They serve as a cornerstone for evidence-based decision-making, enabling clinicians and researchers to refine existing practices, develop new interventions, and address the unique challenges faced by individuals and society to improve fertility and reproductive health. However, there are still avenues for further growth and improvement in this field. Firstly, given the increasing recognition of the emotional and psychological burden of infertility, clinical trials should place a greater emphasis on mental health outcome indicators. Secondly, as numerous novel innovations in infertility are emerging within clinical practice, there is an urgent need for well-executed RCTs to verify the efficacy and safety of these techniques. Thirdly, ensuring the diversity of clinical trial participants is essential to guarantee that trial populations accurately reflect the broader demographic in which a novel drug, device, or procedure will eventually be utilized. As such, future clinical trials should make proactive efforts to strengthen international cooperation in recruiting diverse participants to identify disparities and enhance the generalizability of study findings.

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References

1. United Nations. Transforming our world: the 2030 agenda for sustainable development; 2015. Available from: https://sustainabledevelopment.un.org/content/documents/21252030%20Agenda%20for%20Sustainable%20Development%20web.pdf [Accessed 10 Nov 2023].
2. Zhou Z, Zheng D, Wu H, Li R, Xu S, Kang Y, et al. Epidemiology of infertility in China: a population-based study. BJOG 2018;125:432–41.
3. Inhorn MC, Patrizio P. Infertility around the globe: new thinking on gender, reproductive technologies, and global movements in the 21st century. Hum Reprod Update 2015;21:411–26.
4. Dang VQ, Vuong LN, Luu TM, Pham TD, Ho TM, Ha AN, et al. Intracytoplasmic sperm injection versus conventional in-vitro fertilisation in couples with infertility in whom the male partner has normal total sperm count and motility: an open-label, randomised controlled trial. Lancet 2021;397:1554–63.
5. Zheng D, Zeng L, Yang R, Lian Y, Zhu YM, Liang X, et al. Intracytoplasmic sperm injection (ICSI) versus conventional in vitro fertilisation (IVF) in couples with non-severe male infertility (NSMI-ICSI): protocol for a multicentre randomised controlled trial. BMJ Open 2019;9:e030366.
6. Peipert BJ, Spinosa D, Howell EP, Weber JM, Truong T, Harris BS. Innovations in infertility: a comprehensive analysis of the ClinicalTrials.gov database. Fertil Steril 2021;116:1381–90.
7. Yan J, Qin Y, Zhao H, Sun Y, Gong F, Li R, et al. Live birth with or without preimplantation genetic testing for aneuploidy. N Engl J Med 2021;385:2047–58.
8. Huang J, Rong L, Zeng L, Hu L, Shi J, Cai L, et al. Embryo selection through non-invasive preimplantation genetic testing with cell-free DNA in spent culture media: a protocol for a multicentre, double-blind, randomised controlled trial. BMJ Open 2022;12:e057254.
9. Berry RJ, Li Z, Erickson JD, Li S, Moore CA, Wang H, et al. Prevention of neural-tube defects with folic acid in China. China-U.S. Collaborative project for neural tube defect prevention. N Engl J Med 1999;341:1485–90.
10. Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertil Steril 2018;109:952–63.