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The Potential of Allogeneic Sertoli Cell Transplantation in Kyrgyzstan and Low-and-Middle Income Countries - Overcoming Barriers to Fertility Care: A Narrative Review

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ABSTRACT

Infertility in males associated with cryptorchidism is a relevant but under investigated problem in low-and-middle-income countries (LMICs), including Kyrgyzstan, where the availability of sophisticated fertility services is limited, which only adds more socioeconomic problems. This narrative review aims to determine the therapeutic efficacy of allogeneic transplantation of undifferentiated Sertoli cells (USCs) in the rehabilitation of spermatogenesis in experimental cryptorchidism, and assess its applicability as a non-costly and easily expandable treatment for LMICs. The search strategy employed a systematic approach to the following databases: Scopus, PubMed, Web of Science, and Google Scholar. The search strategy comprised keywords such as “Sertoli cell transplantation,” “cryptorchidism,” “spermatogenesis restoration,” “allogeneic therapy,” and “male infertility in LMICs.” Articles published between the years 2005 and 2024 were included, and the search was restricted to preclinical trials, mechanistic analyses, and reviews that focused on the biology of USC, immune tolerance, and translation. This review concludes that USCs can restore the testicular microenvironment, nurture the development of germ cells, and escape the immune response in experimental models, which could be a better option than current aggressive treatments. Nevertheless, problems including scarcity of donor cells, technical issues, and inadequate infrastructure in LMICs need innovative solutions, including simplified methods and regional capacity building. Given the current situation in the healthcare system of Kyrgyzstan, including the high incidence of cryptorchidism and lack of financial resources, the authors of this article consider it necessary to further explore the possibility of applying USC-based therapies for the treatment of male infertility in LMICs.

Keywords: *Cryptorchidism, LMICs, Allogeneic Sertoli cell transplantation, Spermatogenesis restoration, Preclinical trials*.

1. INTRODUCTION

Cryptorchidism, the failure of one or both testes to descend into the scrotum, is congenital anomaly that is found in 1–4% of full-term male infants globally and is the leading cause of non-obstructive azoospermia and male infertility. Cryptorchidism, if left untreated, affects spermatogenesis through increased temperatures in the abdomen that cause germ cell apoptosis and permanent testicular dysfunction. Orchidopexy and hormone therapy currently used as therapeutic approaches are not always capable of restoring fertility in severe cases especially if done beyond early childhood. This highlights the need for new regenerative approaches to the biological and structural testicular damage.

An allogeneic transplantation of undifferentiated Sertoli cells (USCs) has been identified as a potential experimental intervention in cryptorchidism, exploiting their ability to reconstitute the blood-testis barrier, secrete trophic factors, and support germ cell survival. This review aims to assess the preclinical evidence for USC transplantation in cryptorchidism models and its scalability as a solution for male infertility, with a focus on the possible use in resource-limited settings [1].

The burden of cryptorchidism is especially keen in Low-and-Middle-Income Countries (LMICs), where delayed diagnosis, limited surgical infrastructure, and socioeconomic barriers worsen its long term consequences. Indeed, in Kyrgyzstan, cryptorchidism rates are higher than the world average, with rates of 4–6% among newborns and poor postnatal follow up, and low rates of timely surgical correction. Hence, infertility rates of affected men remain high and create psychosocial and economic hardship in communities where childbearing is culturally and economically significant. Many of the traditional fertility treatments, including ART, are unattainable because of the high costs and absence of such facilities, leaving millions without a choice. This disparity identifies a critical gap in global reproductive health equity and points to the need for cost-effective, minimally invasive therapies tailored to healthcare systems of LMIC. The potential of Sertoli cell transplantation to restore endogenous spermatogenesis represents a paradigm shift from costly, technology-dependent ART to sustainable one time interventions [2].

The importance of enhancing the implementation of USC-based therapies in LMICs, including Kyrgyzstan, is based on their congruence with the priority areas of public health to prevent avoidable infertility and its consequences. Infertility as a result of cryptorchidism affects not only the individual and his well-being but also the healthcare systems and perpetuates stigma on gender basis in cultures where fertility is a key aspect of masculinity. In Kyrgyzstan, where the rural population has challenges in access to advanced care due to topography and economics, a simplified, low-cost intervention like USC transplantation could change the results. However, the challenges of translation, which include making improvements in donor cell sourcing, overcoming the immune compatibility issue, and making the complex laboratory protocols suitable for low-resource settings, are real and require context-specific research and innovation. With the help of this review, the we suggest focused efforts on building capacity, establishing ethical guidelines for cell-based therapies, and collaboration between LMIC researchers and global regenerative medicine networks. These challenges if addressed could make USC transplantation the standard of care for male reproductive health in LMICs, while also trying to bridge the gap between research and practice [3].

2. METHODOLOGY

A systematic search was performed on the following databases; PubMed, Scopus, Web of Science, and Google Scholar to include relevant studies that examined the effectiveness of allogeneic undifferentiated Sertoli cell transplantation in improving spermatogenesis in cryptorchidism models. The search strategy involved the use of Medical Subject Headings (MeSH) and keywords such as “cryptorchidism,” “spermatogenesis restoration,” “Sertoli cell transplantation,” “allogeneic cell therapy,” “male infertility,” and “testicular niche.” The Boolean operators were used to combine the terms and the strategy was to use “OR” within conceptual groups e.g. “cryptorchidism” OR “undescended testes” and “AND” to link constructs e the search was conducted on peer reviewed articles only and the search was done between the years 2005-2024 to capture the developments in cell based therapies. In this review, since the aim was to combine different strategies and translate them into real-life practice, the risk-of-bias or quality assessments were not conducted formally. Instead, the findings were analyzed thematically to identify trends, such as the best sources of cells (neonatal vs. adult Sertoli cells) or challenges to clinical adoption in low-resource settings. Any differences between the reviewers were solved by consensus, and the final strategy, including the specific MeSH/keyword combinations. This approach guaranteed a quite strict but at the same time flexible overview of the premclinical data and revealed the ways to move from USC transplantation from experimental models to equitable fertility care in LMICs such as Kyrgyzstan.

3. LONG-TERM FERTILITY OUTCOMES IN CRYPTORCHIDISM: INSIGHTS INTO SPERMATOGENESIS AND GERM CELL MATURATION

Cryptorchidism or undescended testis is one of the most common congenital anomalies of male infants, with incidence of 2-5% in full term newborns and up to 30% in preterm infants. Cryptorchidism is a common problem, which resolves spontaneously in the first year of life; however, persistent cryptorchidism is associated with important adverse consequences on male fertility. This section looks at how cryptorchidism affects spermatogenesis and germ cell maturation, and focuses on the biological, genetic and hormonal changes that lead to infertility [4]. Spermatogenesis is a complex multi-step process that happens in the seminiferous tubules of the testes where spermatogonial stem cells mature into spermatozoa. This process is particularly sensitive to the testicular microenvironment especially the temperature, hormones and the Sertoli cells. Cryptorchidism is a testicular malposition that affects these essential factors and thereby impedes germ cell development [5].

3.1 Impaired Germ Cell Maturation

Study reports that undescended testes have a progressive reduction in spermatogonial stem cells and that this decline starts as early as six months of age. This early depletion is poor in spermatogenic potential in adulthood and results in poor fertility

outcomes [6]. Cryptorchid testes, for example, have defective differentiation: the transition from gonocytes to spermatogonia is either delayed or blocked. This disruption leads to a low number of spermatogonial stem cells, which are unable to produce mature spermatozoa in large numbers. In addition, there is an increased rate of germ cell apoptosis and fibrosis in the testicular tissue, which worsens the spermatogenesis and increases the risk of infertility in the affected individuals [7].

3.2 Disruptions in the Testicular Microenvironment

This exposes them to higher temperatures, which adversely affects germ cell survival and differentiation, whatever the position of undescended testes, whether intra-abdominal or inguinal. This thermal stress induces oxidative damage and DNA fragmentation in developing sperm, which is also worst for fertility [8]. Furthermore, Sertoli cells that are vital for nurturing germ cells and regulating their differentiation are also immature in cryptorchid testes. This dysfunction also leads to inadequate support of spermatogenesis and bad sperm production. Moreover, Leydig cell abnormalities are also seen, affecting testosterone production. Since Leydig cells are critical to optimal androgen production that is necessary for normal spermatogenesis, their dysfunction contributes to suboptimal hormonal support that worsens the reproductive issues in cryptorchidism [9].

3.3 Hormonal and Genetic Influences on Fertility Outcomes

A. Hormonal Regulation and Its Disruptions

Gonadotropins like FSH and LH are necessary for normal testicular function and control spermatogenesis and testosterone production. Cryptorchidism is a disease characterized by altered levels of these hormones that impair testicular development and fertility. Moreover, cryptorchidism is also characterized by testosterone deficiency, which results in defective spermatogenesis and the disruption of the development of secondary sexual characteristics [10]. Additionally, AMH and inhibin B, both markers of testicular function produced by Sertoli cells, are often reduced in cryptorchid patients. AMH and inhibin B levels are known to decline with poor fertility, which suggests that hormonal dysregulation is a severe problem in cryptorchidism [11].

B. Genetic and Epigenetic Factors

Several genes, including INSL3, RXFP2, and HOXA10, are involved in the control of testicular descent, and mutations in these genes have been associated with cryptorchidism and infertility. Genetic disorders of the aforementioned pathways can result in abnormally positioned testes and long-term adverse reproductive effects [12]. Furthermore, epigenetic changes, including DNA methylation and histone acetylation, have been found in cryptorchid testes. These changes may affect gene activity that is important for germ cell maturation and may also worsen the spermatogenic and fertility outcomes in affected men [13].

4. IMPACT OF ORCHIDOPEXY ON LONG-TERM FERTILITY, FERTILITY PRESERVATION AND ASSISTED REPRODUCTIVE TECHNOLOGIES (ARTS)

Orchidopexy, the surgical correction of undescended testes, is the usual therapy for cryptorchidism and is advised before 18 months of age to enhance fertility. However, its success in preserving fertility depends on several key factors: The timing of surgery is crucial and is done before one year of age improves the likelihood of germ cell populations and higher sperm counts. The extent of cryptorchidism is a critical determinant of fertility outcomes; men with bilateral cryptorchidism are sterilized to a much greater extent than those with unilateral involvement [14]. In addition, some reports suggest that postoperative hormonal therapy with hCG or GnRH analogues may improve spermatogenesis after orchidopexy. However, the long-term benefits of these hormonal treatments are still enigmatic, and more studies are needed to establish their value in enhancing fertility [15].

For individuals with a history of cryptorchidism and persistent infertility, fertility preservation strategies and assisted reproductive technologies (ARTs) provide potential solutions. **Semen analysis and cryopreservation** can be considered early, particularly in adolescents diagnosed with severe oligospermia or azoospermia, to preserve viable sperm for future use [16]. In cases of **non-obstructive azoospermia**, **testicular sperm extraction (TESE)** offers a method to retrieve sperm directly from testicular tissue, which can then be used for intracytoplasmic sperm injection (ICSI) to achieve fertilization. Additionally, **hormonal stimulation therapies** aimed at enhancing spermatogenesis may improve sperm retrieval rates in TESE candidates, increasing the likelihood of successful fertility outcomes. These approaches provide hope for individuals facing infertility due to cryptorchidism [17].

5. GERM CELL MATURATION, REPRODUCTIVE CHALLENGES, AND TESTICULAR MALIGNANCY IN UNDESCENDED TESTES

Cryptorchidism interferes with the properly sequenced process of germ cell development that is critical for male fertility. Testicular descent is a physiological process during which the scrotum environment, with its lower temperature, is necessary for germ cell maturation, meiosis, and spermatogenesis, a process fully described by OA Titi-Lartey et. al (2023) who also established the thermosensitivity of germ cells and the role of insulin-like peptide 3 (INSL3) in testicular descent [18].

Oxidative stress, mitochondrial dysfunction, and germ cell apoptosis, including that of the temperature-sensitive spermatogonia, in cryptorchid testes are higher than in normal testes. This thermal insult discontinues the transition from gonocytes to adult dark spermatogonia, the sperm stem cell reservoir, and thus depletes the germ cell pool. Left untreated, cryptorchidism leads to progressive tubular atrophy, fibrosis and, ultimately, azoospermia. LR França et. al (2016) described the structural role of Sertoli cells in supporting germ cells, a function that is known to be compromised in cryptorchidism through disrupted paracrine signaling and breakdown of the blood-testis barrier [19]. E Chung et. al (2011) have also established that only 10–30% of bilateral cryptorchid adults will have normozoospermia following orchidopexy, which shows that surgery alone is inadequate [20].

The side effect of cryptorchidism is infertility, and it also has been linked to testicular germ cell tumors (TGCTs), the most common cancer in men 15–35 years of age. Cryptorchidism has been found to enhance the TGCT risk by 3 – 8 folds and intra-abernal testes are most sensitive as found out by epidemiological studies by MB Cook et al. (2008) [21]. Abnormal germ cell maturation in the undescended testes is thought to lead to carcinogenesis. Gonocytes, the fetal gonocytes, may become malignant CIS precursors because they are unable to mature due to absence of maturation signals and genomic instability. In addition, epigenetic changes and inflammatory microenvironments may persist after orchidopexy and sustain cancer risk. Untreated cases are worse in low-resource settings such as Kyrgyzstan since late orchidopexy (after the age of 2-3 years) does not eliminate the risk of germ cell loss or TGCT susceptibility as found by K Banks et al. (2013) [21] [22]. The cause of concern is that LMICs have higher mortality rates for TGCTs due to poor diagnosis and treatment, which highlights the importance of preventive measures aimed at cryptorchidism.

The implications for LMICs are substantial, and the germ cell failure, infertility, and malignancy seen in cryptorchidism therefore form a significant clinical entity. In Kyrgyzstan, where cryptorchidism incidence is high and paediatric surgical capacity is low, untreated cases are responsible for both preventable infertility and cancer. Earlier studies have shown that cultural stigma related to male infertility often causes delays in seeking care while financial constraints prevent individuals from accessing ART or oncology services in many settings [23]. Regenerative strategies, including allogeneic Sertoli cell transplantation, may help to overcome these issues by restoring the testicular microenvironment's ability to sustain and induce differentiation of germ cells. Therapies that prevent germ cell loss at a young age may not only preserve fertility but also decrease the population of transformation-prone gonocytes early in life, thus decreasing the incidence of TGCT. But these advantages cannot be obtained for LMICs without solving problems such as the lack of cryopreservation infrastructure and donor cell supply. The Sertoli cell-based interventions, when integrated with public health programs for the early identification of cryptorchidism, may be a two-fold approach towards addressing infertility and cancer effects in resource-constrained areas [24] [25].

6. BREAKING BARRIERS, BUILDING HOPE: STRATEGIC IMPERATIVES FOR CRYPTORCHIDISM CARE IN KYRGYZSTAN AND LMICS

The management of cryptorchidism in low-and-middle-income countries (LMIC) like Kyrgyzstan is a complex process due to multiple factors, including infrastructural, socio-economic, cultural, and systemic factors. The first of these are critical infrastructure and resource deficiencies, including the absence of pediatric urologists, cryobanks, and sophisticated diagnostic equipment. For instance, in the rural areas of Kyrgyzstan, the absence of basic ultrasound machines means that many cases are only diagnosed when complications are already untreatable. These infrastructural constraints are further complicated by socio-cultural and economic factors wherein poverty and gender stereotypes are inextricably linked. Cryptorchidism is still considered a shame, and boys are considered sterile in Kyrgyz society, which makes people consult doctors at the last moment, and many such cases go untreated [26].

The reinforcement of the therapeutic concept, as well as the translation of innovative therapies such as allogeneic Sertoli cell transplantation, into everyday practice is not without its challenges. This advanced approach requires laminar flow sterile laboratories, immunosuppression, and chain logistics, all of which are not readily available in LMICs. The acquisition of the donor cells and the training of the technicians in the cell isolation techniques also add to these challenges, which show the difference between the scientific feasibility and the feasibility in the real world. On the other hand, broken health care systems hinder cooperation; cryptorchidism management is not high on the list of priorities of the national health policies. For instance, Kyrgyzstan’s primary care system that is already overextended has not been able to incorporate cryptorchidism screening into the existing maternal and child health programs, thus missing important opportunities for early diagnosis. Hence, these barriers—infrastructural limitations, cultural stigma, translational challenges, and systemic failure—require immediate focus on the development of context-specific plans that match the technological advancement with the gaps of resource-limited settings [27].

The ideal of equitable cryptorchidism care in LMICs means reimagining global health paradigms. For Kyrgyzstan, this means leveraging its robust network of community health volunteers (sanitary activists) to pioneer grassroots USC therapy trials, and advocating for cryptorchidism to be classified as a neglected tropical disease to unlock WHO funding. LMICs can by aligning regenerative medicine breakthroughs with culturally resonant public health strategies, revolutionize cryptorchidism from a lifelong sentence of infertility to a preventable challenge — and usher in an era where geography no

longer dictates reproductive destiny [28].

7. FUTURE RECOMMENDATION:

7.1 ***Decentralized, Low-Cost Diagnostic Networks: Mobile Health Units and Telemedicine Partnerships:*** Use trained community health workers with portable ultrasound devices to screen newborns in remote Kyrgyz villages. Local clinicians should be linked with international specialists through Telehealth Kyrgyzstan, for real time guidance regarding management of cryptorchidism [29].

7.2 ***LMIC-Tailored Sertoli Cell Transplantation Strategies****: Simplified Cell Delivery and* ***Autologous Cell Banking:*** Develop needle free, hydrogel based USC delivery systems to avoid complex surgical procedures. To avoid donor dependency, investigate harvesting and preserving autologous Sertoli cells at the time of early orchidopexy [30].

7.3 ***Community-Centric Education Campaigns****: Myth-Busting Initiatives and* ***Fatherhood Health Programs****:* Working with local leaders and influencers in Kyrgyzstan, destigmatize male infertility via radio plays and classroom materials. Include instruction on cryptorchidism in prenatal care to equip dads as champions of early pediatric treatments [25] [31]

7.4 ***South-South Research Collaborations****: Regional Biobanks and Capacity-Binding Fellowships:* Create Central Asian consortiums for cooperative USC research using Kyrgyzstan's unique position to pool resources with surrounding LMICs. Through relationships with organizations like the Kyrgyz State Medical Academy, train LMIC experts in reasonably priced cell culture methods [32].

7.5 ***Policy Advocacy and Financing Models****: National Cryptorchidism Registries and* ***Microinsurance Schemes:*** In Kyrgyzstan, mandate case reporting to estimate disease load and draw donor money. For low-income families, pilot subsidized insurance programs providing follow-up treatment and orchidopexy [33].

8. CONCLUSION:

Transplantation of allogeneic undifferentiated Sertoli cells (USC) seems to be a cost effective potential treatment for the induction of spermatogenesis in cryptorchidism associated male infertility and may be especially relevant in resource limited settings such as Kyrgyzstan. The preclinical data shows that USCs are able to restore the testicular microenvironment and overcome the immune rejection, which can be used as less invasive approach than the current treatments. But factors like scarcity of donor cells, technical issues and inadequateness of the healthcare system in LMICs imply that there is a need to think out of the box, for instance by coming up with simpler protocols and building local capacity. To solve the social economic aspect of the problem of infertility in the LMICs it is crucial to continue the research and to develop the necessary implementation strategies for the use of USC therapy as a feasible and sustainable treatment.

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