Environmental Impact in Reproductive Health Care in sustainable development

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Abstract. Reproductive health care plays an important role in sustainable development, but also has significant environmental impacts. This review examines the environmental impact of reproductive health care and explores methods for reducing the environmental footprint of this area. Various aspects are analyzed, including the use of disposable materials, energy costs of procedures, waste emissions, and the use of chemicals and pharmaceuticals. Modern approaches to reducing negative impacts are presented, such as moving towards more efficient use of resources, using biodegradable materials, improving the energy efficiency of clinics and introducing alternative treatments using natural remedies. The work calls for the development and adoption of policies aimed at integrating environmentally sustainable practices into reproductive health care to help achieve sustainable development goals.

1 Introduction

Environmental health encompasses the impact of physical, chemical, biological, and social factors in the environment on human health, including the assessment and management of these factors. It affects various aspects and stages of human life, from conception to adulthood, shaping human reproduction and development. Exposure to environmental contaminants during critical developmental periods, such as pre-conception, prenatal, and early childhood stages, can lead to functional loss and developmental changes through genetic and epigenetic modifications.

Research into the impact of environmental determinants on molecular programming has shed light on the origins of human disease, suggesting that a person's fertility may be influenced by exposures experienced by previous generations. While it may not be feasible to follow human cohorts for decades to observe disease development, insights from in vitro and animal studies have been instrumental. These studies, aided by advanced molecular techniques, have revealed the genetic and epigenetic components of various reproductive disorders, including menstrual irregularities, infertility, pregnancy complications, and reproductive tract cancers.

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Given the link between developmental factors and adult disease outcomes, there is a growing emphasis on preventive approaches rather than treating diseases after they manifest. This underscores the importance of understanding and mitigating the environmental factors influencing human reproduction and development to promote long-term health and well-being.

Infertility, a condition characterized by the prolonged inability to conceive, persists despite advancements in In Vitro Fertilization (IVF), leaving 10-15% of cases untreated. IVF success rates, which decline with age, remain below 40%, highlighting the need for better understanding and addressing unresolved infertility cases on both physiological and molecular levels [1].

The female and male reproductive tracts (FRT and MRT) are intricate systems, each housing primary organs responsible for gamete production—spermatozoa in the testis and oocytes in the ovary. Various factors, such as cancer, genetics, hormonal imbalances, or environmental toxins, can disrupt this process, leading to infertility. However, research and treatment of infertility-related disorders have been hindered by the lack of comprehensive biological models for either reproductive tract [2].

Current biomedical research heavily relies on 2D cell cultures, which have limitations due to their inability to mimic the complex 3D microenvironment of human organs. Although model organisms like mice are used for in vivo studies, differences between species complicate translating findings to humans, especially concerning reproductive physiology differences.

To address these limitations, 3D cell cultures, known as organoids, are emerging as promising alternatives. These models, derived from adult stem cells (ASCs) or pluripotent stem cells, can mimic live organs in vitro and offer a closer representation of human biology. Additionally, cancerous tissues are used to establish tumor models for oncological research. Stem cells are introduced into a culture supplemented with an extracellular matrix (ECM) to facilitate cell-cell interactions and tissue growth. This can be accomplished using a 3D biological matrix like Matrigel, derived from mouse sarcoma tissues, or by utilizing recombinant human extracellular proteins such as collagen and fibrin within an organic gel. Addition of differentiation factors, growth factors, and hormones to the 3D culture medium prompts the development of specific cell types, mimicking the microenvironment of organs. Consequently, the combination of these molecular factors with a supportive 3D biological matrix mirrors natural organ development, resulting in organoids that closely resemble living tissue on a microscopic level. This novel model type offers the advantage of accurately representing human organs and can be maintained long-term in culture. Clinically, organoids hold promise as reliable and cost-effective alternatives to animal testing, with potential applications in developing organotypic cultures for transplantation.

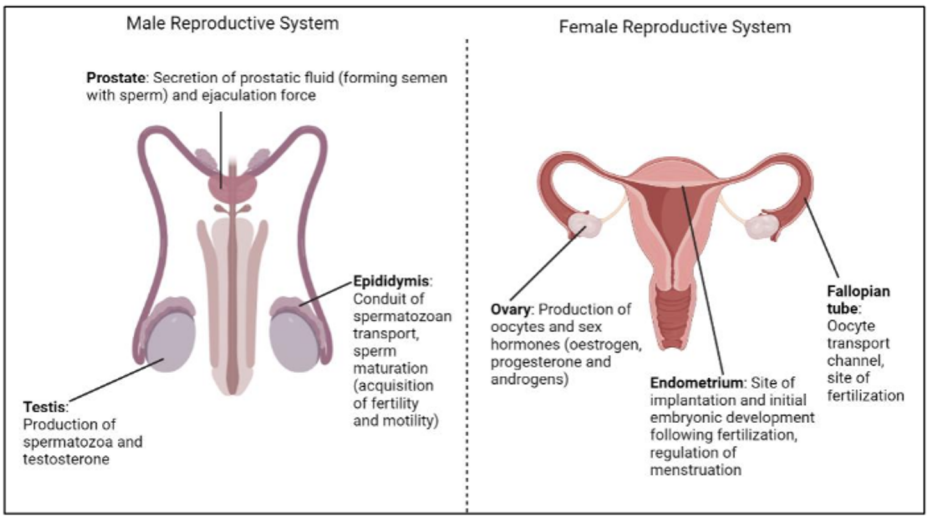

Fig. 1. Targeted reproductive components for organoid-based reproductive health research. Graphical depiction of human male and female reproductive tracts. Organs which are primarily targeted for organoid development relating to infertility research and discussed in this review are identified with their respective functions in the reproductive process stated. Created with BioRender.

Given the insights gleaned from this review, we advocate for the importance of reproductive organoids in advancing research on the primary causes of human infertility. Organoids surpass the limitations of 2D cell cultures and animal models, offering opportunities for developing personalized treatments and enhancing transplantation outcomes. Already, organoid models have been established for various reproductive organs and are being utilized in investigations related to infertility and reproductive mechanisms. This study aims to evaluate recent applications of organoids on a case-specific basis, underscoring their considerable potential and the challenges that remain in implementing them in the field of reproductive health. Our focus lies on reproductive tract organoids directly relevant to infertility research and treatments, including models of the ovary, fallopian tube, endometrium, prostate, testis, and epididymis. (see Figure 1).

2 Research methodology

A multitude of potential factors can contribute to infertility in both men and women. In this segment, we narrow our focus to a selection of prevalent infertility-related conditions and delve into specific research endeavors utilizing organoid technology to advance understanding and treatment of these conditions.

The ovaries play a pivotal role in female fertility, serving as the site for oocyte production and hormone secretion. Ovarian organoids have been engineered to model reproductive disorders and mitigate the risk of infertility. Researchers have primarily concentrated on crafting ovarian organoids using diseased tissue, particularly to establish models for ovarian cancer. Ovarian cancer, characterized by uncontrolled proliferation of ovarian epithelial cells, poses challenges in evaluation and treatment due to its high variability. Current treatments, such as chemotherapy, often lead to infertility by hindering gamete production. For instance, paclitaxel, a common chemotherapy drug, disrupts cell division, resulting in cell death but also impacting fertility. This underscores the urgency for targeted, non-invasive treatment modalities for ovarian cancer.

In 2019, a study proposed the use of ovarian organoids as a potential remedy for highly diverse ovarian cancers [1]. By utilizing patient-derived tumor samples, researchers established organoid cultures representing various ovarian carcinoma subtypes. These models faithfully mirrored the histological and molecular characteristics of original tumors, including distinct drug sensitivities observed clinically. The ability of organoids to replicate patient-specific traits underscores their potential in personalized medicine, facilitating prediction of drug responses based on individual genetic makeup. Moreover, tumor organoids have been generated from minimal tissue samples like needle biopsies, enabling establishment of individualized disease models for chemotherapeutic drug response testing. This approach holds promise for optimizing chemotherapy and enhancing patient outcomes while preserving fertility.

Premature ovarian insufficiency (POI) represents another significant cause of infertility, affecting approximately 1 in 1000 women over 30. It is characterized by declining ovarian function during the expected reproductive years. The molecular mechanisms underlying POI remain poorly understood, with environmental toxins, oxidative damage, and aging hypothesized to contribute to its onset. To elucidate the mechanism of POI, researchers in 2021 concentrated on developing ovarian organoids that faithfully mimic healthy ovarian function rather than focusing solely on disease models. They devised a novel method for generating functional ovarian organoids using female germline stem cells isolated from neonatal mice and cultured on Matrigel. These organoids self-assembled into complex, multi-layered tissue structures resembling native ovaries. Notably, these models were confirmed to produce oocytes, and transplantation of organoid-generated oocytes into infertile mice successfully restored fertility. Additionally, toxicological assessments conducted on the ovarian organoids unveiled decreased oocyte production in the presence of environmental toxicants linked to POI onset, such as bisphenol A. Further exploration of these ovarian organoid models could facilitate identification of potential environmental triggers of POI and the development of novel transplantation therapies. The fallopian tubes (FTs) serve as the primary site for fertilization and facilitate the transit of oocytes from the ovaries to the uterus for implantation. Maintaining the intricate tissue architecture of FTs is essential for their function, as they are lined with secretory and ciliated epithelial cells that aid in oocyte transport through smooth muscle contractions. Researchers have endeavored to create organoids using human adult stem cells (ASCs) and more recently induced pluripotent stem cells (iPSCs) to mimic the complex organization of FT tissue. Although there has been limited progress in combining ovarian and FT organoids to replicate oocyte transport in vitro, FT organoids serve as valuable models for investigating ectopic implantation and reproductive cancers associated with infertility.

Fallopian tube cancers share many clinical challenges with ovarian cancers, including aggressive treatments that often lead to infertility. This underscores the urgent need for targeted, personalized therapies to enhance treatment outcomes. In 2019, a groundbreaking approach to generating organoids was developed using adult mouse FT epithelial cells cultured on Matrigel [2]. These organoid models faithfully represented the genetic makeup of their original donor cells. Subsequently, healthy FT organoids were genetically modified to express common mutations found in tubo-ovarian cancers. This disease model platform facilitated preclinical evaluation of various therapies and identification of synergistic drug combinations that optimized tumor suppression based on individual genetic profiles. Although replicating these findings using human-patient derived organoid systems presents challenges, this research demonstrates the potential of FT organoids in advancing the development of less invasive cancer treatments that may preserve fertility.

3 Results and Discussions

Environmental health encompasses various factors such as physical, chemical, biological, and social elements in our surroundings, affecting human health. This includes not only traditional aspects like air and water quality but also hormones, diet, and lifestyle. As humans progress through different life stages, from conception to adulthood, the environment plays a significant role in shaping reproductive health and development.

In recent decades, there has been a growing interest in studying the environmental impact on molecular reprogramming during critical developmental periods, such as preconception, fetal development, and early childhood. Evidence suggests that gene-environment interactions, rather than just changes in DNA sequence, are crucial in regulating gene expression. Epigenetic modifications, including DNA methylation and alterations to histone proteins, influence genome accessibility and translation across developmental stages.

Understanding the complex interplay between genes and the environment in human development poses challenges in traditional research settings. To address this, cutting-edge technologies are essential for studying these interactions in reproductive health conditions such as infertility, menstrual irregularities, and reproductive tract cancers. Recognizing the developmental origins of adult diseases emphasizes the importance of shifting focus from treating diseases reactively to preventive measures and early diagnosis.

Infections present a significant challenge to reproductive health, particularly in developing regions, where the recent HIV epidemic has led to increased maternal and child mortality rates. Additionally, certain infections like tuberculosis have seen a rise in incidence. These infections can impact maternal health, fertility, and have adverse effects on both the fetus and newborn.

Direct fetal infections can occur with pathogens like rubella, toxoplasma, syphilis, cytomegalovirus, and HIV. Others, which may indirectly affect pregnancy outcomes through placental invasion or premature delivery, include malaria, tuberculosis, chlamydiosis, and listeriosis. Such infections can result in fetal loss, prematurity, and increased prenatal mortality.

During delivery, infections like herpes simplex virus, streptococcus, listeria, gonococcus, and tetanus may be acquired, leading to severe acute infections in newborns. Premature infants are especially susceptible to postnatal infections. Infants contracting hepatitis B from their mothers at birth face the risk of becoming chronic carriers, potentially leading to permanent liver damage and hepatocellular carcinoma, contributing to ongoing infection rates in the population.

Some infections, such as rubella, cytomegalovirus, and toxoplasma, can cause fetal damage not immediately apparent at birth, manifesting later in childhood. These infections are often asymptomatic during pregnancy and in newborns, making congenital infection diagnosis rare except in severely affected children.

Congenital syphilis, while preventable, remains a concern, with reported increases in some regions. Prevention efforts should focus on improving general conditions and hygiene, monitoring disease patterns in communities, and promoting vaccination to reduce the incidence of these infections.

The endometrium, the inner mucosal layer lining the walls of the uterus, undergoes cyclic changes in response to ovarian hormones, including proliferative, secretory, and menstruation phases [4]. Endometrial organoids derived from patient-specific adult stem cells (ASCs) accurately replicate the cellular composition and hormonal responsiveness of the endometrium, enabling simulation of menstrual phases and early pregnancy. These organoids have proven valuable in studying endometrial regulation and disorders associated with infertility.

Endometriosis, a common endometrial disorder characterized by the growth of endometrial tissue outside the uterus, can lead to pelvic inflammation and obstruction of the fallopian tubes, increasing the risk of infertility. Personalized disease models using patient-derived organoids have shown promise in optimizing targeted hormonal therapies by capturing the molecular heterogeneity and drug sensitivities among different patients. However, limitations of these models include the absence of key components of the organ microenvironment, such as the patient's microbiome, which may impact drug responses in vivo.

Organoid technology also holds potential in treating Asherman's Syndrome, a significant cause of infertility worldwide, characterized by the formation of intrauterine adhesions (IUAs) following uterine trauma. Despite modern surgical repairs and estrogen supplementation, moderate to severe cases of Asherman's Syndrome often result in reduced fertility [5]. Recent research demonstrated that endometrial tissue derived from mouse endometrial organoids scaffolded on Matrigel could be transplanted to improve reproductive outcomes in mice with induced IUAs. Successful transplantation resulted in enhanced repair of damaged endometrial tissue, including the restoration of normal thickness and the presence of functional glands and blood vessels. These findings suggest that endometrial organoid transplantation may represent a significant advancement in reproductive medicine if translated to human applications.

The prostate gland plays a crucial role in male reproduction by producing prostatic fluid that supports sperm in ejaculation. Organoids derived from human prostate tumors, adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs) have been developed to model both normal and pathological prostate function.

Metabolic changes affecting prostatic secretions can lead to male infertility, such as inhibited citrate secretion associated with prostate cancer. Recent research utilized ASC-derived mouse and human organoids to study the truncated citric acid cycle pathway as a potential therapeutic target for prostate cancer. By closely replicating in vivo conditions, researchers could precisely regulate metabolic inputs and identify metabolites contributing to citrate production. Inhibiting cancer-specific citrate metabolism could potentially target prostate tumor cells and restore male fertility, highlighting the advantages of organoid models in disease research [6].

The testes are responsible for sperm production, primarily requiring the coordination of spermatogonial stem cells (SSCs), Sertoli cells, and Leydig cells. Testicular organoids aim to mimic testicular tissue architecture and support normal spermatogenesis in vitro, with ongoing efforts to improve human-specific models.

Up to 25% of infertility cases are attributed to insufficient sperm quality, influenced by environmental conditions. Testicular organoids have been utilized for toxicological assays to assess the impact of toxins on sperm production. Human testicular organoids demonstrated low frequency in vitro spermatogenesis, providing a platform to identify gonadotoxic agents and assess their effects on sperm production.

Age also affects male fertility, with declining sperm count, viability, and motility over time. Testicular organoids derived from mouse ASCs were developed to mimic in vivo structure and hormone responsiveness. This relatively inexpensive system offers meaningful models to understand the mechanisms of male fertility over time and propose personalized therapies.

The epididymis, responsible for sperm maturation and transport, significantly impacts male fertility. Organoids are being used to model mammalian epididymis development and functionality, which decline with aging, leading to lower sperm maturation rates over time.

A more serious form of male infertility, azoospermia, may be genetic or caused by trauma to the male reproductive tract [7]. A recent study devised a method for treating azoospermia in mice using a 3D culture system. This system produced sufficient

proliferated SSCs for successful transplantation into azoospermic mice, offering a promising alternative treatment for non-obstructive azoospermic patients. Reproductive organoid technology is advancing infertility research and treatment for both sexes. Organotypic cultures represent live tissue architecture and functions, offering human-specific models that are becoming more cost-effective than traditional mammalian research populations [8]. This shift toward organoid models also aligns with moral considerations regarding animal welfare. However, ethical concerns arise regarding the use of human tissue, necessitating strict regulations and a transition from animal to human cell models, which requires significant investment in new methodologies.

Patient-derived organoids, particularly from adult stem cells (ASCs), exhibit genetic similarities to their tissue of origin, paving the way for personalized medicine based on individual patient genetics [9]. This approach is revolutionizing regenerative medicine, enabling targeted treatments for reproductive disorders like cancers while minimizing side effects. Yet, modern organoids lack multi-organ communication and microbiome interactions, limiting their application.

Effective therapeutic delivery to diseased organs often relies on the interaction of multiple organ systems. Incorporating multiple tissue types in organoid cultures, such as the co-culture of spermatogonial stem cells (SSCs) and epididymosomes, can mimic cross-organ communication. However, accurately representing the reproductive microbiome's impact on organ function remains a challenge, hindering our understanding of how reproductive systems respond to environmental and clinical exposures [10].

Addressing these challenges requires developing human-specific organoid systems that accurately reflect inter-organ interactions and microbial influences. By focusing on increasing the complexity of organoid models, scientists can optimize this technology for infertility research and treatment, unlocking its full potential in personalized reproductive medicine.

4 Conclusions

Concerns about the impact of the environment on human reproduction are widespread, particularly heightened by disasters like those at Chernobyl and Bhopal, which have demonstrated potential adverse effects. Accurate information on reproductive consequences is crucial and can be provided through epidemiological studies when sufficient data are collected.

Epidemiology, the fundamental science of public health, investigates the determinants of disease, assessing the magnitude of effects and identifying associated risk factors to inform prevention strategies. Accurate and systematic collection of relevant information is essential.

Modern epidemiological methods incorporate various controls to simultaneously consider multiple risk factors and exposures while evaluating diverse outcomes. Surveillance, involving continuous monitoring and analysis of health data, plays a vital role. In the context of reproductive health, surveillance can establish baseline rates of reproductive events, track trends in different geographic areas, provide early indications of risk factors affecting reproduction, and offer a system for monitoring acute events like disasters or the introduction of new chemicals, including therapeutic drugs and agricultural or industrial chemicals.The emergence of organoids representing the male and female reproductive tracts presents significant opportunities in infertility research. This study has outlined recent advancements in reproductive organoid development, showcasing their potential in modeling personalized diseases, conducting pharmaceutical or toxicological assays, and innovating transplantation methods. By addressing the challenges identified here, such as the need for more accurate representation of multi-organ interactions and the

reproductive microbiome, we can expedite progress and establish organoids as valuable alternatives to conventional cell culture or animal models in reproductive health science.

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