Review

Stem Cells and Infertility: A Review of Clinical Applications and Legal Frameworks

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Review

Stem Cells and Infertility: A Review of Clinical Applications and Legal Frameworks

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Abstract: Infertility" is a condition defined by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner'. The authors have set out to succinctly investigate, explore and assess infertility treatments harnessing the potential of stem cells to effectively and safely treat infertility, in addition to the legal and regulatory complexities at the heart of stem cell research, with an overview of the legislative state of affairs in six major European countries. In couples who cannot benefit from assisted reproductive technologies (ART) to treat their infertility, stem cells-based approaches have been shown to be a highly promising approach. Nonetheless, lingering ethical and immunological uncertainties require more conclusive findings and data before such treatment avenues can become mainstream and applied large scale. The isolation of human embryonic stem cells (ESCs) is ethically controversial, since their collection involves the destruction of human embryonic tissue. Overall, stem cell research has resulted in important new breakthroughs in the treatment of infertility. The effort to untangle the complex web of ethical and legal issues associated with such therapeutic approaches will have to rely on evidence-based, broadly shared standards, guidelines and best practices to make sure that the procreative rights of patients can be effectively reconciled with the core values at the heart of medical ethics.

Keywords: infertility; assisted reproductive technologies (ART); human embryonic stem cells (ESCs); induced pluripotent stem cells (iPSCs); mesenchymal stem cells (MSCs); ovarian stem cells (OSCs); spermatogonial stem cells (SSCs); ethics and legal implications

1. Introduction

With the term "infertility" we refer to 'a disease characterized by the failure to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse or due to an impairment of a person's capacity to reproduce either as an individual or with his/her partner'. There are several risk factors connected with this condition, first woman's age. Other potential risk factors are lifestyle (drugs, smoking, alcohol), sexually transmitted diseases, pelvic inflammatory disease, obesity, PCOS, diabetes. Also tubal, ovarian, uterine diseases can contribute to female infertility (endometriosis for example). Finally, infertility may be connected to endocrinological diseases or genetic disorders (Turner syndrome, Klinefelter syndrome, etc.). Infertility has an etiology which is linked to female causes in 40% of cases, and to male ones in 40%, while 10-20% involve both and 10% is idiopathic [1]. Conventional treatments include improvement of sperm quality, surgical treatment of varicocele, administration of gonadotropins or antioxidants [2,3] if we refer to male infertility. As far as female infertility, there are several possible treatments: gonadotropins, GnRH, FSH, LH as ovulation – inducing drugs; clomiphene citrate or letrozole in case of PCOS; bromocriptine or cabergoline to treat hyperprolactinemia. After the administration of these different treatment, chosen in correlation to

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patient, regular follicular monitoring is necessary with ultrasonography [4-6]. Currently, the most widespread assisted reproductive technologies (ART) are intrauterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic injection (ICSI). But if a gamete deficiency is proved, because of genetic defects, ART is not the best choice. In these terms, stem cells show new hopes. The aim of this review is the evaluation of stem cells, their efficacy and safety, in infertility treatment.

2. Materials and Methods

A broad-ranging search was performed in PubMed/MedLine, Web of Science (WoS), Cochrane Database to retrieve studies that analyze the application of stem cells as a therapeutic option for infertility. The search string for the clinical applications of stem cells in infertility treatments included the combination of the key words "stem cells" and "infertility – IVF", whereas the ethical, legislative and regulatory research comprised the string "stem cell research ethics", "legal and regulatory frameworks", "stem cell research guidelines and best practices". All studies were analyzed and selected for their relevance and data quality. Ultimately, 106 sources were included, spanning the 1988-2023 time period.

3. Results

3.1. stem cells variants:

Stem cells are undifferentiated cells that, if necessary, can self-renew and differentiate. They can repair damaged tissues. Like Sarama Saha et al [7]. describe in their paper, there are several kinds of stem cells. Table 1 summarizes and succinctly elaborates on the stem cells used in infertility treatments, their distinctive traits and current therapeutic applications in reproductive medicine:

Table 1. Stem cells variants with potential use in reproductive medicine.

Stem cell type	Distinctive features	Reproductive application
Embryonic stem cells (ESCs)	They are capable of self-renewal and can differentiate into different tissues (ectoderm, endoderm, mesoderm) [7]. They originate from blastocysts and express factor Oct 4 [8]. Even if hES cells can give rise to all somatic tissues, they cannot form all of the other 'extraembryonic' needed for thorough development, e.g. the placenta and membranes, hence they cannot form a whole new human being. Such features differentiates them from 'totipotent' fertilized oocyte and blastomere cells, which originate from the first cleavage divisions.	They can yield male and female gametes [9] through meiosis. ESCs play a key role in endometrial restoration [10].
Induced pluripotent stem cells (iPSCs)	As described by Takahashi and Yamanaka [11]in 2006, such cells express different transcription factors such as Oct 4, klf 4, sox 2, c – myc.	They originate from adult cells, thus are not as ethically controversial as ESCs, which originate from embryos. In addition, they are developed from patient' somatic cells, avoiding immune reaction

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		[12,13], while the main drawback is genetic instability is [14].
Mesenchymal Stem Cells (MSCs)	They have plastic – adhesion quality, they express CD105, CD73, CD90 as markers and they can give origin to osteoblast, adipocytes and chondroblasts [15,16]. The principal kinds of MSCs are documented by Saha et al [7] in their review: ✓ Bone Marrow Mesenchymal Stem Cells: they were studied by Owen et al [17] for the first time in 1988. The injection of this kind of stem cells has been reported to improve endometrial thickness by a 2014 study by Jing et al [18]. On the other hand, Wang et al [19] used bone marrow mesenchymal stem cells to increase endometrial estrogen receptors in mice. ✓ Menstrual Blood Mesenchymal Stem Cells: Liu et al [20] demonstrated these cells improving ovarian function in mice, thanks to the transcription factor OCT-4. ✓ Endometrial Stem Cells. ✓ Umbilical Cord Mesenchymal Stem Cells: easily obtainable, and with low immunological risk; can support ovarian function, reduce inflammatory cytokines and improve fertility [21]. ✓ Amniotic Fluid Stem Cells: thanks to VEGF, EGF, BMP they can increase ovarian function, preventing atresia [22]. ✓ Amnion-Derived Mesenchymal Stem Cells ✓ Placenta-Derived Mesenchymal Stem Cells: they can improve folliculogenesis, thanks to the pathway PI3K/Akt [23]. ✓ Adipose-Tissue-Derived Stem Cells: in mice, they increase neovascularization and follicle proliferation [24].	These cells can be beneficial in ovarian and endometrial dysfunction by reaching ovarian tissue and restore its function via several cytokines and growth factors. MSCs are able to create new vessels, inhibit apoptosis and fibrosis [7]. Among these cells, fetal ones can reportedly rely on better telomerase activity and longer survival. They can be found in blood, bone marrow, liver, cordon blood, Wharton's Jelly, amnion and placenta [16].
Ovarian Stem Cells (OSCs)	They include pluripotent, very small embryonic-like stem cells (VSELs) and larger OSCs which are easily visualized in smears by scraping the ovarian surface. The potential of OSCs to differentiate into oocyte-like structures in vitro has been reported [25].	Johnson et al [26] observed OSCs ability to induce follicle synthesis in mouse's ovaries. In 2012, White et al [27] used specific VASA markers to isolate ovarian stem cells from human ovarian cortex [18].

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Spermatogonial Stem Cells (SSCs)	SSCs develop to form spermatozoa. During testicular homeostasis, SSCs self-renew to maintain the stem cell pool or differentiate to constitute a progeny of germ cells which sequentially transform into spermatozoa [28].	They play a key role in unlimited spermatogenesis in seminiferorous tubules [29].

To generate PGCs (primordial germ cells, precursors of sperm and egg cells) and induce iPSCs, adult stem cells from male and female gonads and pluripotent stem cells such as ESCs were used [30]. Although, different papers reported the attempt of generating blastocyst-like structures from stem cells. In their systematic review, Saha et al [7] describe the use of stem cells in various disorders such as Asherman Syndrome, a condition characterized by amenorrhea following uterine cavity injury. The resulting adhesions give rise to infertility, abortion and chronic pelvic pain [31]. The main cause has been reported to be postpartum endometrial courettage [32]. Several clinical studies have shown improvement of fertility in animal models through bone marrow stem cells, menstrual blood and mesenchymal ones [33]. That makes their use in human infertility treatments rather promising. Saha et al [7] reported another important cause of infertility: premature ovarian insufficiency (POI). Several papers show the efficacy of ovarian stem cells with stimulation of the AKT pathway to improve fertility in this condition [34-36]. There is another disorder linked to irregular menstruation, obesity, atypical hair growth and infertility: polycystic ovarian syndrome [37]. Stem cells could be used to keep at bay PCOS clinical symptoms, suppressing inflammation and producing anti inflammatory cytokines. Finally, different studies are testing the use of stem cells in endometriosis and azoospermia with promising results. Saha et al [7] in their paper, have elaborated on the future prospects for stem cells and infertility. They cite Very Small Embryonic Like Stem Cells (VSELs) found also in human bone marrow [38] with capacity to be differentiated into germinal cells and into different organs cells during embryonic development. They also repair any organ damage [39]. On the other hand, Saha et al [***Error! Bookmark not defined.***] describe Micro RNA and Stem Cell-Based Therapy. miRNA plays an important role in genetic expression of stem cells and in mRNA stability [40]. For example, miR-10 and miR-146a isolated in stem cells, they improve ovarian function in mice and prevent granulosa cells apoptosis [41].

3.2. Ethics and legal implications

Ethics and moral implications arising from embryonic stem cells have obviously a lot to do with how the legal and moral status of the embryo is assessed, and whether, and to what extent, it is deemed worthy of protection. It is therefore quite different a scenario from the one involving induced pluripotent stem cells (iPSCs) and adult stem cells, which are unrelated to embryo status [42]. Ethics and legal assessment standards for such types of stem cells necessarily revolve around the possible risks linked to stem cell interventions, what kind of damage could arise from still underresearched and inadequately validated stem cell procedures, how the informed consent process should be structured in order for such procedures to be sound from a medicolegal perspective, and lingering questions involving ownership and confidentiality of donor information [42].

Ethical considerations are of utmost importance to all medicine, and eminently relevant in the practice of reproductive medicine, endocrinology and infertility care as well. In addition, when treatments relying on stem cells are applied to medically-assisted reproduction, the ethics and legal quandaries arising from the latter should be taken into account as well [43-46]. It is no wonder that several countries allow for conscience-based refusal from healthcare professionals who feel that such practices conflict with their deeply-held moral beliefs [47-49], yet it is of utmost importance to find viable ways to reconcile such a right with the reproductive rights of couples [50,51]. Such complexities need to be governed by unequivocal standards and criteria that are both evidence-based and as broadly shared as possible at the international level, especially as fast-developing technological advancements seem to outpace our ability to devise tenable, well-balanced and evidence-based guidelines and best practices to maximize effectiveness while at the same time safeguarding the core

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values that shape medical ethics [52-56]. Embryonic stem cells are undifferentiated pluripotent cells that can indefinitely grow in vitro. They are derived from the inner mass of early embryos. Because of their ability to differentiate into all three embryonic germ layers, and finally into specialized somatic cell types, human embryonic stem cells certainly constitute a valuable element for research focused on developmental biology and cell replacement therapy. They are usually isolated from excess human IVF-embryos [57,58]. Research centered around stem cells and their use in the creation of human embryos is viewed by many as challenging and controversial, if not outright untenable, from the bioethics perspective. The lack of a clean cut consensus is reflected in the different legislative and regulatory approaches put in place by national lawmakers. Yet the unavailability and illegality of a therapeutic option in a given countries may drive those who seek such treatments, and can afford it, to travel o countries where such practices are legal. That poses an element of access inequality and financial discrimination, as it happens for instance with "procreative tourism" [43,44,59]. European countries have varying degrees of restrictions affecting the way and extent to which stem cell research can be lawfully undertaken. Table 2 briefly summarizes the legal and regulatory scenarios in 6 major European countries, selected as meaningful samples in terms of population size.

Table 2. Legislative and regulatory state of affairs in major European countries.

Country	Legislation currently in place	Relevant Legislative Provisions	Bioethics oversight
Italy	Law 40, enacted on 24th February 2004, Regulation of Medically Assisted Human Reproduction [60].	The current legislative situation in the country is the outcome of a heated and drawn-out debate between supporters and opponents of embryonic stem cell research and ART. In 2005 the law was challenged in Italy's highest court, the Constitutional Court, by opponents who included scientists seeking a review of the ban on the use of embryos for research. The Court allowed a referendum on several parts of the law, including on whether or not the prohibition on embryo research could be relaxed. The referendum was held in 2005 but failed to reach the minimum 50% voter turnout. A 2009 Ministerial Decree that confined research funding to tissue (adult) stem cell research, so excluding embryonic stem cell research, has so far been unsuccessfully challenged by a number of Italian scientists following several appeal cases before the Italian courts.	The Italian National Ethics Committee instituted in 1990 to deal with the ethical legal and social implications linked to scientific research and technological applications on persons. The committee is made up of government-appointed scientists, physicians and bioethicists. The Committee has published many reports on embryo research and other related issues, but these have no binding authority. Other committees have recommended opposing opinions on some issues, including embryonic stem cell research [61].
France	Law on Bioethics, LOI n° 2011-814 [62] ; French Public Health Code (article L1121-1) [63] ;	Research on human participants need to meet specific standards (a protocol must be submitted in writing including the information document and the consent form).	Local Ethics Committee ("Comité de Protection des Personnes") for ethical approval of the research project.

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		Specific criteria govern the collection of human material, including biobanking. According to article L1121-1 of the French Public Health Code, three research classes are deemed to involve human subjects: ✓ Interventional study (clinical trial) ✓ Interventional study (clinical trial) with minimal risk study ✓ Non-interventional study (clinical trial) [63]. The 2011 law on bioethics as amended in 2013 allows for research on human embryos and embryonic stem cells, provided that the following conditions are met: - Scientific relevance is acknowledged. - The research has a medical objective. - The research cannot be conducted otherwise, i.e. without relying on human embryos or embryonic stem cells. - The research project meets the ethical standards for research on embryos and embryonic stem cells. -Moreover, embryos used for research must come from IVF, and no longer be part of a family project. Informed consent must be obtained from the donors' couple, to be renewed after three months and revocable at any time.	French National Agency for the Safety of Medicines and Health Products (ANSM) for authorization of interventional studies and to be informed in case of other studies (interventional study with minimal risk and non-interventional study) French Ministry of Research and Health Regional Agency ("Agence Régionale de Santé"): The French Biomedicine Agency ("Agence de la Biomédicine") authorizes research on human embryos and embryonic stem cells [62,63].
Germany	Embryo Protection Act (Embryonenschutzgesetz) 1991 [64]; 2002 Stem Cell Act (Stammzellgesetz) [65]; 2008 Act ensuring Protection of Embryos in connection with the importation and use	The use of embryos for research is heavily restricted in Germany: the derivation of embryonic stem cell lines is in fact a crime. The German Constitution (Grundgesetz) itself enshrines embryo protection by stating that "human dignity is inviolable" and "everyone has the right to life and inviolability of his person." At the same time the freedom to pursue scientific research is also upheld.	The importation of stem cell lines for research must be approved by the Central Ethics Commission for Stem Cell Research (ZES), made up of scientists, physicians and bioethicists. The German National Ethics Council (Geschäftsselle des Nationalen Ethikrat), instituted in 2007, provides guidance to policy- and law-makers and the public on scientific and medical issues that affect society and human health.

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	of human embryonic stem cells [66].	For research purposes, German law prioritizes adult stem cells under the 2002 Stem Cell Act (Stammzellgesetz) [65]. Embryonic stem cell lines can however be imported under strict conditions outlined by parliament. The 2002 Act included a 'cut-off date' of 1 January 2002 – imported ES cell lines must have been derived before that date. The cut-off point was moved to 1 May 2007. In addition to these criteria, embryonic stem cell lines can only be used for research if they are vital in developing new medical and scientific knowledge.	
United Kingdom	Human Fertilisation and Embryology Act 1990, Schedule 2 [67]. Human Tissue Act 2004, Section 1 (9) [68]; Human Tissue (Quality and Safety for Human Application) Regulations 2007 [69].	An ethical approval is required for specific research projects. Human tissue held for a specific research project needs approval by a recognized Research Ethics Committee (REC) (or where approval is pending). Research on embryos and human embryonic stem cells is legal under the Human Fertilisation and Embryology Act 1990, Schedule 2 [67].	The ethical approval is delivered by a Research Ethics Committee (REC) and it must be applied for using the guidance provided by National Research Ethics Service (NRES) at the Health Research Authority. Tissue banks that have been approved by a REC can provide human tissues to researchers, who do not need to store them under a Human Tissue Authority licence during the period of the research project, subject to certain requirements. The Human Fertilisation and Embryology Authority (HFEA) is in charge of regulating the storage of gametes and embryos. It also grants licenses for research projects involving human embryos where the following conditions are met
Spain	Law on Biomedical Research (Law 14/2007) [70].	Spanish law expressly bans the creation of human pre-embryos (i.e. an embryo formed in vitro by a group of cells resulting from the progressive division of the egg cell, from the time it is fertilized until 14 days after) and embryos exclusively for experimentation purposes. In keeping with the gradualist	Guarantees Commission for the Donation and Use of Human Cells and Tissues, established under the Real Decreto 1527/2010 [71] National Commission on Assisted Human Reproduction, established under Real Decreto 42/2010 [72].

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		perspective on the protection of human life outlined by Constitutional Court rulings 53/1985, 212/1996 and 116/1999. Still, techniques aimed at collecting embryonic stem cells for therapeutic or research purposes, without the creation of a pre-embryo or of an embryo exclusively for this purpose, are legal, in compliance with legislative standards.	
Portugal	No specific legislation in Portugal currently governs stem cell research. Law n.º 32/2006, enacted on July 26, which regulates the use of medically assisted procreation [73], establishes the legal framework relative to quality and safety standards governing donation, collection, analysis, processing, preservation, storage, distribution and application of human tissues and cells [74]; Law No. 21/2014, of April 16 (Clinical Investigation Law) [75].	The creation of embryos through MAP for research purposes is banned. Still, the scientific investigation of embryos for prevention, diagnosis or therapeutic purposes, or to improve MAP procedures is allowed under supervision. Legally usable embryos are: ✓ Cryopreserved, surplus embryos not part of a parental project (depends on prior, express, informed and conscious consent of the intended beneficiaries); ✓ Embryos not viable for transfer or cryopreservation; ✓ Embryos with major genetic abnormalities, in the case of pre-implantation genetic diagnosis (on informed consent of those for which they were intended); ✓ Embryos obtained without fertilisation by spermatozoa.	The use of embryos for scientific research purposes, limited to embryos produced for other purposes, always depends on the authorization of the experimentation by the National Council for Medically Assisted Procreation (CNPMA), established by Law 32/2006, of 26 July [73], which is charged with passing judgement on the ethical, social and legal issues of the medically assisted procreation.

It is worth remarking that when stem cells are isolated, embryos are not fully killed: at least one embryonic cell, that is a stem cell, does survive. The life of stem cells cannot be qualified as independent. Nevertheless, the embryo's life is not completely destroyed and continues in a primitive way of life, hence there is no outright destruction in the strict sense [76]. In the United States, the 2016 Guidelines for Stem Cell Research and Clinical Translation (ISSCR), updated in 2021 based the prohibition of research on embryoids after 14 days on a "broad international consensus that such experiments lack a compelling scientific rationale, raise substantial ethical concerns and/or are illegal in many jurisdictions"[77]. Nicolas P et al. [78] pointed to the need to start a public debate involving all stakeholders, scientists, research policy experts, bioethicists, and community members in order to weigh an extension of the 14-day rule and possibly revise the Dickey-Wicker Amendment which

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prohibits the United States Department of Health and Human Services (HHS) from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. In 2001, under the George W. Bush administration, such guidelines were amended, limiting federal funds to only the stem cell lines existing as of August 9, 2001, which was then estimated at approximately 60 cell lines; however, many of those lines eventually proved unusable [79].

4. Discussion

One of the main cornerstones of reproductive biology is that women have a finite ovarian reserve, which is set from the very time they are born. This theory has been questioned recently by the discovery of ovarian stem cells which are purported to have the ability to form new oocytes under specific conditions post-natally. Almost a decade after their discovery, ovarian, or oogonial, stem cells (OSCs) have been isolated in mice and humans but remain the subject of much debate. The ideal fertility preservation approach would prevent delays in commencing life-saving treatment and avoid transplanting malignant cells back into a woman after treatment: OSCs can be a viable route to such an end [80]. Based on the recent encouraging results of studies [81] conducted on OTC, particularly several involving patients with oncological or autoimmune conditions predisposing them to premature ovarian insufficiency and/or infertility, OTC and its subsequent transplantation could be proposed as an alternative to HRT [82,83].

Menstrual stem cells (hMensSCs) increased the ovarian weight, plasma E2 levels, and follicle numbers in mice [84]. Amniotic fluid stem cells can differentiate into granulosa cells, which inhibit follicular atresia and maintain healthy follicles [85]. Wang J al. [10] found that hESC-derived endometrial cells can support endometrial repair and functional recovery [86]. ESCs (Embryonic stem cells) were obtained from cloned blastocysts, themselves obtained from somatic cell nuclear transfers (SCNTs) (the resulting embryonic stem cells were called Kitw/Kitwv, ntESCs) [87]. Marinaro F.et al. demonstrated that extracellular vesicles derived from endometrial mesenchymal stem cells (EV-endMSCs) can elicit an antioxidant effect and be helpful when used as IVF coadjutants. In this work, endMSCs were isolated from human menstrual blood and characterized according to multipotentiality and surface marker expression prior EV-endMSCs isolation, so they suggested that the increased developmental competence of the embryos could be partly mediated by the EV-endMSCs' ROS scavenger activity [88]. The Endometrial Side Population (ESP) constitute mixed population, mostly made up of precursors of endothelial cells [89]. Adequate uterine vascularity and the regulating cells/factors are necessary preconditions at the time of implantation, while inappropriate endometrial angiogenesis and immunity can result in reproductive failure, especially in recurrent miscarriage and recurrent implantation failure (RIF) [90].

Tersoglio et al. have accounted for endometrial changes before and after the transfer of endometrial mesenchymal stem cells (enMSCs) in a population of thinned endometrium women, with absence or hypo-responsiveness to estrogen and RIF; a substantially high level of increase in endometrial thickness was ultimately reported following the inoculation of enMSCs, pointing to the considerable regenerative potential of such an approach [91].

Although it is not yet a well-established technology, oocyte cryopreservation has been getting increasingly widespread in assisted reproductive technologies in response to the growing demands of patients' sociological and pathological conditions. Oocyte mitochondria are critical cellular organisms that regulate the potentiality of embryo development. Has been reported that human and animal oocytes' mitochondrial structure and function are seriously diminished following cryopreservation [92,93]. Kankanam Gamage US et al. demonstrated how a supplementation of adipose stem cell mitochondria can positively affect the declined embryo development caused by cryopreservation-mediated cellular stresses and damages, and thus live birth rates [94].

As far as male fertility is concerned, spermatogenesis is known to be a gradual, orderly cascade process which comes to fruition through the precise regulation of genes, proteins, and various cytokines [95].

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The protective effects of MSCs (Human umbilical cord mesenchymal stem cells) are likely associated with their ability to secrete various cytokines which participate in testis development and hormone synthesis, improve spermatogenesis and the sperm maturation micro-environment, and affect sperm quality and male fertility [96]. Nagano M et al. provide a mechanism to evaluate the status of the stem cell population in selected infertile male patients that had shown how a xenogeneic transplantation of human germ cells using mice as recipients is feasible and could be used as a biological assay system to further characterize human spermatogonial stem cells [97].

Chemotherapeutic drugs can cause reproductive damage due its gonadotoxyc effects on sperm quality and other aspects of male fertility. Zhang Y et al. focus their study showing how stem cells are thought to alleviate the damage caused by chemotherapy drugs and to play roles in reproductive protection and treatment [98], in order to investigate whether exosomes derived from human umbilical cord mesenchymal stem cells (hucMSC-derived exosomes) can repair injured endometrial epithelial cells (EECs) and reduce their death, and exhibit an anti-inflammatory effect against OGD/R (oxygen and glucose deprivation/reoxygenation) [99]. As reported in 2016 by multiple groups, scientists developed the ability to culture human embryos for 12 or 13 days [100], ethicists have also called for the policy to be revisited, and some have suggested that research should be allowed until the 21st or 28th day after fertilization [101].

Fertility preservation (FP) emerged as a treatment aiming to preserve future reproductive capacity of individuals facing therapies that could potentially affect their gonads [102] or if needed to perform a fertility sparing surgery treatments in case of diagnosis of malignancies and especially in reproductive age [103-107]. The majority being patients diagnosed with cancer, cryopreservation of oocytes or embryos by vitrification [108] is the most common way to preserve fertility and for future needed especially at the parentinghood time. Stress reduction through relaxation training or behavioral treatment has been demonstrated to improve conception rates, especially by virtue of the beneficial psychological support it can provide [109].

5. Conclusions

In couples who cannot benefit from ART to treat their infertility, stem cells-based approaches can constitute a highly promising option, despite lingering ethical quandaries and immunological uncertainties that require more conclusive scientific data to be viable for mainstream use. The isolation of human ESCs (embryonic stem cells) is ethically controversial. Although ESCs are genetically unrelated to patients, their collection does entail the destruction of human embryonic tissue.

Overall, stem cell research has brought about important new breakthroughs in the treatment of infertility. The common efforts towards untangling the complex web of ethical issues associated with this therapy need to be continued and expanded. International consensus will be vital, in order to avoid that citizens of countries where a given technique is illegal will have to travel to a country where it is not, which would discriminate against those who cannot afford such an option. The ultimate purpose is the devising a well-balanced set of guidelines and evidence-based standards to harness the full potential of stem cells-based therapeutic approaches, in an ethically and legally tenable fashion, for the sake of all those in need for help in the exercise of their reproductive rights.

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