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REVIEW

What will the future hold for artificial organs in the service of assisted reproduction: prospects and considerations

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Abstract **Assisted reproduction provides a wide spectrum of treatments and strategies addressing infertility. However, distinct groups of infertile patients with unexplained infertility, congenital disorders, and other complex cases pose a challenge in *in vitro* fertilization (IVF) practices. This special cohort of patients is associated with futile attempts, IVF overuse, and dead ends in management. Cutting edge research on animal models introduced this concept, along with the development of artificial organs with the aim to mimic the respective physiological functions in reproduction. Extrapolation on clinical application leads to the future use of infertility management in humans. To date, the successful clinical application of artificial reproductive organs in humans is not feasible because further animal model studies are required prior to clinical trials. The application of these artificial organs could provide a solution to infertility cases with no other options. This manuscript presents an overview on the current status, future prospects, and considerations on the potential clinical application of artificial ovary, uterus, and gametes in humans. This paper presents how the IVF practice landscape may be shaped and challenged in the future, along with the subsequent concerns in assisted reproductive treatments.**

Keywords artificial ovary; artificial uterus; artificial gametes; assisted reproduction; considerations; *in vitro* fertilization

Introduction

Since the birth of the first *in vitro* fertilization (IVF) baby in 1978, tremendous advances in assisted reproduction technologies (ART) have been documented based on established science and techniques regarding the delivery of healthy infants [1]. Assisted reproduction relies on various complex methods performed by clinicians outside the human body with the use of challenging and innovative methodology. Techniques, such as intracytoplasmic sperm injection (ICSI), assisted hatching, vitrification, and preimplantation genetic diagnosis, disrupt the overall physiological processes [2,3].

Numerous improvements in fertility treatment fail to enhance the success rates, and fertility specialists continually aim to optimize the techniques [4]. Nevertheless, various situations, including issues regarding the ovarian, uterine, and gametes' physiology and their respective contribution to infertility, still challenge the current IVF practices. Over the past decade, the scientific community has witnessed incredible advances in organ transplantation and in exploring the possibility of the use of artificial organs to replace, enhance, and mimic physiology [5]. However, this approach is currently not clinically feasible because additional experiments on animal models are required prior to clinical trials in humans to validate its safe application.

Infertility etiology involving human gametes and ovarian and/or uterine factor is the common denominator in the infertility equation, and IVF treatment can be the

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solution. Herein, the authors focus on exploring the perspectives on the use of artificial reproductive organs for assisted reproduction. The factors affecting the future implementation of artificial organs in ART are outlined in Fig. 1.

This article presents the prospective use of artificial ovary (AO), artificial uterus (AU), and artificial gametes (AGs). The review's content is outlined in Fig. 2 and is organized in three sections that analyze perspectives regarding AO, AU, and AGs. This manuscript discusses the definition, origin, and applications and describes the current status for each artificial organ. The analysis highlights the need for a viable respective artificial model. The manuscript also reports experiments on animal models and identifies patients that may benefit from this application while highlighting the value of such method. This timely and innovative study explores the possible contribution of artificial reproductive organs and gametes in addressing challenging cases in IVF practice with considerations and concerns toward their clinical application in humans.

Perspectives regarding AO

Different strategies that presented promising results and several weak points during their clinical application have been developed to achieve fertility preservation and overcome infertility factors regarding the ovaries. Cryopreservation of the patient's mature or immature oocytes [6,7], autotransplantation of ovarian tissue following cryopreservation [8,9], hormone therapy, and oocyte donation [10] are considered to be tolerable alternative options for cases with compromised ovarian physiology and function. Moreover, ovarian stem cells [7] and platelet-rich plasma (PRP) ovarian injection [11] are novel and innovative options with positive preliminary data available on ovarian rejuvenation [12]. However, further tests on animal models and cautious clinical trials on humans are necessary prior to the declaration of horizontal clinical use. Regardless of the availability of these treatments, numerous ovarian pathologies are still presented as a conundrum. These conditions may be detrimental for the women's reproductive ability and fertility potential and could complicate and jeopardize optimal IVF management [13,14].

The aforementioned treatments, which have been in the research spotlight for many decades, still fail to completely address infertility by improving ovarian function. Hence, the urgent need for an alternative approach should be emphasized. The lack of a full-proof approach in managing such issues may be effectively addressed and bypassed in opting for the possible use of artificial organs. Research on infertility must further incorporate technological advancements and turn cutting edge technological expertise into an ally. According to a thorough literature search, the AO may indeed provide a radical solution. The development of AO must heed a dyadic direction as suggested by Amorim and Shikanov [10]. The "transplantable" form of AO used in most animal model studies essentially serves as a scaffold and hence contributes on the implantation of pre-isolated preantral follicles back into the ovary. Furthermore, the hypothesis of the "*in vitro*" form of AO could be used to support the folliculogenesis procedure outside the human's body *ex vivo*. Kim *et al*. initially defined AO as a 2D system for the culture and maturation of follicles [15]. This definition later evolved into a unique 3D system that enhances follicular survival and supports folliculogenesis as a viable scaffold [15,16]. This scaffold, which serves as a successful biological support, was constructed from

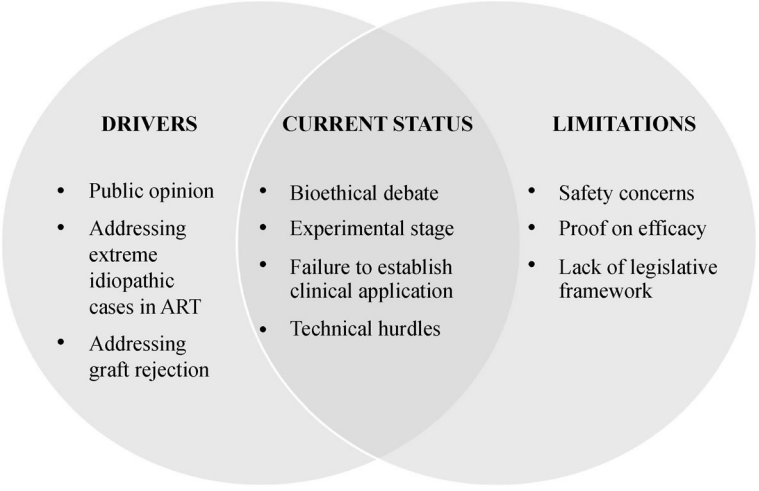

Fig. 1 Factors affecting the future implementation of artificial organs in assisted reproduction.

different biomaterials and was previously examined on animal models, thus ensuring its sustainability.

The principal hazard associated with organ transplantation is graft rejection by the host's immune system. This unfavorable complication could be effectively addressed and bypassed with the use of AO. Scientists attempted to mimic the natural role of the ovary by designing an artificial one through animal models. Selecting the appropriate materials is challenging, and *in vitro* and *in vivo* tests were conducted to ensure safe application. The biomaterials used for the supportive basis of an AO could be either natural (fibrin or collagen) [10,17] or synthetic (poly(ethylene glycol) vinyl sulfone) [6]. This well-defined biological scaffold entails the implantation of stem cells that have been isolated from the intended recipient [10,18] and succeeds in establishing contact among cells up to the point when the ultimate physically-shaped tissues may be able to incorporate them [16]. The follicular development following the autotransplantation of pre-isolated follicles developed through an AO was assessed in mice. The results were encouraging and revealed follicular survival and growth *in vivo* for up to 7 days [17], and another study reached up to 60 days [6]. Researchers focused on identifying the most compatible material for AO in order to provide a sustainable environment for the follicles' survival, and serve as their support for viable growth. Following experiments using different biomaterials, they concluded that a fibrin scaffold may be a favorable option [19]. Similarly, another study used primordial and primary murine follicles and seeded them in scaffolds created with different biomaterial combinations; the fibrin structure exhibited good follicular survival outcomes and resulted in live births [20]. One recent study employed human-based materials, namely, ovarian cortex and follicles, to examine the optimal fibrin combination and ensure a stable and viable platform that successfully imitates human ovarian construction [21]. In 2017, Laronda *et al*. used gelatin scaffolds to print a 3D ovary with an optimal pore architecture, in which follicles could nest, normally survive, and develop. Following the transplantation of the AO scaffold including follicles on an ovariectomized female mice, a normal ovarian function along with hormonal production and vascularization throughout the graft was impressively documented. These outstanding experiments led to live births of the carrier mice's own offspring up to the lactation period [22]. The differences on organ morphology and physiology between animal models and humans reflect the true conundrum highlighted in experimental attempts on animal models and may challenge the extrapolation on the use of AO in humans. For this reason, researchers focused their trials on follicular culture in the ovaries of non-human primates (NHP), especially Rhesus monkeys, to regulate the culture conditions. These attempts resulted in a remarkable success [23,24] and an improved ovarian function following the auto transplantation of cryopreserved ovarian tissue in monkeys [23,25]. Recent studies on NHP reported that folliculogenesis maturation is affected by gonadotropin ration following the intraovarian culture of preantral follicles [26]. The principal driver for these works is the evolutionary resemblance between NHP and humans. Therefore, the research on NHP models brings the scientific community a step closer to the prospective use of AO in humans [23].

The results from current animal experiments seem to be promising and certainly broaden the possibility of AO applications in humans. With the assumption that human AO will be clinically available and accompanied by improved treatment options, the management of infertility patients referring to ART could be revolutionized [27]. The scientific community could extrapolate on the true benefits that a sustainable model of AO would offer. This approach could be a unique opportunity for patients exploring ovarian function restoration and fertility maintenance.

The future availability of a human transplantable AO could endow the chance of motherhood to women with congenital absence and/or hypoplasia of ovaries, which is depicted in cases of ovarian dysgenesis syndrome [28], or with acquired absence mainly due to an urgent need for ovariectomy [29]. In addition, women with hormonal imbalance stemming from either menstruation abnormalities or ovulation disorders could be the candidates for this novel technology [29]. Most importantly, oncology patients who should elude the peril of re-introducing cancer cells through cryopreserved ovarian tissue transplantation may benefit from a transplantable ovary.

In investigating this special cohort of oncology patients and their current options on fertility preservation, cryopreservation appears to be the only resort. Studies revealed that oocyte and embryo cryopreservations are valid options [30] with a satisfactory live birth rate of almost 25% [31]. However, patients who are in urgent need of anticancer treatment or girls prior to puberty cannot provide mature oocytes through a controlled ovarian stimulation protocol. These patients should undergo ovarian tissue cryopreservation with the intent of autotransplantation [8,32]. In current clinical practices, cryopreservation of ovarian cortex tissue, or of the whole ovary, could be achieved through gradual freezing or vitrification protocols but is still considered an experimental procedure [33]. However, latest meta-analysis data contributed toward its shift from an experimental stage into a routine clinical procedure [34]. On the one hand, gradual freezing follows a certain cooling program [33]. However, a significant risk of ice crystal formation occurs, thus jeopardizing the tissue and the oocyte DNA integrity and physiological function [35]. Nonetheless, a recent meta-analysis on oncology patients with various benign diseases reported an optimistic 37.7% of live birth rate following an autologous cryopreserved ovarian transplantation with slow freezing [36]. On the

other hand, vitrification has revolutionized cryobiology with its high survival rates and flexibility in clinical application [30]. This process circumvents the jeopardy of crystal formation owing to the high concentrations of cryoprotectants along with a short timeframe of exposure [33]. In this case, toxicity may pose a major challenge [33]. The two methods showed no differences on the number of intact primordial follicles following the thawing or warming process; however, vitrification seems to exert less DNA damage [34]. Reports on slow freezing and vitrification revealed that oncology patients may achieve healthy delivery after undergoing ovarian tissue cryopreservation prior to chemotherapy [32,37,38]. The recipients of thawed ovarian tissue following cryopreservation have 30%–70% possibility of childbearing [39]. Another important observation is that orthotopic (at the pelvic wall) ovarian tissue transplantation has remarkably positive pregnancy and live birth outcomes compared with heterotopic (outside the pelvic wall) ovarian tissue plantation [33,36].

Autotransplantation studies on humans and animal models regarding autologous frozen–thawed transplantation of ovarian tissues reported the reactivation of hormonal production and reproductive function [32,39]. However, a risk of reintroducing malignant cells back into the recipient may occur [19]. Furthermore, numerous studies documented a direct reinstatement of the graft's blood supply after the thawing procedure [23]. A considerable percentage of patients may lack the required time or proper consultation to protect and preserve their fertility before entering a timely and efficient cryopreservation protocol. Thus, an AO model may be a viable option, especially for these cases.

Another case scenario for the use of AO is for women prior to the age of 40 who spontaneously experienced premature ovarian failure, which is possibly related to autoimmunity or induced by ovariectomy or anticancer treatment, leading to their inability for natural conception [7,40]. Women over the age of 35 [41,42] or at shift to perimenopausal period struggling to get pregnant due to a dysfunctional and aging ovary are classified under poor or diminished ovarian reserve [13,14]. Finally, the distinct category of "advanced maternal age" women who postpone gestation because of various personal and/or social reasons could potentially find their path through maternity with the use of AO [41].

The currently hypothetical *in vitro* AO could be actualized with further advancements deviating from the strict frame of applied medicine. An *in vitro* AO may stand as an alternative approach for testing the toxicity of several drugs employed in the IVF set-up or observing their effect on follicles and subsequent oocytes' quality. This finding is an important contribution because it would allow clinical trials to directly assess the experimental conditions on human ovarian tissue *in vitro*. Such an approach would be anticipated to circumvent or alternatively enrich the strength of animal models [10]. Furthermore, the availability of AO in the research field could uncover the mechanisms involved in human folliculogenesis and delineate various disorders associated with female infertility [10]. The size or development of human follicles differs from those of murine [8]. Therefore, a human AO is highly covetable because it could adequately enable ideal experimental conditions that are not depicted in animal

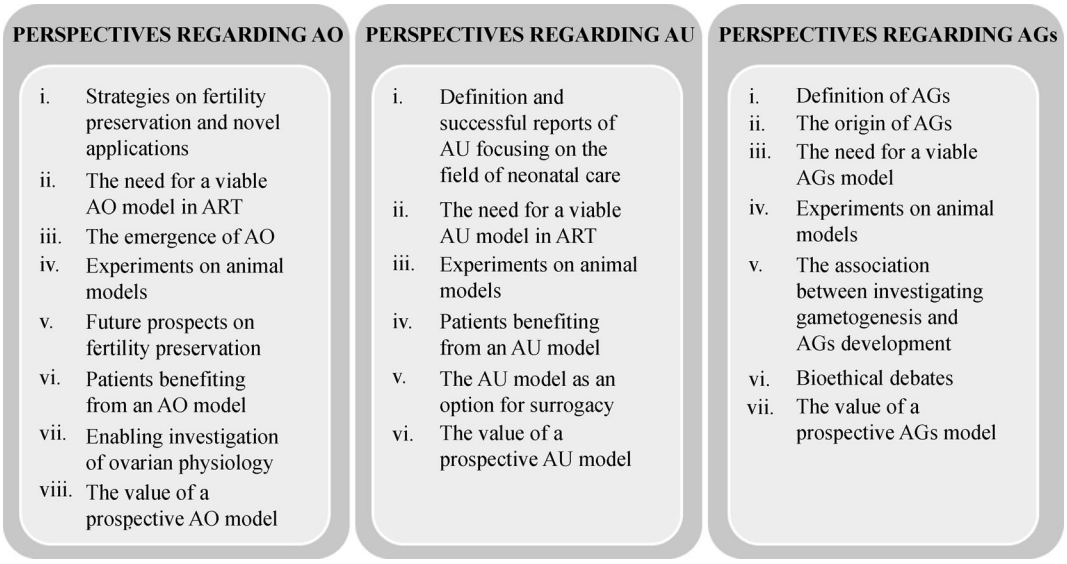

Fig. 2 Outline of the review content. AO, artificial ovary; AU, artificial uterus; AGs, artificial gametes; ART, assisted reproductive technologies.

model studies. In an IVF laboratory, the current consumables for gamete and embryo culture are plastic ware, thereby presenting limitations and contraindications, such as an epigenetic influence on oocytes and embryos [43]. The scaffold of an AO could be employed for culturing oocytes, particularly during *in vitro* maturation, to provide optimal environment for such biological process and convey favorable results while mimicking nature.

All aforementioned successful trials of the use of AO on animal and NHP models may encourage the scientific community to further its application in infertile women, IVF laboratories, and IVF research. This approach may benefit patients toward overcoming infertility related to ovarian etiology by providing them with a functional and vital, albeit artificial, ovary.

Perspectives regarding the AU

AU or artificial womb stands for an extracorporeal support and supplementation with all appropriate nutrients and oxygen for fetal development to imitate a female intrauterine environment [44]. The first successful *ex vivo* human embryo implantation, specifically into a surgically-removed human uterus, was conducted in 1988 by Bulletti and colleagues who presented an artificially perfused uterus. This system was supported by a perfused machine with an oxygenated medium representing the artificial component and providing the appropriate hormonal profile. However, this study was immediately abandoned due to ethical and legal conflicts [45]. The scientific community proceeded with experiments on animal models. Studies primarily focused on the *ex vivo* survival ability of an undeveloped goat fetus via an oxygenation system [46]. Another innovative work constructed a uterus-like artificial organ, which consisted of rubber balloons containing water, that can mimic the acoustic maternal environment and positively affect the fetus to develop consciousness [47]. Researchers' interest expanded to the field of neonatal care; the importance of an AU model has been acknowledged in the reduction of gradually increasing complications originating from preterm and extremely preterm deliveries [48]. In line with this concept, the survival of shark embryos, which were accompanied by an observing system, was evaluated for a few days following operative detachment from the uterus and subsequent development within a synthetic artificial womb [49]. A recent striking experiment presented normal organ growth of a prematurely born lamb fetus using a "biobag" that contains artificial amniotic fluid and is linked to an umbilical cord and an oxygenation supply; the fetus developed for up to 4 weeks [50]. This experiment may serve as a breakthrough in the neonatal care of preterm offspring, a major challenge even for an efficient neonatal intensive care unit [48]. The approach of Partridge and colleagues may provide a safe alternative to uterine environment and as an incubator with similar conditions.

Other researchers focused on uterine tissue engineering. Hellström *et al.* first examined the biochemical and mechanical properties of uterus by introducing the scaffold in a rat model [51]. Another research group adequately managed to sustain embryos for 14 days of testing an engineered uterine tissue, which was constructed by seeding epithelial cells onto a rabbit's smooth uterine muscle using a collagen scaffold [52]. Similarities of the uterine anatomy and physiology between human and NHP models are apparent. This finding could serve as an effective platform in representing human AU *in vivo*. Promising trials on uterine transplantation in rhesus monkeys (*Macaca mulatta*) [23,24] and cynomolgus monkeys (*Macaca fascicularis*) [23,53] reported short-term menstruation. However, the latter ended up with ischemia accompanied with uterine atrophy and subsequent graft rejection. In humans, recent advances have led to the documentation of live births following uterus transplantation [54–56]. This breakthrough is revolutionizing options and management of patients with absolute uterine factor infertility [57]. Nonetheless, great compromises come with such complex procedures. The possibility of complications or unsustainability may present a true risk and challenging management for some cases. The prospect of a viable AU model may be employed synergistically or independently and could offer a solution to the issues and risks entailed and hitherto documented with regard to the transplantation of uterus.

The prospective use of a sustainable AU in early pre- and peri-implantation stages, specifically in assisted reproduction, remains a hypothesis for now. Successful implantation is a complex hormonal, immunological, and molecular dialog between the embryo and endometrium. The "window of receptivity" [58] or "implantation window" [59] favors a normal decidualization for a successful implantation. A feasible AU could provide and enable a safe intrauterine environment with standardized conditions, thus challenging the consensus on the optimal management of implantation failure attributed to uterine etiology [60].

IVF failures attributed to implantation failure due to the lack of receptivity in the endometrium are important infertility cases that merit investigation and require strategic management [61]. The majority of infertile couples pursue various assisted reproductive techniques to achieve pregnancy. IVF failures attributed to implantation problems can be determined using widely employed invasive procedures, namely, hysteroscopy and laparoscopy [61,62]. However, these methods are accompanied by uncertain diagnostic results in addition to the already established lively debates and highlighted conflict regarding their application and optimal practice. This reality results from the lack of a universal standardized protocol

for successfully managing these cases [63]. Alternative approaches to unexplained implantation failure cases may include gamete donation, which is suitable when idiopathic factors pertain to the preimplantation embryo's implantation ability [61]. When failure is attributed to endometrial receptivity, surrogacy may be valid option [61]. On another note, the possibility of inflammation related to chronic endometritis managed by antibiotic treatment [64,65] and to endometrial scratching in an effort to "awaken" the receptivity of the endometrium [11,66] and improve implantation rates must be investigated. Novel approaches with interesting potential for therapeutic approach, such as stem cells derived from bone marrow [67] or intrauterine PRP infusion to increase endometrial thickness [68], were recently suggested in literature. With the serious limitations in all aforementioned methods, the need for an alternative method that could alleviate these restrictions is highlighted. Given the low efficiency and cost-effectiveness of existing management strategies regarding female uterine infertility, an effective treatment still remains elusive, uncertain, and ambiguous. In an era of precision medicine, the goal remains to be providing the patient with optimal personalized treatment. Developing a sustainable AU model may contribute to a thorough investigation on the unknown side of the implantation procedure, thus providing us with valuable insights into physiology or reproduction.

Despite the enormous and significant contributions in the field of AU, scientists still cannot offer a sustainable AU model for infertility treatment and IVF patients by addressing the failure of implantation issues. However, science fiction scenarios may clearly evolve into reality depending on the time points of examination between the birth of an idea and its realization [27]. Addressing the implantation failure of patients using an AU model while covering the needs of pregnancy establishment and early post implantation stages is a future possibility. Meanwhile, intense research focus is given on how a mature AU model can support the final gestation stages for appropriate candidates at risk of extremely preterm delivery. ART could be applied for women pursuing IVF procedures and especially those with recurrent implantation failure or IVF cycle cancellation [69]. Furthermore, the distinct group of women of advanced maternal age is compromised by time, which is important for pregnancy [69,70]. All these aforementioned special infertility groups could ultimately opt for an efficient AU model if available. The right to reproductive autonomy extending to the desire to procreate might be the driving force behind multiple failed IVF attempts and ART overuse. The same motive fuels the eagerness of women to resort to innovative and novel approaches even at the risk of embarking on a treatment without randomized controlled trial (RCT) data. Such options may assist them to achieve their reproductive goals, and an optimistic novel approach may contribute toward managing their anxiety [71]. Perhaps an AU model with ART may be directly associated with IVF success rates that may be remarkably improved and depicted by high implantation rates [48].

Surrogate mothers' replacement could become a solid perspective in AU development. Women with congenital uterine anomalies [72] or congenital absence of uterus [73,74] or even hysterectomized women previously diagnosed with endometrial or cervical cancer [75] could be candidates for gestational surrogacy or uterine transplantation [48,74]. The latter requires an organ donor and is always accompanied by the possibility of rejection of the transplanted organ, thus adding another level of complexity [76,77]. AU is safe because the embryo and subsequent fetus could avoid any perils associated with the surrogate's behavior during gestation [18,71]. Women without a uterus experience further psychological strain and depression related to loss or failure to develop and "own" the feeling of femininity [78]. A successful AU model could alleviate such strains and psychological conditions related to depression and hence could serve as a solution for this special category of patients without uterus.

Public opinion regarding the potential use of AU is poorly understood. One interview study revealed that although Israel women may describe "fear" of the idea of AU implementation claiming that it could distort the maternal–child's bond, they were positive regarding its employment in special cases, especially when no alternative option for childbearing is available [79]. Another pilot study employing questionnaires in Israel community is in agreement with the aforementioned results and highlighted that male partners are more optimistic toward AU development compared with females [71].

During an IVF routine, an adequate number of embryos are classified as surplus in successful cases of fertilization and subsequent live birth. Scientists suggest that surplus embryos from IVF procedure could be used in investigating the implantation potential through the use of an AU model [80]. However, the embryos' hypostasis, which poses the conflicting question of the embryo's rights and when human life is supposed to start, is the main issue to consider. With the development of AU, the term "ectogenesis," which refers to the whole gestation outside the woman's womb, is introduced. Such matters could severely challenge the field of bioethics. Along with ethical issues, the potential implication of AU would also challenge the known 14-day limit for human embryos, exposing further conflicts regarding the legacy because embryos could be implanted and grow for more than 14 days into artificial wombs [44]. The media reported Dr. Hung-Ching Liu's first attempt to grow a human embryo on a scaffold incorporated with endometrial tissue for 10 days and was claimed to be a successful implantation (Hung-Ching Liu, unpublished observations). However, this trial remains unpublished because of the numerous

ethical and legal issues that have emerged. An AU could be feasible and safe for embryo development as compared with pathological or absent uterus [81]. The world of science awaits future developments.

Further studies should be performed on animal and NHP models prior to the implementation of AU in humans because this method is still at preliminary stages. The focus of research on this field is to provide a neonatal care option for prematurely delivered embryos. Such resort has been successfully documented and is highly promising for future clinical practice. Nonetheless, the AU's role in ART is of essence and a focal point of this manuscript. A sustainable AU model could be a radical solution for women with absolute uterine infertility etiology and could be a viable option in ART.

Perspectives regarding AGs

AGs refer to female and male gametes created in the laboratory using other types of cells [82]. This method was introduced in ART for infertile patients with donor gametes as their sole option. Infertile men and women, postmenopausal women, and same gender couples who value a genetically linked pregnancy may benefit from the implementation of AGs [83]. However, introducing AGs in the name of a genetically linked offspring raises concern and major debate due to the unknown elements involved, thus serving as a true "black box." This issue is amplified by the controversy on the value of a genetic parenthood. Furthermore, some AGs' producing methods fail to accrue the genetic correlation desired by the parents [84].

AGs formation relies on various methods with a main differential point: the origin of the cells used. The four basic lines of approach are germ line stem cells, pluripotent stem cells (iPSCs), somatic cell nuclear transfer to embryonic stem cells (SCNT), and SCNT to donor oocytes [83]. However, not all of these methods are accompanied by solid data. How these techniques could facilitate a successful outcome in infertility issues remain unknown. Limited animal studies reported live birth following AGs' employment; nonetheless, promising results remain preliminary. No reports have been documented regarding the gamete's chromosomal normality or the offspring's long-term complications and health [83]. AGs could either be transferred into the testicles or the ovaries and possibly contribute to natural conception or be employed in an IVF cycle or ICSI procedure [83]. Hitherto, successful AGs manipulation resulting to pregnancy has been documented solely in animal models. Live mouse birth where female embryonic and induced pluripotent stem cells (ESC/iPSCs) were induced into primordial germ-like cells has already been recorded [85]. These cells were properly developed in reconstitution ovaries *in vitro* and further matured into germinal vesicle oocytes prior to transplantation. However, the underlying mechanisms remain to be further addressed and investigated.

Optimization of AGs formation and implementation may be viewed as a "by-product" rather than an outcome from the ongoing investigation of gametogenesis [82]. The core of gametogenesis is characterized by unknown mechanisms, and the epigenetic changes during this period remain as the focus of respective research [86]. Valuable knowledge may be acquired by opening a new line of investigation to delineate gametogenesis, and this may inevitably result to approaching gametes in an artificial context and in turn revolutionize assisted reproduction.

The rationale behind AGs implementation may be criticized from a bio-ethical stance. The scientific community can recognize that AGs could play a role in ART while considering "It is possible, but is it wise?" However, while contemplating on the true colors of AGs, one should never fail to consider that the aim of many ART approaches, such as ICSI, is to fulfill the parents' desire and need for genetic parenthood [82]. Despite the debate and concerns regarding female gametes derived from men and vice-versa [87] or the concept of an individual person reproducing on his/her own [88], AGs should be excluded from this science fiction context and actually assist toward eradicating some liabilities in infertility issues.

AGs could be a solution for extreme cases of female and/or male infertility and provide them with the unique opportunity of bearing their genetic child. Many studies support this point [83]. Pregnancy and live birth have been documented in animal models, and this treatment could be an option for patients that naturally fail to contribute to the creation of a zygote using their gametes [85]. However, AGs becoming a feasible option in humans may harbor significant concerns of bioethical nature. A well-defined and robust legislative framework with guidelines structuring clinical practice based on the good code of practice should support future implementation of this method.

Conclusions

The development of artificial organs offers significant medical benefits for a large number of patients [89]. Extrapolating on current applications and technologies, we could foresee the safe application of AO. Similar to other fields, ART may benefit majorly from this implementation. Provided that research and development includes proper animal experiments, pilot studies and RCTs, artificial organs in the service of IVF can possibly address challenging infertility cases regarding the gametes and uterus. Implementation and communication with patients for possible clinical application should be guided by the moral issues surrounding the bioethical nature of pre-implantation and *in utero* embryo. Several theses have been submitted on how the ethical stance of the embryo is

shaped from zygote to neonate. From the embryo's rights to legislative framework, this topic is a gray zone requiring cautious navigation on behalf of the scientific community. However, today's transplantation of artificial organs still poses technical and ethical risks and uncertainties [90]. This review article presents perspectives on the application of artificial reproductive organs, such as AO, AU, and AGs, in the field of ART. Table 1 provides a technical overview of the current status and limitations along with the future direction on clinical application and research using artificial organs in ART.

Extreme cases of male infertility, congenital pathologies, women with poor ovarian reserve, infertile couples who pursue a genetically linked child, or even unexplained infertility are some of the candidate patients that may benefit from the clinical application of artificial reproductive organs [10,60,82]. A graphical representation of ART patients benefiting from the future application of artificial organs is illustrated in Fig. 3.

However, no successful clinical application of artificial reproductive organs in humans has been reported. Nonetheless, the existing animal studies highlight the need for further investigations. Research and development of novel technologies should involve studies on animal models, followed by *in vitro* tests on embryos that are donated to research and RCTs that aim to ensure validity and safety prior to the clinical application and introduction of IVF practices [91]. A wide range of ethical dilemmas associated with organ transplantation exist, and artificial organs may "carry" many bioethical issues. During the first human heart transplantation in 1967, the emotional shock and ethical dilemmas led to questions such as "do we not feel and love with our heart and if so how can you replace a person's heart?" [90,92]. Numerous bioethical issues in

Table 1 Technical overview of current status and limitations and possibilities regarding future direction on the clinical application and research of artificial organs in assisted reproduction

Artificial organs	*In vitro* experiments employing human cells	Animal model experiments	Clinical trials on humans	Fields of future implementation of artificial reproductive organs in assisted reproduction		
				Clinical application	Application in the IVF laboratory	Research application
AO	Yes [21]	Mouse [6,9,15–20,22]	No	Ovarian function restoration Fertility preservation/maintenance	Oocyte culture *In vitro* maturation of oocytes	Toxicity tests Investigate folliculogenesis
AU	Yes [45][a]	Goat [46] Shark [49] Lamb [50] Rat [51] Rabbit [52]	No	Absolute uterine etiology RIF Unexplained infertility Surrogacy replacement	Embryo culture	Toxicity tests Investigate implantation procedure
AGs	No	Mouse [85]	No	Enable genetic parenthood	Test IVF consumables and conditions	Toxicity tests Investigate gametogenesis

[a] Conducted research was prohibited following commencement. Data remains unpublished and communicated through media.
AO, artificial ovary; AU, artificial uterus; AGs, artificial gametes; RIF, recurrent implantation failure; IVF, *in vitro* fertilization.

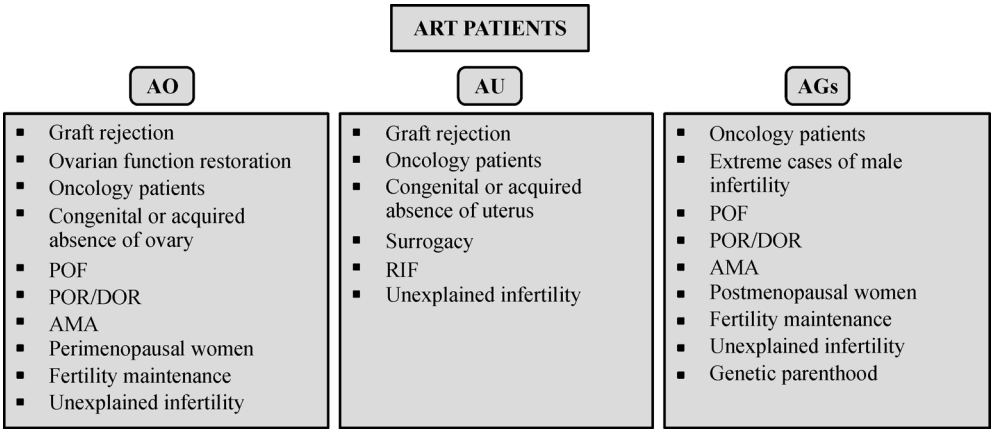

Fig. 3 Graphical representation of ART patients benefiting from future application of artificial organs. AO, artificial ovary; AU, artificial uterus; AGs, artificial gametes; ART, assisted reproduction technologies; RIF, recurrent implantation failure; POF, premature ovarian failure; POR, poor ovarian reserve; DOR, diminished ovarian reserve; AMA, advanced maternal age.

reproductive medicine arise from the future clinical application of artificial organs in humans. The authors refrain from presenting an analysis on the bioethical status of the human embryo. A line should be drawn by the field experts during this era of novel techniques that bombard practitioners with dilemmas and questioning. Reproductive medicine guided by perceived patients' demands, profit, and scientific curiosity is notorious for the immature implementation of innovations, thus failing to convey sufficient effectiveness and safety assessments [91,93]. Consequently, all these findings led to the question, "when will researchers, clinicians and society be ready to welcome this new era"? To answer, the scientific community must examine patients who are in real need of artificial reproductive organs, such as women with absolute uterine factor infertility [78]. A misselection on who would finally have access to this option might lead to the possible misuse of this technology which is originally aiming to bypass pregnancy and birth complications [71,94]. Artificial organs are and will be an increasingly essential part of modern medicine because they address human needs to improve the quality of life [89]. This option is offered through artificial organs that provide substantive equality and reproductive autonomy. Furthermore, public opinion voiced through limited studies [79] may serve as a support for future implementation. On the basis of the etiology of infertility, certain challenging cases could be managed by using artificial organs as the last resort. Until then, animal model studies and clinical trials must be successfully established, and legislation and bioethical dilemmas must be well defined and effectively addressed.

Compliance with ethics guidelines

Mara Simopoulou, Konstantinos Sfakianoudis, Petroula Tsioulou, Anna Rapani, Polina Giannelou, Nikolaos Kiriakopoulos, Agni Pantou, Nikolaos Vlahos, George Anifandis, Stamatis Bolaris, Konstantinos Pantos, and Michael Koutsilieris declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring the approval of a relevant institutional review board or ethics committee.

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