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REPRODUCTIVE BIOLOGY: REVIEW

# Artificial Gametes and Human Reproduction in the 21st Century: An Ethical Analysis

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**Abstract**
Artificial gametes, derived from stem cells, have the potential to enable in vitro fertilization of embryos. Currently, artificial gametes are only being generated in laboratory animals; however, considerable efforts are underway to develop artificial gametes using human cell sources. These artificial gametes are being proposed as a means to address infertility through assisted reproductive technologies. Nonetheless, the availability of artificial gametes obtained from adult organisms can potentially expand the possibilities of reproduction. Various groups, such as same-sex couples, post-menopausal women, and deceased donors, could potentially utilize artificial gametes to conceive genetically related offspring. The advent of artificial gametes raises significant bioethical questions. Should all these reproductive scenarios be accepted? How can we delineate the range of future reproductive choices? A normative bioethical framework may be necessary to establish a consensus regarding the use of human artificial gametes. This review aims to present the current state of research on the biological roadmap for generating artificial gametes, while also summarizing proposed approaches to establish a normative framework that delineates ethically acceptable paths for reproduction.

**Keywords** Artificial gametes · In vitro gametogenesis · Assisted reproduction techniques · Reproduction · Bioethics of reproduction

## Introduction

Stem cells, possessing the ability to differentiate into various adult cell types, are recognized for their therapeutic potential in treating degenerative diseases [1–3]. Artificial Gametes (AGs), comprising in vitro-derived eggs and sperm, aim to address infertility [4, 5]. However, the development of human AGs would introduce new reproductive choices for social groups unable to conceive naturally [6–8]. This study investigates the differentiation of AGs in non-human animals, explores the feasibility of generating them from human cells, and delves into the ethical considerations surrounding diverse reproductive possibilities facilitated by AGs. Through a comprehensive literature review, it synthesizes biological and bioethical perspectives to offer insights and potential resolutions.

The introduction outlines advancements in generating AGs biologically, initially successful in laboratory animals, with ongoing efforts for translation to human cells. Section "Framing the Normative Ground for Reproductive Purposes" explores normative frameworks proposed by previous authors. Then, bioethical questions regarding the use of AGs are comprised into subsections within the Section "Summarising the Bioethical Perspective". Next, section "Proposed Normative Frameworks to Discern Reproductive Scenarios" addresses limitations of these proposals while highlighting intriguing points from previous research on the ethical acceptability or prohibition on different reproductive scenarios, emphasizing AGs' potential to provide genetically related offspring to various groups, including same-sex couples, post-menopausal women, prepubertal children, deceased donors, and single individuals. Section "Ethical Consequences Derived from the Ontology of AGs" refers to whether AGs should be considered as naturally obtained gametes. Section "Bodily Integrity: When Autonomy Meets Consent" focuses on the autonomy and consent on the use of AGs. Finally, Section "Insights from the Ethical Analysis of

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Individual Cases" analysis the previously depicted reproductive cases one by one.

Infertility rates have risen in recent decades, attributed to both pathological factors and delayed pregnancies, nearing optimal reproductive age limits [9–12]. However, current ART success rates fall short in cases of complete absence of gamete formation, as seen in conditions like testicular agenesis or polycystic ovary syndrome [13]. AGs emerge as a potential clinical solution for individuals unable to produce sex cells, offering genetic relatedness and extending therapeutic scope to idiopathic infertility cases. AGs show promise in addressing a broader range of infertility issues beyond gamete formation deficiencies. AGs are in vitro-generated sex cells derived from stem cells, showcasing functionality by producing viable and fertile offspring [4, 14, 15].

Stem cells, possessing self-renewal and differentiation capabilities, have been successfully directed into organ-specific cells using distinct protocols in various species, including humans [16]. ESCs are derived from early-stage embryos, while iPSCs are generated by reprogramming adult somatic cells, such as skin cells, to regain pluripotency [17–19]. Both ESCs and iPSCs offer valuable resources for studying cellular development and tissue engineering, including the potential generation of AGs [20]. ESCs, originating from early-stage embryos, exhibit immunogenicity limitations for clinical use, prompting the exploration of alternative approaches such as somatic cell nuclear transfer (SCNT) for patient-matched ESCs [21–23]. However, SCNT raises substantial bioethical concerns due to its involvement in manipulating human embryos [24, 25].

Induced pluripotent stem cells (iPSCs) offer a non-embryonic alternative, reprogrammed from adult cells to a pluripotent state without embryo manipulation, sidestepping ethical concerns associated with ESCs [18, 19]. iPSCs, directly derived from patients, present ethical advantages and practical applications, eliminating the need for embryo formation or destruction [18, 26]. In vitro generation of eggs or sperm from human ESCs or iPSCs remains unreported, but substantial progress has been achieved in obtaining AGs from non-human mammals in the past decade [4, 14, 15, 27]. These advancements have resulted in the successful generation of AGs leading to the birth of fertile offspring in mice [28, 29]. Efforts towards human AGs primarily focus on understanding the physiological gamete biogenesis during embryo development, recognizing shared processes across mammalian species [30, 72].

The natural process of gametogenesis involves the formation of primordial germ cells (PGCs) within the embryo, developing into gonadal precursors and eventually differentiating into mature sperm or oocytes through meiosis [31–33]. Current in vitro strategies for deriving AGs from iPSCs mimic this natural process, utilizing specific factors and culture conditions to promote gamete differentiation and maturation [27]. Success has been demonstrated in mice and human studies, emphasizing the potential of these approaches [28, 29, 34–37]. The ultimate measure of success in obtaining AGs lies in evaluating their ability to fertilize and generate equally fertile embryos [14].

A significant breakthrough in the field of AGs was achieved by Hayashi and colleagues in 2011 and 2012 [28, 34]. Combining these cells with gonadal tissue in vivo facilitated maturation to a post-meiotic stage. Notably, mature oocytes derived from AGs were fertilized with normal sperm, resulting in the birth of fertile offspring. The same research group later reconstituted the entire gametogenesis process in vitro, showcasing the feasibility of generating functional AGs and offering insights into gamete development complexity. On the male side, in 2006, a pioneering trial by Nayernia et al. demonstrated the production of mice sperm in vitro, which resulted in successful fertilization. However, the offspring resulting from this experiment exhibited abnormalities due to improper reconstitution of spermatogenesis [35]. In 2011, the group achieved the in vitro generation of functional male sperm, leading to the birth of fertile offspring after fertilizing healthy embryos.. However, Zhou et al. made further progress in 2016 by developing a protocol that allowed for the complete derivation of spermatids in vitro, bypassing the need for in vivo recombination. This achievement led to the successful fertilization of mice embryos using in vitro-derived spermatids [37]. These milestones demonstrate the successful in vitro generation of both male and female AGs from mice, showing promising outcomes in producing fertile offspring.

Efforts to translate AG generation protocols from mice to human cells have encountered limited success. Silvestris et al. reported the furthest stage of differentiation using a completely in vitro protocol for human cells [38]. However, functional assays were lacking to assess the maturity and functionality of these oocytes. In the case of human sperm, functional AGs have not yet been successfully obtained, despite achieving intermediate stages of differentiation in both sperm and oocyte pathways in studies over the past decade [39–41]. While progress has been made, further research and protocol refinement are necessary to achieve fully mature and functional human AGs. A notable breakthrough in AG research with human cells is the protocol proposed by the Japanese group led by Saitou, representing the first successful generation of human oogonia (egg precursors) using a complete in vitro procedure [40]. Precisely recapitulating the process of human gametogenesis in vitro remains a challenge. However, the remarkable progress achieved in a relatively short period of time, from the discovery of iPSCs in 2006 to the successful generation of mice AGs (sperm in 2011 and oocytes in 2012), suggests the potential for obtaining

human AGs in the coming years. Continued efforts in AG research, along with advancements in our understanding of the intricacies of human gametogenesis, hold promise for the future development of human AGs.

| Article reference | Species | Differentiated cell type | Fertile offspring? |
|---|---|---|---|
| [35] | Mouse | Mature sperm | Yes |
| [34] | Mouse | Male primordial germ cells | Yes |
| [28] | Mouse | Female primordial germ cells | Yes |
| [37] | Mouse | Mature sperm | Yes |
| [39] | Human | Ovarian follicle-like cells | No |
| [38] | Human | Oocyte-like cells | No |
| [40] | Mouse | Primordial follicle cells | No |
| [41] | Human | Oocyte-like cells | No |
| [36] | Mouse | Primordial follicle cells | Yes |
| [29] | Mouse | Mature oocytes | Yes |

AGs have been proposed for diverse purposes, presenting intriguing implications within the realms of philosophy and bioethics [6, 7]. In terms of basic research, AGs offer opportunities for in vitro disease modelling, enhancing our understanding of infertility issues and facilitating drug screening [42]. Additionally, AGs have the potential to preserve the fertility of prepuberal individuals and cancer patients who may face infertility due to chemotherapy treatment. Such applications necessitate ethical considerations, as they raise questions about reproductive autonomy and the pursuit of genetically related offspring. The overarching goal of AG development is to enable individuals with infertility to have viable offspring when other assisted reproductive techniques are not viable options [4]. To ensure a comprehensive examination of the ethical implications surrounding AGs, this paper explores their varied applications, including disease modelling, fertility preservation, and the pursuit of genetically related offspring, taking into account individual autonomy, societal values, and the well-being of all the players involved.

This review aims to elucidate nuanced aspects in AG application scenarios often overlooked in normative bioethics discussions. By offering insights into the ethical implications, the goal is to stimulate thoughtful reflection on values, consequences, and dilemmas associated with AG utilization. The objective is not to advocate a specific normative standpoint but to enhance understanding, fostering a well-rounded and informed decision-making process. Through this approach, the aim is to contribute to an enriched dialogue in the ethical considerations surrounding AG techniques.

## Framing the Normative Ground for Reproductive Purposes

AGs offer a multifaceted contribution, serving not only as a solution for overcoming infertility but also as a means to broaden reproductive prospects for individuals currently not anticipated to have genetic heirs [6–8]. The development of AGs derived from adult cells holds significant promise for same-sex couples, offering them the opportunity to have genetically related children. This breakthrough can be achieved through the generation of cross-gametes, involving the production of oocytes from XY-individuals and sperm from XX-individuals [29, 43]. Once AGs, including cross-gametes, are successfully created in a laboratory setting, they can undergo in vitro fertilization and subsequent implantation. While this approach holds potential for lesbian couples, a unique challenge arises for gay partners regarding the availability of a suitable uterus for carrying the pregnancy [44–47]. However, this ethical question fails outside the scope of the use of AGs and will not be analysed in the present article.

The utilization of AGs derived from adult cells, such as skin cells, has the potential to extend the boundaries of reproductive age. This advancement proves particularly advantageous for post-menstrual women who, although unable to produce oocytes naturally, can benefit from the generation of AGs [48]. Furthermore, the application of AGs is not limited to post-menstrual women alone. Prepubertal individuals can also reap the benefits by obtaining AGs prior to reaching the age of natural oocyte or sperm production. This approach provides a unique opportunity to overcome the constraints imposed by age and facilitate reproductive possibilities for individuals even before they reach the pubertal stage.

The potential of AGs to extend the limits of reproductive age is indeed attributed to their source, which encompasses adult cells. As AGs can be generated from cells obtained from any postnatal individual, it follows that functional AGs could potentially be derived from post-mortem subjects as well. This notion suggests that the boundaries of reproductive possibilities could be expanded beyond the constraints of both the living and the deceased, allowing for the generation of AGs from individuals who have already passed away [6, 49]. And again, AGs are likely to be functional from fertilized embryos that are not even born since they display cells able to differentiate into oocytes or sperm. The concept of fertilizing embryos using gametes obtained from unborn individuals is commonly referred to as multiplex parenting. This innovative approach opens up new possibilities in reproductive technologies, allowing for the exploration of alternative methods to conceive and expand genetic lineages [50, 51].

Another intriguing possibility is single reproduction, whereby both sperm and oocytes could be differentiated from the cells of a single individual, making cross-gamete acquisition feasible. This breakthrough would enable the fertilization of embryos using gametes exclusively from one donor. Such an approach challenges traditional notions of reproduction by eliminating the requirement of two separate genetic contributors. Single reproduction, if successfully realized, could offer unique opportunities for individuals to have offspring with their own genetic material, further expanding the boundaries of reproductive options [52, 53].

The above-mentioned scenarios explore the possibilities offered by functional AGs in unconventional methods of reproduction and parenting [6]. However, the acceptability of these scenarios and where to draw the ethical boundaries of AG usage are subjects of ongoing debate and consideration. The assessment of the acceptability of scenarios involving AGs entails navigating complex ethical considerations. Diverse perspectives on reproductive technologies exist among individuals, societies, and cultures, prompting discussions that revolve around autonomy, consent, the welfare of individuals, potential risks and benefits, societal implications, and overarching moral frameworks guiding reproductive practices. Establishing ethical boundaries for AG usage necessitates engaging in thoughtful interdisciplinary dialogue involving experts in philosophy, bioethics, medicine, and law. This collaborative approach aims to address the multifaceted ethical dilemmas associated with AGs and seeks consensus that upholds principles of justice, respect, and the well-being of individuals involved.

To offer a comprehensive overview of the current discourse, this article references esteemed works in philosophy and bioethics. Subsequent subsections delve into these references, summarizing and analyzing pertinent literature. By critically assessing the strengths and weaknesses of existing proposals, the article aims to contribute to ongoing philosophical and bioethical discussions surrounding AG usage. Ultimately, the goal is to inform the development of a robust normative framework capable of addressing the inherent complexities in this emerging field of reproductive technology.

## Summarising the Bioethical Perspective

Initially, it is important to recognize that incorporating AGs into traditional Assisted Reproductive Technologies (ART) with heterosexual couples has not raised significant bioethical concerns. Some authors argue that using AGs in ART as a substitute for naturally generated gametes is ethically permissible within the scope of in vitro reproduction [54, 55]. Galea argues for the acceptance of AGs from a utilitarian perspective, drawing parallels to how we embraced in vitro fertilization and artificial insemination as additional means to achieve genetically related offspring. Additionally, Cutas and her team conducted a social study involving surveys of prospective users, revealing that this viewpoint is widely held among them. However, the primary concerns surrounding the use of AGs in ART extend beyond their application solely within opposite-sex couples of reproductive age. Instead, the focus lies in exploring the diverse reproductive scenarios that may arise due to the utilization of AGs.

## Proposed Normative Frameworks to Discern Reproductive Scenarios

Although various scenarios have been individually discussed in prior works, both Gooßens [50] and Cutas and Smajdor [52] stand out as the only proponents seeking a comprehensive analysis within a unified normative framework. This is significant because examining individual cases in isolation fails to converge towards a shared framework. The pursuit of a universal principle becomes necessary to subject all scenarios to the same moral guidelines, thereby mitigating bias in independent analyses.

Therefore, the quest for a universal principle becomes imperative to evaluate all scenarios impartially. In this regard, both authors direct their attention to the Principle of Reproductive Autonomy, also known as reproductive freedom, as a systematic lens for assessing the diverse applications of AGs. By adopting this principle, which emphasizes the freedom of parents to determine when and how to reproduce, they seek to establish a comprehensive framework that accounts for the various ethical considerations involved. Consequently, substantial justifications are required to prohibit or hinder an individual's reproductive choices. The principle can be approached from two distinct perspectives: (i) as a derived form of the right to freedom, or (ii) by defining the concept of freedom within the context of reproduction.Gooßens proposes to ground the use of AGs using John Robertson's theory, named "modern traditionalism" [56]. Robertson considers this position as "*modern in its acceptance of new technologies, but traditional in demanding that those techniques ordinarily serve traditional reproductive goals of having biologically related offspring to rear*". Considering the Roberston's conception, there are two elements needed to determine if an act can fall inside the scope of reproductive autonomy or not, to consider: *parenthood* and *necessity for fulfilling the reproductive interest*. Gooßens highlights that both concepts of parenthood and necessity, as proposed by Robertson, suffer from vagueness and lack of clarity. This vagueness makes it challenging to discern between different options and evaluate their ethical implications. However, Gooßens suggests a potential framework for understanding these concepts: parenthood could be considered relevant for individuals who desire genetically

related descendants, while the concept of necessity would apply to the use of AGs.

Gooßens takes a firm stance against single and multiplex parenting, posing a significant challenge to the application of Robertson's theory. While the theory provides strong arguments in favour of Assisted Gametes (AGs) for same-sex couples and post-menopausal women, it encounters difficulties when it comes to prohibiting the use of AGs in single reproduction and multiplex parenting. Gooßens firmly rejects the acceptability of these two forms of reproduction on the grounds that they do not fulfill the requirement of reasonable parenthood, which is a pivotal element in Robertson's theory for delineating acceptable reproductive uses. This presents a considerable hurdle in using the theory as a comprehensive ethical framework. Moreover, the question of single reproduction and multiplex parenting goes beyond the mere use of embryos for prospective parenting. César Palacios-González and colleagues have delved into the complexities of multiplex parenting, shedding light on the various ethical considerations surrounding this reproductive approach [51].

Gooßens deserves recognition as one of the pioneering philosophers who acknowledged the need for a common framework in evaluating the use of AGs. However, when applying Robertson's statements to assess the ethical implications of AGs, certain weaknesses emerge, particularly the vagueness of the proposed criteria. The concept of parenthood, for instance, can be understood in various ways and is not solely limited to genetic connections. Societies have long accepted adoption, where non-genetic parents assume the role of parenthood for adopted children. Taking this into consideration, Robertson's theory does not provide sufficient justification for banning single reproduction. Furthermore, the genetic diversity of children resulting from single reproduction is comparable to that of children born from the reproduction of twins (a reproductive practice acknowledged by Robertson's statements, such as same-sex couples). To establish a robust normative framework, well-defined concepts and criteria are required. For that reason and considering that AGs can be obtained from several diverse sources, it would be valuable to build a framework considering the genetic aspect of AGs.

## Ethical Consequences Derived from the Ontology of AGs

One of the primary criticisms levelled against the use of AGs revolves around the question of their nature. As Smajdor and colleagues pointed [57], some philosophers have fallen into the trap of the naturalistic fallacy by asserting that AGs are morally unacceptable simply because they are not natural. The naturalistic fallacy involves erroneously attributing moral values based on natural properties. Merely deeming something acceptable because it is natural falls within the realm of this fallacy. To navigate this issue, authors like Zwart [58] have introduced the concepts of "working with or against nature" as an alternative approach. According to this viewpoint, if an action aligns with nature, it is considered acceptable, whereas actions that work against nature are deemed unacceptable. Zwart applies this perspective to argue against the use of AGs for post-menopausal women, asserting that it goes against nature by surpassing the reproductive age. However, the notion of working with or against nature is subjective and open to interpretation. Smajdor offers a reframed understanding of the concept of working against nature when it comes to overcoming the reproductive age. Instead, she proposes viewing the use of AGs for post-menopausal women as working with nature. This perspective suggests that the aging ovaries of post-menopausal women can be regarded as failing biological structures. Consequently, employing AGs to enable reproductive capabilities can be seen as working with nature and therefore ethically permissible.

The debate surrounding working with or against nature in the context of AGs reveals the subjective nature of the concept itself. The re-evaluation of aging ovaries as failing biological structures provides an alternative perspective that challenges the notion of working against nature, making room for the ethical acceptance of AGs for post-menopausal women in reproductive contexts [7, 8, 57]. Zwart's attempt to address the naturalistic fallacy is based on a similar premise to the fallacy itself, as it still involves attributing moral values to nature-related properties. However, Harris and Testa [7, 8], present a different perspective by arguing that AGs can be considered natural since they have the potential to produce fertile offspring, similar to physiological gametes. Their viewpoint emphasizes that the in vitro generation of AGs does not undermine their naturalness. Smajdor offers an alternative approach by proposing that the concept of naturalness should be seen as a continuum, drawing from Kant's perspective [59], and introduces thought-provoking inquiries, such as the ethical responsibility associated with the creation of human life.

Summarizing the relevant points in the AGs discussion, Smajdor highlights a fundamental question: Do we have valid reasons for pursuing the use of AGs? It is crucial to recognize that there can be diverse answers to these questions. Smajdor asserts that this question serves as a fertile ground for engaging in meaningful discussions about the morality of AGs. However, it is important to acknowledge that societies, which typically regulate the use of ART, may require a unified response in order to legally delineate the parameters of AG usage.

## Bodily Integrity: When Autonomy Meets Consent

On a different piece of work, Anna Smajdor [60] examines the use of AGs to extend the fertility of post-menopausal women, which holds particular significance in societies experiencing declining birth rates due to delayed parenthood. The central question raised by Smajdor is whether governments should prohibit, tolerate, or even prioritize the expansion of reproductive age limits through the use of AGs. Smajdor argues that women have had to consider both social and biological factors when making reproductive decisions. While women can negatively control their fertility through contraception, they currently lack the ability to positively control their fertility through ART. It is true that ART procedures can be effective for some individuals, but their success rates are heavily influenced by the age of the women involved. Smajdor references the work of Bewley [61] to highlight the "false promises and spurious hopes" associated with in vitro fertilization for women beyond their reproductive window. However, if AGs were available for clinical use, they could potentially overcome these age-related challenges. It is important to note that older women are more likely to accumulate genetic mutations throughout their lifetime, which could be inherited by their offspring. Furthermore, there is an increased risk of pregnancy-related complications such as gestational diabetes and high blood pressure as a woman's age advances. These health conditions can impact both the development and birth of the baby.

Smajdor argues that even for younger women, pregnancy is not without risks. Based on this premise, the philosopher asserts that there is no valid justification for exclusively relying on sexual reproduction. According to Smajdor, this issue extends beyond the realm of medicine and becomes a societal concern. It is socially unrealistic to expect "early and prolific motherhood." Therefore, AGs should be embraced as a means to enable reproduction beyond the limitations imposed by age. Smajdor emphasizes the importance of engaging in a broader discussion about the value of reproduction within our society before making decisions regarding future technologies like AGs. Such a discussion would provide a necessary framework for evaluating the ethical implications and societal impact of these reproductive techniques. By considering the societal context and values surrounding reproduction, a more comprehensive understanding of the role of AGs can be achieved.

In her previous work, Smajdor explores the possibility of obtaining AGs from post-mortem individuals, which presents a more extreme scenario in terms of reproductive age extension. One might initially assume that deriving AGs from deceased individuals should be ethically unacceptable. However, a comparable situation has already occurred even without the use of AGs. Smajdor highlights a case in which a man's sperm was extracted shortly after his death through an invasive procedure [49]. This sperm was then used for in vitro fertilization, ultimately resulting in the birth of offspring through implantation. The key question raised by Smajdor is the issue of reproductive autonomy in this context, particularly considering the lack of explicit consent from the deceased individual. The case brings into question the ethical implications of using reproductive material from deceased individuals without their prior consent. It raises concerns about respecting the autonomy and wishes of individuals, even after their death. Smajdor's exploration of this case serves as a reminder that the ethical considerations surrounding the use of AGs extend beyond the realm of reproductive age limits and touch upon broader issues of consent, autonomy, and the moral implications of posthumous reproduction.

While there is a consensus that rape is sex without consent, primarily because it violates bodily integrity, the comparison to the use of AGs brings forth different considerations. AGs can be obtained through minimally invasive procedures, such as collecting skin cells that naturally shed from the body. Unlike traditional methods of reproduction that may violate bodily integrity, the use of AGs does not pose the same violation. However, the question of consent remains crucial. Reproductive autonomy asserts that no one should be forced to become a parent without their consent. This principle is often applied to women, who have the right to decide whether to continue or terminate a pregnancy, as it directly affects their bodily integrity. According to Smajdor, the consent of the mother is imperative in determining the direction of a pregnancy. In light of this, Smajdor argues that the consent of the man should be equally considered, and that sperm should not be taken without consent. However, when bodily integrity remains intact, as is the case with AGs, the question of consent becomes more nuanced. The work of Anna Smajdor highlights the discrepancy between theoretical reproductive rights built on principles like autonomy and the realities of reproductive practices. It becomes necessary to reevaluate the use of AGs in reproductive scenarios and develop new tools and frameworks that go beyond our current assumptions and address the unique ethical challenges posed by these technologies.

Smajdor's argument regarding the derivation of AGs from unconsented individuals is based on the idea that it does not violate bodily integrity. While this may be true, it is important to consider other ethical dimensions related to the use of AGs. One aspect to consider is the desire to live in a world without genetically related descendants. While individuals may have this preference, it is worth noting that we already coexist with genetically related individuals, such as grandchildren or nephews, without necessarily being directly involved in their creation. The decision to have genetically related offspring rests with the progenitors, who have the most direct genetic link. This observation might lead to a

justification for the use of AGs from post-mortem individuals. However, Smajdor argues against the use of AGs without impunity. The philosopher warns against instrumentalizing individuals for their genetic information and emphasizes the importance of reproductive autonomy. By respecting reproductive autonomy, we can avoid treating individuals as mere means to achieve genetic potential or as objects for the creation of offspring through AGs.

### Insights from the Ethical Analysis of Individual Cases

Beyond the immediate reproductive use of AGs in ART like in vitro *fertilization*. AGs could be also employed for gamete donation as we do nowadays. For that, Carter [62] raises an important question regarding the acceptability of current methods of egg donation when safe and costless AGs could be generated. The philosopher argues that existing procedures for egg donation are highly invasive compared to the relatively easy process of sperm donation. Obtaining eggs involves hormonal treatments to stimulate egg production and follicle puncture to retrieve the eggs, which carries risks such as ovarian hyperstimulation syndrome and damage to the ovaries and surrounding tissues. Given the potential harms and risks associated with egg donation, Carter questions why we should continue to accept it if AGs offer a safer alternative. Some might argue that there will still be individuals who prefer conventional egg donation due to the perceived "natural" nature of the resulting eggs compared to AGs [63, 64]. However, Carter counters this argument using the points raised earlier about naturalness, as summarized by Smajdor. In Carter's view, conventional egg donation should not be allowed if AGs exist, considering the risks and harms associated with the procedure. Carter also rejects the notion that individual preferences should dictate the acceptability of a procedure. Even if someone willingly chooses a clinical procedure like egg donation, which carries more risks than a safer alternative, they do not have the right to proceed. However, there is a scenario in which Carter would accept conventional egg donation over the derivation of artificial oocytes. If current procedures for egg donation were to evolve and become minimally invasive, with reduced risks and harms, then egg donation would hold a similar status to AG differentiation in terms of acceptability.

Regarding to indirect reproductive purposes due to the generation of AGs, Mattawanon and colleagues [65] highlight the potential role of AGs in fertility preservation. Procedures such as egg and sperm cryopreservation are currently used to preserve fertility in individuals who may face reproductive harm due to various treatments, such as chemotherapy for cancer patients or hormonal therapy for transgender individuals. However, if AGs can be derived from any biological source, such as a skin cell, there would be no need to continue relying on egg and sperm cryopreservation. One of the ethical concerns surrounding gamete cryopreservation is related to the issue of consent [66–69]. When an individual decides to cryopreserve their gametes for future reproductive purposes, determining the duration of their consent becomes a challenge. If an individual later wishes to withdraw their consent, the cryopreserved gametes need to be either kept on hold or destroyed. However, with the development of AGs, the timeline for consent becomes significantly reduced. The generation of AGs allows for the possibility of obtaining gametes at the time of need, eliminating the need for long-term storage and potential conflicts regarding consent withdrawal. AGs could be derived when the individual is ready to proceed with reproduction, avoiding the ethical complexities associated with the duration of consent for cryopreserved gametes. This raises new ethical considerations and discussions regarding the use of AGs in fertility preservation, including the implications for informed consent, decision-making autonomy, and the future use of gametes for reproductive purposes.

This section delves into the normative frameworks proposed in the field of bioethics, analyzing their strengths and weaknesses. While previous authors have explored individual scenarios related to the use of AGs in reproduction, there is a need for a comprehensive framework that can encompass all these cases. This unified framework becomes particularly important as AG technology is not yet a reality for human use. Furthermore, it is anticipated that the use of AGs, especially when combined with other technologies like gene editing, may give rise to novel and unexpected reproductive scenarios in the future. One notable contribution is the global framework proposed by Gooßens, based on Robertson's theory of reproductive autonomy. However, this framework relies on vague concepts such as parenthood, as acknowledged by Gooßens. Additionally, Robertson's modern traditionalism faces challenges in addressing single reproduction while accepting single parenting, and it does not adequately address the genetic source of AGs. Other authors, such as Smajdor, have also made valuable contributions by carefully examining the role of AGs and raising moral questions regarding the personal and social value of reproduction. Their work provides a fertile ground for discussing the ethical implications of AGs.

## Conclusions

This study aims to comprehensively summarize the current state of biological development in human AGs and provide insights into the associated bioethical considerations. While AGs have evolved from conceptual ideas to tangible biological tools, primarily in non-human mammals, successful translation to humans remains elusive. Despite challenges,

ongoing efforts suggest the potential emergence of functional human AGs in the near future, necessitating timely bioethical discussions on reproductive implications. In the realm of bioethics, scholars like Gooßens and Smajdor propose normative frameworks based on the Principle of Reproductive Autonomy, emphasizing aspects like consent and bodily integrity. However, these frameworks may lack comprehensive coverage, particularly regarding the genetic origin of AGs. Universal normative frameworks gain significance in evaluating complex cases involving the integration of AGs with techniques like gene editing, as suggested by certain authors. The bioethical discourse extends beyond normative frameworks, raising new moral questions concerning reproduction.

In conclusion, as AG generation advances, addressing associated bioethical considerations becomes imperative. While normative frameworks provide a foundation, further exploration is required to encompass all pertinent factors. Ongoing bioethical discussions contribute to an expanding dialogue on the morality of reproduction, fostering a nuanced understanding of the ethical implications involved.

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