

Potential consequences of clinical application of artificial gametes: a systematic review of stakeholder views

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Potential consequences of clinical application of artificial gametes: a systematic review of stakeholder views

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BACKGROUND: Recent progress in the formation of artificial gametes, i.e. gametes generated from progenitors or somatic cells, has led to scientific and societal discussion about their use in medically assisted reproduction. In animals, live births have already been achieved using artificial gametes of varying (cell type) sources and biological research seems to be progressing steadily toward clinical application in humans. Artificial gametes could potentially help not only infertile heterosexual couples of reproductive age of which one or both partners lacks functional gametes, but also post-menopausal women and same-sex couples, to conceive a child who will be genetically related to them. But as clinical application of these new technologies may have wider societal consequences, a proactive consideration of the possible impact seems timely and important. This review aims to contribute to this by providing a systematic overview of the potential consequences of clinical application of artificial gametes anticipated by different stakeholders.

METHODS: The electronic database 'Medline/Pubmed' was systematically searched with medical subject heading terms (MeSH) for articles published in English between January 1970 and December 2013. Articles were selected based on eligibility and reference lists of eligible studies were hand searched. The reported potential consequences of clinical application of artificial gametes were extracted from the articles and were grouped into categories by content analysis. Per category, we noted which stakeholders referred to which potential consequences, based on author affiliations and, if applicable, study participants.

RESULTS: The systematic search yielded 2424 articles, and 84 studies were included after screening. Nine positive consequences, 21 specific consequences requiring consideration and 22 recommendations referring to clinical application of artificial gametes were documented. All positive consequences, consequences requiring consideration and recommendations could be categorized under the following eight objectives to be safeguarded during clinical application of artificial gametes: (i) timing the implementation of new treatments correctly, (ii) meeting 'plausible demands of patients', (iii) improving and safeguarding public health, (iv) promoting the progress of medical science in the interest of future patients,

(v) providing treatments that are morally acceptable for the general public, (vi) controlling medical practice, (vii) offering treatments that allow acquisition of informed consent and (viii) funding treatments fairly. Professionals specialized in biomedical science, science journalists and professionals specialized in ethics all addressed these eight objectives on artificial gametes, whereas professionals specialized in law or political science addressed seven objectives. Although one study reported on the perspective of parents of under-aged patients on three objectives, the perspectives of patients themselves were not reported by the reviewed literature.

CONCLUSION: Of course, clinical introduction of artificial gametes should only be considered on the basis of reassuring outcomes of appropriate preclinical effectiveness and safety studies. In addition, potential users' views on the desirability and acceptability of artificial gametes should be studied before clinical introduction. A societal debate including all stakeholders is needed to determine the relative importance of all arguments in favor of and against the introduction of artificial gametes into clinical practice. More broadly, establishing pre-implementation processes for new medical techniques is relevant for all fields of medicine.

Key words: artificial gametes / gametogenesis / assisted reproductive technologies / ethics

Introduction

Medically assisted reproduction (MAR) for four groups of patients is currently dependent on donor material: heterosexual couples of reproductive age where one or both partners do not have functional gametes (either congenital or acquired), couples in which the woman is postmenopausal, same-sex couples and singles. Male same-sex couples and single men additionally need to resort to using a gestational carrier.

Although the use of donor material contributes to reproductive medicine's ability to fulfill patients' wish for a child, it does not result in genetic parenthood for both partners, and donor material (especially oocytes) is scarce. Although the importance of genetic parenthood is debated (e.g. donor conception does not appear to have a negative impact on parent-child relationships or the psychological well-being of mothers, fathers or children; [Golombok et al., 2006, 2013](#)), parents-to-be value achieving genetic parenthood for both partners ([Mertes and Pennings, 2008](#); [Hendriks et al., 2014](#)).

Current MAR, relying either on patients' own gametes or on donor gametes, will not result in the birth of a child for about one-third of the estimated 40.5 million infertile women currently seeking medical care ([Boivin et al., 2007](#); [Pinborg et al., 2008](#)).

In the near future, MAR could potentially rely on 'artificial gametes', i.e. gametes generated from progenitors or somatic cells. The use of artificial gametes could contribute to the birth of genetically their 'own' children in heterosexual couples with all sorts of fertility problems, and, if reprogramming cells to the other sex becomes an option, it could also help same-sex couples to conceive a child of which both partners are genetic parents. If such reprogramming is not possible, the use of artificial gametes may still add to the reproductive options of same-sex couples with a fertility problem.

A systematic overview of the progress toward clinical applications of biological research on animal and human artificial gametes has recently been conducted ([Hendriks et al., 2015](#)). Different theoretically plausible routes to create artificial gametes were classified based on their biological starting point, including: (i) patients' germ-line stem cells (GSCs, i.e. the natural precursors of gametes), (ii) patients' induced pluripotent stem cells (iPSCs, i.e. cells capable of differentiating into a variety of cell types that result from reprogramming patients' somatic cells), (iii) somatic cell nuclear transfer (SCNT) to embryonic stem cells (ESCs, i.e. patient's somatic nucleus transplanted into an enucleated donor ESC) and (iv) SCNT to donor oocytes (i.e. patient somatic cell nucleus transplanted into an enucleated donor oocyte; this can only lead to the

generation of artificial oocytes). All four starting points may be used to generate artificial gametes *in vitro* that can be used for ICSI. GSCs, iPSCs and ESCs can after *in vitro* generation (iPSCs and ESCs) or *in vitro* proliferation (GSCs) theoretically be autotransplanted into the testicles or the ovaries of the patient at a GSC stage, after which further differentiation into functional gametes takes place *in vivo*, allowing for conception to occur via sexual intercourse and in essence curing infertility. For several of these theoretically plausible routes to create artificial gametes, live births in animals provided proof of principle and human artificial oocytes and sperm have been created. These findings should, however, for several reasons, be considered as preliminary evidence for possible future clinical applications of artificial gametes in humans. More specifically, the following has not unambiguously been proven: functionality of the human artificial sperm and oocytes, chromosomal and epigenetic normality of the animal and human artificial gametes, and the viability and long-term health of artificial gamete-derived animal offspring. Furthermore, the previous biological findings are yet to be validated by different research groups repeating the experiments and enhancing the efficiency of the biological techniques. The pace of scientific progress, and therefore, the timeframe of clinical applications of artificial gametes in humans is difficult to predict ([Hixon Group, 2008](#)).

Reproductive medicine, led by perceived patients' demands, profit and scientific curiosity, is notorious for its (too) rapid implementation of innovations, without sufficient effectiveness and safety assessments ([Steele et al., 1999](#); [Leese and Whittall, 2001](#); [Schatten, 2002](#); [Winston and Hardy, 2002](#); [van Steirteghem, 2008](#); [Dondorp and De Wert, 2011](#); [Harper et al., 2012](#)). However, for responsible innovation in this field, it is not only important that there is sufficient evidence of effectiveness and safety, but also that the wider possible consequences for individuals and society have been considered proactively, in order to inform adequate policy making. This seems especially important with regard to artificial gametes, as this technology has the potential to further bring down natural barriers to human reproduction.

This review aims to provide a systematic overview of the potential consequences of clinical application of artificial gametes anticipated by different stakeholders.

Methods

Search strategy

The electronic database MEDLINE was systematically searched with the search engine PubMed using the following medical subject heading terms

(MeSH-terms): 'cell differentiation', 'cells, cultured', 'cell culture techniques', 'cytoplasm/transplantation', 'diploidy', 'DNA, mitochondrial', 'embryonic stem cells', 'embryo transfer', 'female', 'fertilization', 'genotype', 'germ cells', 'germ cells/cytology', 'haploidy', 'human reproduction, assisted', 'meiosis', 'microinjections', 'micromanipulation', 'nuclear transfer techniques', 'oocytes', 'oocytes/cytology', 'oocytes/physiology', 'oocytes/transplantation', 'oogenesis', 'oogonia/cytology', 'pluripotent stem cells', 'pregnancy', 'pregnancy outcome', 'reproductive techniques, assisted/ethics', 'reproductive techniques/ethics', 'spermatogenesis', 'spermatogonia/cytology', 'spermatozoa/cytology', 'stem cells/cytology' and 'stem cells/metabolism'. The reference lists of the eligible articles were subsequently hand searched (i.e. snowball strategy).

Article selection

Articles on artificial gametes, published in English between January 1970 and December 2013, were considered for inclusion by screening their titles, abstracts and if necessary full-text reports. All types of articles were included (e.g. original non-biological research, reviews, opinion articles or debates) except for studies with a focus on original biological research.

Meta-synthesis

Given the nature of the collected data, meta-synthesis, rather than meta-analysis, was performed. Two reviewers performed all steps of data collection and analysis independently, using a standardized data extraction sheet and discussing any discrepancies until consensus was met.

Potential consequences of future clinical application of artificial gametes

To structure the literature on the perspectives of different stakeholder groups on the potential consequences of the clinical application of artificial gametes, we differentiated between reported positive consequences, consequences requiring consideration (i.e. some of the authors feel that these consequences require consideration as they expect or cannot exclude negative consequences) and recommendations for preventing negative consequences. The specific positive consequences, consequences requiring consideration and recommendations for preventing negative consequences were inductively (i.e. from specific to general rather than deductively which works from general to specific; [Elo and Kyngäs, 2008](#)) grouped into categories by content analysis with constant comparison. This process involved the following consecutive steps: (i) multiple readings (i.e. to grasp the context), (ii) highlighting meaningful units, (iii) grouping meaningful units into categories and (iv) comparing meaningful units between categories in order to integrate categories (i.e. constant comparison; [Glaser, 1965](#); [Hycner, 1985](#); [Graneheim, 2004](#)). The content analysis was conducted by two reviewers independently, who, if necessary, discussed until consensus was met.

For each positive consequence, consequence requiring consideration or recommendation, the considering stakeholder group was specified based on the authors' affiliations of the articles describing them or, if relevant, based on study participants (e.g. parents of under-aged patients).

Ethical sensitivity depending on biological starting point and patient group

For each of the four biological starting points, GSCs, iPSCs, ESCs and enucleated donor oocytes ([Hendriks et al., 2015](#)), the relevance of each positive consequence, consequence requiring consideration and recommendation preventing negative consequences, was specified.

Six patient groups were differentiated based on the number of intended parents (single or couple), gender of both partners and infertility diagnosis of the intended parent(s) and included: (i) heterosexual couples lacking

functional male gametes, (ii) heterosexual couples lacking functional female gametes, (iii) lesbian couples desiring genetic parenthood for both partners, (iv) gay couples desiring genetic parenthood for both partners, (v) single infertile women using donor sperm and (vi) single infertile males using a donor oocyte and a surrogate (Fig. 1). For each of these patient groups, the relevance of each positive consequence, consequence requiring consideration and recommendation preventing negative consequences was specified.

The number of gametes that require the use of ethically sensitive donor material (none, for one of the partners, or for both partners) was specified for the 24 combinations of (six) patient groups and (four) biological starting points. Biological plausibility was based on a recent systematic review ([Hendriks et al., 2015](#)).

Results

The systematic search yielded 2424 articles (Fig. 2). Based on eligibility, 68 studies were included. Hand searches of the reference lists of these 68 articles, resulted in the inclusion of 16 additional articles. Thus, in total, 84 studies were included.

Included article types were: literature reviews ($n = 32$), opinion papers ($n = 16$), reports on scientific breakthroughs ($n = 15$), commentaries ($n = 7$), editorials ($n = 4$), debates ($n = 3$), other articles not reporting original data, e.g. correspondence ($n = 6$) and one retrospective cohort study on the attitudes toward fertility preservation of parents of children with cancer.

Meta-synthesis

Potential consequences of, and recommendations for, future clinical application of artificial gametes

Nine positive consequences, 21 consequences requiring consideration and 22 recommendations for preventing negative consequences of clinical application of artificial gametes were identified in our systematic search of the literature (Table 1). All positive consequences, consequences requiring consideration and recommendations for preventing negative consequences could be categorized into eight different objectives to be safeguarded during clinical application of artificial gametes: (i) timing the implementation of new treatments correctly, (ii) meeting 'plausible demands of patients' [i.e. these are demands reported by professionals, which are not (always) documented by research into the patients' perspective], (iii) improving and safeguarding public health, (iv) promoting the progress of medical science in the interest of future patients, (v) providing treatments that are morally acceptable for the general public, (vi) controlling the medical practice, (vii) offering treatments that allow acquisition of informed consent and (viii) funding treatments fairly. Of these eight objectives, one was only covered by positive consequences (i.e. promoting the progress of science), four were covered by both consequences requiring consideration and recommendations (e.g. 'improving and safeguarding public health') and three by all three (e.g. 'meeting plausible demands of patients').

Timing the implementation of new treatments correctly. The differences between animal models and human physiology, and thus the difficulty to predict the outcomes in humans despite solid animal studies were considered ($n = 6/84$). Furthermore, two types of pressures, which may push (premature) implementation, were specified: patients' eagerness ($n = 6/84$), and special interests of politicians ($n = 1/84$).

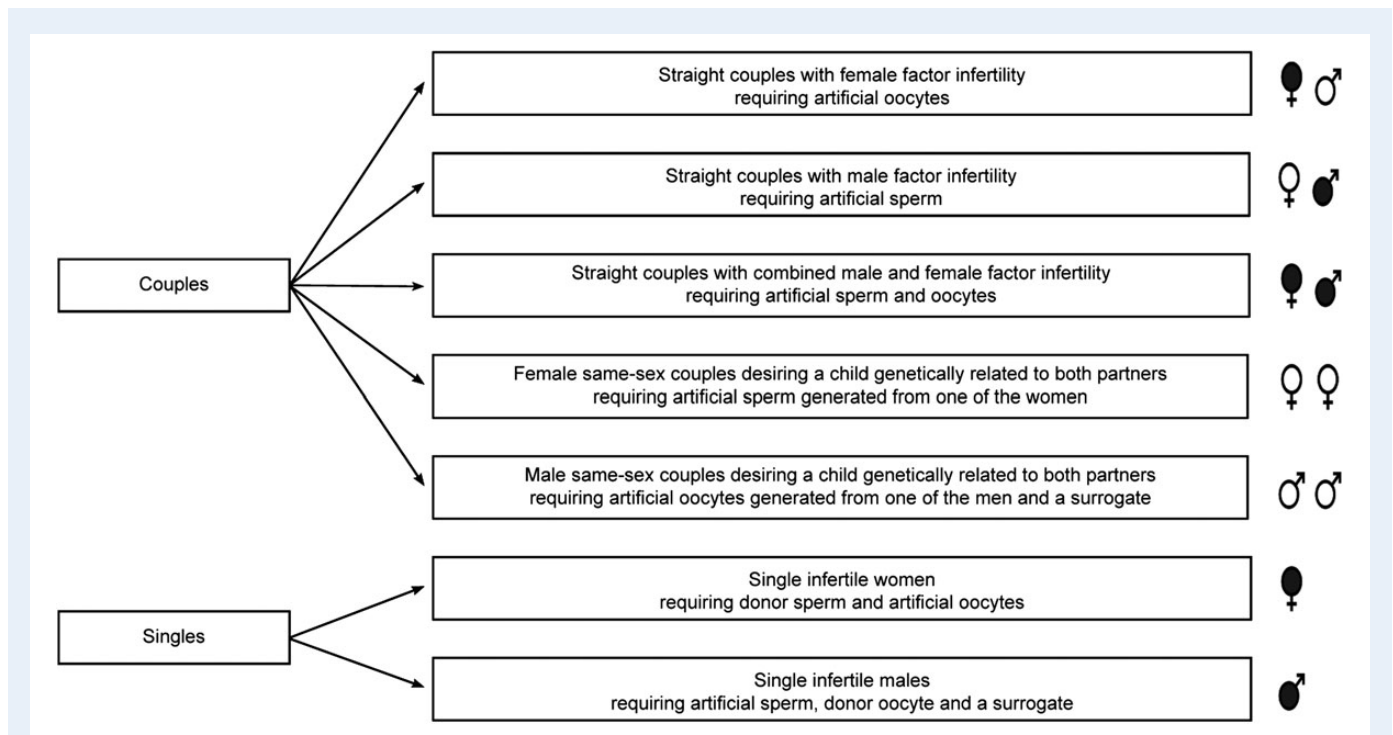


Figure 1 Potential patient groups treated with artificial gametes. ♀, fertile woman; ♀, infertile woman; ♂, fertile man; ♂, infertile man.

Consequently, it was recommended to perform (sufficient) preclinical research ($n = 83/84$). Moreover, making considerations timely was recommended (i.e. before implementation; $n = 15/84$).

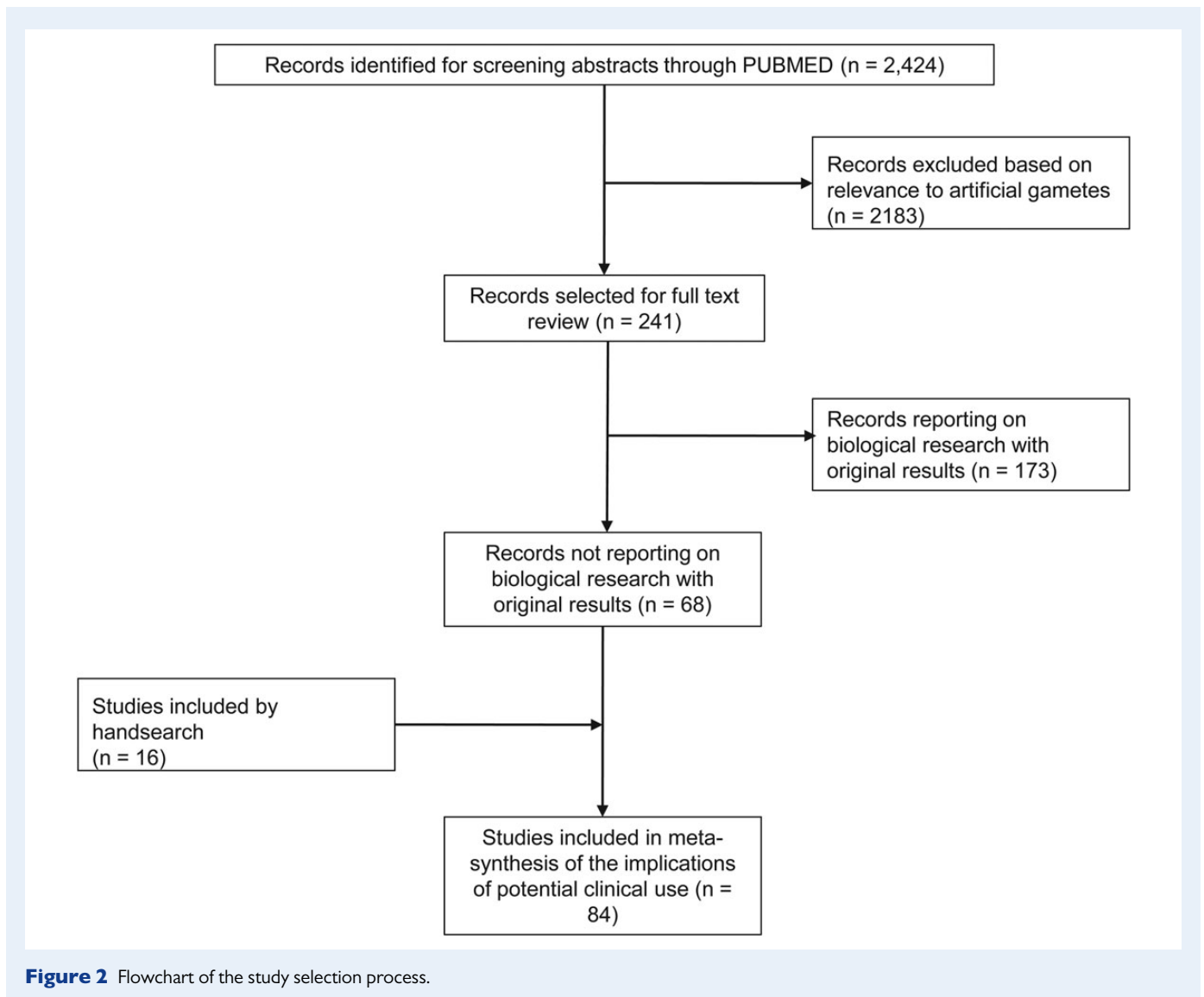
Meeting plausible demands of patients. The ability of artificial gametes to meet plausible demands of patients was reflected on. The most frequently reported positive consequence was treating infertile heterosexual couples in a way that allows genetic parenthood ($n = 72/84$). For instance, artificial gametes would allow individuals who lack gametes due to premature ovarian failure or non-obstructive azoospermia to conceive a child who will be genetically related to them. A special group of patients aided by artificial gametes are individuals threatened with infertility by an illness or by its treatment ($n = 29/84$, for example, childhood cancer survivors). Additionally, helping infertile patients to achieve genetic parenthood with the aid of artificial gametes could, as a positive side effect, increase job satisfaction of fertility clinic's healthcare providers ($n = 2/84$).

Some consequences of clinical application of artificial gametes relating to meeting plausible demands of patients require some consideration: (limited) success rates ($n = 41/84$), out-of-pocket costs ($n = 2/84$) and the balance between providing cancer patients with a positive prospect and burdening them with yet another decision ($n = 2/84$). Furthermore, the fact that clinical application of artificial gametes would offer ways to form unconventional families was considered. More specifically: male and female somatic cells might be successfully reprogrammed to form germ cells of the opposite sex providing opportunities for same-sex couples to have a child who will be genetically related to them ($n = 20/84$), and post-menopausal women might conceive children who will be genetically related ($n = 16/84$). For example,

Newson and Smajdor (2005) have called for reflection on whether a man whose DNA is contained in the egg will be recognized as the biological 'mother'? The most extreme possibility would be the conception of children with just one genetic parent that would deliver both the natural gamete and the artificial gamete ($n = 5$). Noticeably, although it can be seen as the 'ultimate incest', this would not create a clone of the genetic parent because through the process of gametogenesis the genetic material would be reshuffled, meaning for instance a man as single genetic parent can conceive a daughter. Respecting patients' reproductive liberty ($n = 11/84$) and discouraging discrimination was recommended ($n = 6/84$). For instance, the acceptability of a treatment should depend on (heterosexual and same-sex) couples' unfulfilled wish for a child rather than on their medical infertility cause (Master, 2006; Smajdor, 2008; Mertes and Pennings, 2010). Finally, protecting patients against false hope ($n = 4/84$) was recommended.

Improving and safeguarding public health. Two positive consequences of artificial gametes' clinical application for public health were identified. First, autotransplantation of oogonial stem cells (OSCs) could prevent the decrease in physical and mental well-being due to loss of ovarian function in aging women ($n = 2/84$). Second, the complications of IVF cycles for intended mothers could be circumvented by techniques using autotransplantation ($n = 1/84$). Finally, producing artificial gametes could provide training material for assisted reproductive technology (ART) professionals, resulting in better results in patients' ART cycles ($n = 1/84$).

Several public health-related consequences of clinical application of artificial gametes require consideration. The physical and psychological health of children conceived with artificial gametes should be considered ($n = 69/84$), as well as the physical health of infertile patients ($n = 20/84$),



which is for instance threatened by potential risk of re-introducing cancerous cryopreserved tissue in cancer survivors. Using artificial gametes, more children could be created than would have otherwise existed ($n = 4/84$) which was positively appraised as well as critically appraised in terms of overpopulation. Finally, the use of artificial gametes may lead to an increased prevalence of infertility in future generations by passing on genetic disorders of infertile patients to their children ($n = 2/84$).

Given the safety concerns, the following was recommended: prioritization of the health of mother and/or child ($n = 4/84$), creation and usage of artificial gamete screening techniques prior to inducing clinical pregnancy ($n = 3/84$) and insurance of proper follow-up of children conceived via artificial gametes ($n = 3/84$).

Promoting the progress of science. Artificial gametes would likely result in advancement of biological knowledge, which has both an intrinsic value ($n = 52/84$) and an instrumental value, in the sense that it may lead to other (clinical) applications ($n = 36/84$) for instance, new ways to prevent and treat infertility, genetic disease and some cancers (Hixon Group, 2008).

Providing treatments that are morally acceptable for the general public. Artificial gametes could provide an alternative to the use of donor gametes, which are scarce, result in burden for (and possible exploitation of) donors and raise several other ethical concerns ($n = 33/84$).

Several factors requiring consideration related to the societal acceptance of artificial gametes were reported. Accepting artificial gametes could start a 'slippery slope' to morally unacceptable applications ($n = 23/84$), for instance, applications leading to designer babies (embryo selection based on characteristics desired for non-medical reasons such as eye color; e.g. Mathews et al., 2009). Additionally, creating artificial gametes for clinical application (with the aid of SCNT in ESC) requires using human embryos, of which acceptability was considered doubtful in light of the moral status of embryos ($n = 21/84$). (Intuitive) Resistance against interference with natural reproduction was considered ($n = 9/84$). Finally, the fact that due to artificial gametes reproduction might no longer require men (gestation still requires women; $n = 1/84$) required consideration.

Regarding societal acceptance, the following actions (of which some mentioned by different articles cannot easily co-exist) were

Table 1 Stakeholder groups reporting on consequences of and recommendations for clinical application of artificial gametes sorted by objectives to be safeguarded during clinical application of artificial gametes

(Type of) Consequences or recommendations	Specific consideration or recommendation	Stakeholder groups that have reported the consequences and references for these reports ^a					Parents of under-aged patients (n = 1/84)
		Professionals in biomedical sciences (n = 57/84)	Professionals in (science) journalism (n = 17/84)	Professionals in ethics (n = 15/84)	Professionals in law (n = 4/84)	Professionals in political science (n = 1/84)	
Timing the implementation of new treatments correctly							
Consequences requiring consideration	Patients' eagerness may encourage (premature) clinical implementation (n = 6)	1, 14, 19, 22, 69		7, 14, 69			
	Differences between animal models and human physiology (n = 6)	5, 13, 45, 81	42		8		
	Special interests of politicians may unjustly affect implementation (n = 1)			16		16	
Recommendations	Perform (sufficient) preclinical research (n = 83)	1-5, 9, 10, 12, 13, 15, 17-26, 29, 30, 32, 33, 36-41, 43, 45, 48-50, 54-59, 62, 64-66, 68-72, 78, 79, 81-83	6, 11, 18, 27, 28, 42, 46, 50-53, 73-77, 80	7, 14, 16, 18, 31, 32, 34, 35, 44, 47, 50, 61, 63, 69, 70	8, 18, 60, 84	16	56
	Make considerations timely (i.e. before implementation) (n = 15)	5, 15, 18-20, 22, 32, 68, 69, 81	18, 76, 80	16, 18, 32, 47, 63, 69	18	16	
Meeting plausible demands of patients							
Positive consequences	Treating infertile heterosexual couples to allow genetic parenthood ^b (n = 72)	1, 3-5, 9, 10, 12, 13, 15, 17-23, 25, 26, 29, 30, 32, 33, 36-41, 43, 45, 48, 50, 58, 59, 62, 64-70, 72, 78, 79, 81-83	6, 11, 18, 28, 42, 46, 51, 52, 73-75, 77, 80	7, 16, 18, 31, 32, 34, 35, 44, 47, 61, 63, 69, 70	8, 18, 60, 84	16	
	Fertility preservation during illness (n = 29)	1, 2, 14, 17, 23-25, 29, 32, 36-40, 48, 57, 62, 66, 68, 71	28, 46, 51, 53, 74, 75	14, 32, 35	60		56
	Increasing the job satisfaction of health care providers (n = 2)	1, 19					
Consequences requiring consideration	Success rates (n = 41)	1, 10, 12-14, 17, 20-26, 29, 33, 39-41, 43, 45, 50, 55-57, 59, 62, 64, 65, 70-72, 78, 81	6, 42, 50, 51, 73	14, 16, 31, 35, 44, 50, 70	84	16	56
	Genetic parenthood for both partners of same-sex couples ^b (n = 20)	18, 19, 32, 37, 69, 70, 81	18, 42, 51, 77, 80	7, 16, 18, 31, 32, 34, 35, 44, 61, 69, 70	8, 18, 60	16	
	Genetic parenthood for post-menopausal women ^b (n = 16)	3, 4, 25, 30, 41, 45, 50, 71, 72, 79	11, 50, 52, 74	35, 44, 50, 61			
	One genetic parent that would deliver both the natural gamete and the artificial gamete (n = 5)	81		34, 44, 61	60		
	Personal costs (n = 2)	14, 81		14			
	Provides cancer patients with a choice regarding future child wish (n = 2)	14		14			56

Recommendations	Respect reproductive liberty (n = 11)	1, 22, 37, 50, 69, 70	50	7, 16, 31, 50, 63, 69, 70	60	16	
	Discourage discrimination (a.o. based on sexual orientation) (n = 6)	69, 70, 81		16, 35, 61, 69, 70		16	
	Protect patients against false hope (n = 4)	12-14, 25		14			
Improving and safeguarding public health							
Positive consequences	Prevent the decrease in physical and mental well-being due to loss of ovarian function in aging women ^b (n = 2)	71	74				
	Circumvent complications of IVF cycles ^b (n = 1)				35		
	Providing training material for ART (n = 1)				31		
Consequences requiring consideration	Health of children conceived with artificial gametes (n = 69)	1, 3-5, 9, 12-15, 17-23, 25, 29, 32, 33, 36-43, 45, 50, 54, 57-59, 62, 64-66, 68-72, 78, 79, 81-83	6, 11, 18, 28, 42, 46, 50, 51, 53, 73, 76, 77, 80	7, 14, 16, 18, 31, 32, 34, 35, 44, 47, 50, 63, 69, 70	8, 18, 60, 84	16	
	Physical health of infertile patient (n = 20)	1, 14, 18, 24, 25, 32, 48, 56, 57, 59, 69, 71, 79, 81, 83	18	14, 16, 18, 31, 32, 35, 44, 69	18, 84	16	56
	Creating more children than would have otherwise existed (n = 4)	19, 22		63	8		
	Increased prevalence of infertility and genetic mutations for future generations ^b (n = 2)	22, 81					
Recommendations	Prioritize health of mother and/or child (n = 4)	1, 14, 37, 39		14			
	Create and use screening techniques (n = 3)	14	42, 51	14			
	Ensure proper follow-up (n = 3)	4, 18, 32	18	18, 32	18		
Promoting the progress of science							
Positive consequences	Advancing biological knowledge (as intrinsic motivation; n = 52)	2, 4, 5, 9, 10, 12, 13, 15, 17, 18, 20-23, 25, 26, 30, 33, 36, 38, 41, 43, 45, 48, 50, 54, 55, 57, 62, 64, 66, 70, 78, 79, 81, 83	6, 11, 18, 27, 42, 50, 51, 73-75, 77	18, 31, 34, 44, 50, 63, 70	8, 18, 60		
	Advancing biological knowledge possibly leading to other (clinical) applications (n = 36)	2-4, 9, 10, 15, 18, 20-23, 25, 26, 33, 48, 50, 62, 64, 70, 78, 79, 81, 83	11, 18, 27, 42, 50-52, 73, 74, 76, 77	18, 31, 35, 44, 50, 63, 70	18, 60		
Providing treatments that are morally acceptable to the general public							
Positive consequences	Alternative for donor gametes ^c (n = 33)	1, 9, 10, 18, 20, 29, 32, 33, 38, 45, 50, 59, 64, 70, 72, 78, 81, 83	11, 18, 27, 42, 50, 51, 52, 76, 77	7, 18, 31, 32, 35, 44, 47, 50, 63, 70	8, 18, 60		

Continued

Table I Continued

(Type of) Consequences or recommendations	Specific consideration or recommendation	Stakeholder groups that have reported the consequences and references for these reports ^a					Parents of under-aged patients (n = 1/84)
		Professionals in biomedical sciences (n = 57/84)	Professionals in (science) journalism (n = 17/84)	Professionals in ethics (n = 15/84)	Professionals in law (n = 4/84)	Professionals in political science (n = 1/84)	
Consequences requiring consideration consideration	Slippery slope to morally unacceptable applications (n = 23)	1, 2, 18, 23, 25, 26, 32, 38, 41, 50, 57, 70, 81	18, 42, 50, 51, 77	7, 16, 18, 32, 35, 44, 50, 63, 70	8, 18, 60	16	
	Requires research on and/or destruction of human embryos which were never intended to become a child themselves ^c (n = 21)	1, 18, 23, 29, 32, 37, 38, 45, 50, 81	18, 42, 50, 52, 76, 77	7, 16, 18, 32, 35, 44, 47, 50, 63	8, 18	16	
	(Intuitive) resistance against interference with natural reproduction (n = 9)	1, 18, 69	18	7, 18, 31, 35, 44, 69	8, 18, 60		
	Reproduction no longer requires men ^{b,c} (n = 1)		77				
Recommendations	Further reflection on ethics (n = 35)	1, 2, 4, 9, 15, 18, 20, 22, 25, 32, 36, 37, 57, 67–70, 81	11, 18, 28, 73–76, 80	7, 16, 18, 31, 32, 35, 44, 47, 61, 63, 69, 70	8, 18, 60	16	
	Explore and take into account the perspectives of scientists, physicians, the general public, and policy makers (n = 14)	1, 15, 18–20, 25, 32, 36, 37, 81	18, 76	16, 18, 32	8, 18, 60	16	
	Provide proper information for the general public and clinicians (n = 8 and n = 1 respectively)	1, 18, 19, 25, 70, 71	18	18, 47, 70	18, 60		
	Prevent the birth of biological orphans ^c (n = 8)	32	11	7, 31, 32, 34, 35, 63	8		
	Discourage unjustified objections (n = 7)	19, 22, 32, 66, 70, 71		32, 35, 70			
	Respect culture and religion (n = 9)	14, 18, 37, 45	18, 77	14, 18, 31, 35, 44	18, 60		
	Discourage natural law objections (n = 5)	69, 70		31, 35, 69, 70	60		
	Discourage slippery slope arguments (n = 2)			35	60		
Controlling the medical practice							
Consequences requiring consideration	Centres in an unclear legal framework (n = 11)	1, 14, 22, 25, 66, 81		14, 16, 44, 61	8, 60	16	
Recommendations	Oversight by governmental/legal bodies (n = 23)	1, 14, 18, 19, 22, 32, 36, 37, 66, 69, 70	18, 19, 28, 42, 76, 80	7, 14, 16, 18, 19, 31, 32, 35, 61, 69, 70	8, 18, 19, 60, 84		
	Oversight by professional associations (n = 9)	1, 2, 18, 19, 22	18, 19, 28, 42, 52,	16, 18, 19	18, 19, 60	16	
	Identify appropriate oversight body (n = 5)	1, 19, 81	28, 75	19			
	Create flexible policy to accommodate rapid changes in technologies or moral values (n = 5)	1, 18, 37	18, 76	16, 18	18	16	

Offering treatments that allow acquisition of informed consent

Consequences requiring consideration	1, 14, 32, 33	42	7, 14, 32, 35	8
Recommendations	1, 14, 18, 24, 32, 56 (n = 10)	18	14, 16, 18, 32, 35	8, 18, 60

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Funding treatments fairly

Consequences requiring consideration	14, 22, 69, 81, 83	52	14, 35, 44, 61, 63, 69
Recommendations	1	1	16

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ART, assisted reproductive technologies.

^aNumbers indicate the appropriate reference (see Supplementary data).

^bRelevance of the item depends on the patient group for whom the artificial gamete is generated.

^cRelevance of the item depends on the biological starting point used to generate the artificial gamete.

recommended: (i) reflect further on ethics (n = 35/84); (ii) explore and take account of the perspectives of scientists, physicians, the general public and policy makers (n = 14/84); (iii) inform the general public (n = 8/84) and clinicians (n = 1/84), (iv) prevent the birth of biological orphans, considering the dignity of human procreation as children born using ESCs could be considered to have no (living) biological parents (n = 8/84); (v) discourage objections not based on data (e.g. in principle objections n = 7/84); (vi) respect culture and religion (n = 9/84; culture and/or religion might affect perspectives on artificial gametes in general, or on specific applications of artificial gametes, such as parenting by same-sex couples, or the use of human embryos for research); (vii) discourage natural law objections (e.g. artificial is intrinsically inferior to natural; n = 5/84) and (viii) discourage 'slippery slope' arguments (n = 2/84).

Controlling the medical practice. An aspect requiring consideration is that the legal framework for the clinical application of artificial gametes is unclear (n = 11/84). It is recommended to control the medical practice through governmental/legal bodies (n = 23/84), professional associations (n = 9/84) and/or to identify (which of the two is) the appropriate oversight body (n = 5/84). Furthermore, creating policies that are flexible to accommodate rapid changes in technologies or moral values is recommended (n = 5/84).

Offering treatments that allow acquisition of informed consent. The complexity of acquiring informed consent was considered (n = 8/84), for example, attaining informed consent from childhood cancer patients is difficult (e.g. Bahadur, 2004) and attaining informed consent from embryos serving as ESC donor is impossible (e.g. Mertes and Pennings, 2010). Steps to safeguard informed consent (n = 10/84) were recommended, for example, it was recommended to not use gametes derived from tissue sources from whom valid informed consent cannot be obtained (Mathews et al., 2009).

Funding treatments fairly. The costs of artificial gamete research and treatment were considered in light of societal distributive justice (n = 10/84). Moreover, actions to limit commercialization were recommended (n = 2/84).

Stakeholders reporting on each consequence of and recommendation for future clinical application of artificial gametes

The perspectives of the following stakeholders were represented in the 84 included articles: professionals specialized in biomedical sciences (n = 57/84), (science) journalists (n = 17/84), professionals specialized in ethics (n = 15/84), professionals specialized in law (n = 4/84), professionals specialized in political science (n = 1/84) and parents of under-aged patients (n = 1/84; Table I). Eight articles represent the perspective of more than one stakeholder group.

Table I documents the stakeholder groups reporting on consequences of and recommendation for clinical application of artificial gametes, sorted by the eight objectives to be safeguarded during clinical application of artificial gametes. All stakeholder groups, except for the two groups who were least often questioned (i.e. professionals specialized in political science and parents of under-aged patients), had addressed at least half of the positive consequences, at least half of the consequences requiring consideration and at least half of the recommendations. Overall, professionals specialized in biomedical sciences, (science) journalists and professionals specialized in ethics addressed consequences and/

or recommendations relevant to all the eight objectives to be safeguarded during clinical application of artificial gametes. Professionals specialized in law and professionals specialized in political science each addressed all except one objective (funding treatment fairly and promoting progress in science, respectively). The single study on the perspective of parents of under-aged patients only focused on consequences and/or recommendations relevant to three objectives (i.e. meeting plausible demands of patients, improving and safeguarding public health and offering treatments that allow acquisition of informed consent).

Relating consequences and recommendations to biological starting points and patient groups

Table 1 specifies for each of the consequences and recommendations for preventing negative consequences, whether it depends on the used biological starting point to create artificial gametes and whether it depends on the treated patient group.

The consequence requiring consideration related to research and/or destruction of human embryos and the recommendation to prevent the birth of biological orphans mainly applies to the biological starting point 'somatic cell nuclear transfer (SCNT) in donor embryonic stem cells'. The other techniques do not require embryos to create artificial gametes. However, preclinical safety studies in which human embryos are created using artificial gametes and then examined and discarded may still be a necessary element of the responsible development and introduction of those techniques.

Several other consequences and recommendations for preventing negative consequences depend on the patient group treated with artificial gametes. The following consequences of the future clinical application of artificial gametes are clearly relevant to specific patient groups: (i) being able to treat heterosexual couples confronted with male or female factor infertility within a normal reproductive age range, (ii) contributing to genetic parenthood for same-sex couples and (iii) contributing to genetic parenthood for post-menopausal women. Furthermore, the consequence that men will no longer be required for reproduction is relevant to the treatment of lesbian couples desiring genetic parenthood for both partners. The consequence requiring consideration that artificial gametes could increase the prevalence of infertility and genetic mutations in future generations is less applicable to gay couples than to heterosexual couples with proven infertility. Being able to prevent complications of IVF is relevant when the use of IVF is replaced by artificial gametes in infertile heterosexual couples or infertile single women. The positive consequence of being able to prevent the decrease in physical and mental well-being due to loss of ovarian function in aging women is relevant to infertile women treated with autotransplantation of germ-line stem cells.

Finally, the provision of artificial gametes as an alternative to donor gametes depends both on the biological starting point and on the treated patient group: more specifically, it applies to creating artificial gametes from patients' GSCs or patients' iPSCs, for couples that do not require additional donor material. However, the reasons for individual couples preferring non-donor gametes may vary, for instance, a couple that is opposed to the idea of involvement of the donor in their child's life may not oppose the use of donor ESCs.

Discussion

As biological research into artificial gametes seems to be progressing steadily toward clinical application, this systematic review on the

potential consequences of their clinical application is timely and relevant to all MAR' professionals. To our knowledge, no previous review was dedicated to systematically synthesizing the perspectives of different stakeholders on potential consequences of the clinical application of artificial gametes.

The potential consequences of clinical application of artificial gametes and recommendations preventing negative consequences were mainly reported by biomedical professionals ($n = 57/84$). The perspectives of other professionals (e.g. ethicists) or parents of under-aged patients were reported less often (17/84 or 1/84 articles, respectively). Strikingly, the perspectives of patients themselves were not reported by the reviewed literature.

Several challenges had to be overcome to apply this reviews' systematic rather than narrative approach in order to acquire a complete overview of the reported positive consequences, consequences requiring consideration and recommendations for preventing negative consequences of clinical application of artificial gametes.

First, the search strategy had to be very broad to identify articles covering different novel techniques. Our search had to rely on the snowball strategy for thoroughness because articles on artificial gametes are generally poorly indexed.

Second, risk of bias in the included studies could not be assessed, as both studies and a variety of other types of published articles were included and as there are no quality criteria for, for example, opinion papers.

Third, as for all meta-synthesis, synthesis required interpretation of authors' text by reviewers instead of combining quantified data. This built-in limitation, which could result in misinterpretation of the articles' message, was (partly) compensated for by using two reviewers who independently extracted and synthesized the data and discussed discrepancies until consensus was met.

Fourth, it is unlikely that this review anticipates all possible consequences as research on artificial gametes is still in a preclinical phase and it is difficult to obtain a full overview of all possible consequences.

Finally, although we quantified for each stakeholder group how often they reported on each specific consequence or recommendation, this quantification is linked to the frequency with which the stakeholder groups' perspectives have been reported and is not to be confused with a prescriptive claim of which arguments are ethically more sound or of higher weight than others.

The Results section of this review serves descriptive ethics by summarizing and quantifying anticipated consequences and recommendations. In this Discussion, we will provide a brief evaluation of the most frequently cited positive consequences and recommendations as they are central arguments in the debate on artificial gametes. We will do so by comparing artificial gametes with currently available ART, by referring to consensus papers and the most recent evidence, and by reflecting on (the establishment of) the relative weight of the positive consequences, and alternative threats that might result from not following recommendations. The aim is to contribute to the development of ethically sustainable recommendations that will help public policy of our democratic, pluralist society to build on rational arguments valid to all interested parties.

The recommendation that there should be (sufficient) preclinical research focused on, amongst others, effectiveness and safety has indeed been considered a requirement for the responsible introduction of new reproductive technologies (Dondorp and de Wert

2011; Harper *et al.*, 2012; Provoost *et al.*, 2014). As insisted in the Hinxton consensus statement on artificial gametes, this may require creating human embryos for research (Hixon Group, 2008). In several European countries including those that have ratified the European Convention on Human Rights and Biomedicine, this form of embryo research is, however, forbidden. This hurdle for preclinical research does not seem to be based on sound ethical reasoning. If the (low) moral status of the early human embryo does not prohibit the deliberate creation of supernumerary embryos in IVF, nor the subsequent use of such left over embryos in research, it is difficult to see why creating embryos for research (under certain conditions) should not be acceptable (Health Council, 1998; Devolder, 2005). Prohibiting the creation of human embryos for research after having received informed consent of the gamete donors might result in skipping important preclinical safety studies and thus exposing (parents and) children to unnecessary risks (McLaren, 1989). Obviously, the acceptability of creating embryos for research also depends on whether the autonomy and health interests of the women and men who would donate the necessary gametes is sufficiently guaranteed. Still, despite all possible preclinical steps, safety can only be established with certainty after the results of a step-wise introduction into clinical practice are gathered. Finally, it is unclear which exact level of increased risk is acceptable and who (politicians, physicians, patients or society) should define these thresholds. For, for example, the slightly higher risk of birth defects with IVF/ICSI did not prevent patients and physicians from, respectively, undergoing or prescribing these treatments (Wen *et al.*, 2012).

The most cited advantage of the clinical application of artificial gametes was providing a treatment option helping infertile heterosexual couples conceive their genetically 'own' child. As an extension to the present artificial reproductive technologies, this application does not in itself seem to raise any new questions. As was the case with the introduction of ICSI in the 1990s, the improvement would consist in helping couples achieve genetic parenthood for both partners, instead of a donor-conceived child, to which only one of them would be a genetic parent. The value of the genetic link between parents and children has been taken for granted in the field of assisted reproduction. Although some commentators argued that it is irrational to prefer a genetically 'own' child over a donor-conceived child (Mertes and Pennings, 2010), the treatment choices of fertility patients show that this preference is in fact widespread and strongly held on to. For example, if donor conception is the only option, some couples deliberately choose a known donor over an anonymous donor because of 'fear of genetic material of unknown origin' (56%) and 'the genetic link between the donor and themselves' (33%) (Baetens *et al.*, 2000). The reasons for valuing genetic parenthood so highly may be sought in couples expecting shared genetic parenthood to give proof of their relationship and to result in shared responsibility for the well-being of the child. Moreover, as donor-anonymity is no longer possible in many countries and cannot be guaranteed in other countries (Borry *et al.*, 2014), couples may regard the prospect of contact between the child and the donor a threat to their family life (Nuffield Council, 2013).

The positive consequences were identified that artificial gametes may lead to the advancement of biological knowledge and, subsequently, to other clinical applications. However, for a number of research purposes previously ascribed to be studied with artificial gametes, iPSCs are currently a more logical source of further knowledge; therefore, the value

of artificial gametes in the advancement of biological knowledge has decreased when compared with when some of the included articles were written. Using artificial gametes is, nevertheless, likely to result in other biological knowledge than using iPSCs and is therefore still relevant.

Several stakeholders commented on the societal acceptability of artificial gametes in general and on specific forms and/or uses of them, but this should be placed in perspective. Whether a practice is morally problematic does not depend on whether it is problematized or condemned by some stakeholders. For example, (intuitive) resistance against interference with natural reproduction is not as such a sound ethical argument. Public policy in a democratic, pluralist society, should build on rational arguments that can in principle be recognized as valid by all stakeholders. For example, the fact that genetic parenthood for both partners of same-sex couples would not be in the interest of the child is a morally relevant consideration, but as evidence shows that children of lesbian couples are doing well (Golombok *et al.*, 2013), the 'welfare of the child' argument cannot be used to limit lesbian couple's reproductive freedom (Pennings, 2011). In order to ethically assess the impact of other specific applications of artificial gametes, more empirical research will be needed. Furthermore, whether donor conception or using artificial gametes is morally acceptable as a way of helping people to have children depends on whether conditions can be put in place that sufficiently safeguard the interests of all persons involved (ESHRE, 2002; De Wert *et al.*, 2014). For certain possible applications of artificial gametes defining specific conditions for acceptability might require further discussion and assessments of the balance of possible benefits and harms. As described, the required monetary investments also incite a distributive justice question, wherein the advantages of artificial gametes should be weighted against investing money in other important healthcare needs. Therein, the importance of a genetic link between parents and children plays a central role. The societal debate on how much a country is willing to spend on research and clinical application of artificial gametes depends on (cultural) differences in weighting the importance of the different consequences, and, for example, influenced by a country's wealth and whether local religion and/or culture allows donor conception (e.g. Saudi Arabia). The societal debate on the importance of genetic parenthood should also take account of the local scarcity of donor gametes (especially oocytes) and the risks of donor exploitation related to cross border reproductive travel (Pennings *et al.*, 2008). Considering the gathered data on the societal acceptability of artificial gametes, it seems that fertility restoration in heterosexual couples by autotransplanting precursors of artificial gametes into patients' testicles or ovaries is, for several reasons, likely to be the most widely accepted application of artificial gametes. It does not require using (e.g. ESCs) or creating (e.g. IVF) human embryos with a sensitive moral status or using donor gametes, and it may be regarded as interfering less with natural reproduction than other techniques because the child could be conceived spontaneously.

However, as these data could not be extracted from the included studies, future studies could explore the cultural/religious/moral beliefs and background considerations underlying the potential consequences of using artificial gametes, as identified by our review.

The reported reflection on the consequences of and recommendations for the clinical application of artificial gametes require defining a set of conditions to be met prior to clinical application of artificial gametes. A set of conditions is in place for the clinical application of

new drugs (e.g. of the Food and Drug Administration; [Hamburg, 2010](#)) and attention for the need to develop such a set of conditions for the clinical application of new techniques—in all fields of medicine—has been asked previously ([Antman et al., 2001](#); [Wilson, 2006](#)).

Conclusions

Based on our systematic review of the literature on the consequences of and recommendations for the clinical application of artificial gametes according to different stakeholders and on our own evaluation, we come to the following three conclusions.

First, more research is needed to get a complete picture of the views of all stakeholder groups, especially focusing on patients, on all positive consequences and all consequences requiring consideration of the potential reproductive use of artificial gametes.

Second, a societal debate with the input of all stakeholders, including patients, is needed to determine the relative importance both of the genetic link between parents and children and of the consequences of the clinical application of artificial gametes identified by this review. This debate should take account of how different applications of artificial gametes may serve the interests and needs of specific patient groups, should consider the proportionality of developing this technology in light of (financial and societal) costs and benefits and the balance of investing in other technologies and should aim at making recommendations that can in principle be recognized as valid by all interested parties based on understanding that the recommendation was the result of rational reasoning.

Third, if the reproductive use of artificial gametes is regarded as acceptable for specific applications, further conditions for the responsible development and introduction of this technology will have to be developed by professionals in close collaboration with other interested stakeholder groups. Crucially, the clinical introduction of artificial gametes should only be considered on the basis of reassuring outcomes of appropriate preclinical effectiveness and safety studies. Even so, balancing between erring on the side of caution ([Leese and Whittall, 2001](#)) and not paralyzing the benefits of innovation ([Sunstein, 2003](#)) is, and will remain, difficult.

Supplementary data

Supplementary data are available at <http://humupd.oxfordjournals.org/> online.

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Authors' roles

S.H. and E.A.F.D. contributed to the study design, execution, analysis, manuscript drafting and critical discussion. G.H. and S.R. contributed to the study design, manuscript drafting and critical discussion. G.W. and W.D. contributed to manuscript drafting and critical discussion.

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Conflict of interest

The author(s) report no financial or other conflict of interest relevant to the subject of this article.

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