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Enthusiasm, concern and ambivalence in the Belgian public's attitude towards in-vitro gametogenesis


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Abstract Given the controversial nature of research into in-vitro gametogenesis (IVG), this study set out to investigate the current attitudes towards IVG in the general Belgian population in order to anticipate potential future barriers and misunderstandings. A questionnaire was developed and incorporated into a web-based online survey and sent out to Belgians aged ≥ 18 years in September 2018 until a representative sample (by age, gender and region) of 1000 participants was reached. Respondents expressed an overall positive attitude towards IVG and its possible future applications, with the exception of the use of IVG in postmenopausal women. They were ambivalent about the importance of genetic parenthood and about the necessary experiments on animals and embryos to bring IVG to the clinic. While the willingness to accept greater risks for IVG than for other assisted reproductive technology treatments was low (17.5%), the use of spare in-vitro fertilization embryos to study those risks was acceptable for 55.8% of participants; embryo creation was acceptable for 38.1%; and experiments on mice and monkeys were acceptable for 45.3% and 30.4%, respectively. Finally, 85.6% of participants agreed that the Belgian Government should strictly regulate IVG. In conclusion, preclinical research into IVG and other reproductive technologies elicits a great diversity of attitudes towards the importance of genetic parenthood and the acceptability of embryo and animal research. There is a need for public dialogue on these topics. 

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Introduction

In past decades, the field of reproductive technology has witnessed huge scientific breakthroughs. One of the most

revolutionary projects is the production of sperm and egg cells from human stem cells in vitro, called 'in-vitro gametogenesis' (IVG). The production of functional human gametes *in vitro* would allow several downstream applications,

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and advance both fundamental research and reproductive opportunities in the field of assisted reproduction. Establishing genetic parenthood for those people who do not produce functional gametes (any more) or potentially for same-sex couples is considered an important aim of IVG (Hendriks et al., 2017; Mishra et al., 2018; Taelman et al., 2018). The derivation of gametes from stem cells, thus far only successful in mice, may also be realistically attainable for clinical use in human assisted reproduction (Mishra et al., 2018; Taelman et al., 2018). If IVG were to become sufficiently safe and successful in the future (which, it is granted, is a very big 'if'), it may open up the possibility of having genetically related offspring to a group of people for whom this is currently not an option (Hendriks et al., 2015). Parenting options could theoretically even be expanded to include postmenopausal, prepubertal, single, same-sex and multiplex genetic parenthood.

While most of the concern revolves around testing the safety and effectiveness of stem-cell-derived human gametes, exploring the ethical and societal implications of this technology could not be more timely. A study by Segers et al. (2017) investigated the moral acceptability and desirability of IVG, and how this maps on to the normative significance of satisfying the desire for genetically related offspring. Although some other studies have been conducted on the ethical implications of IVG, the attitudes of the general public towards IVG remain insufficiently explored. Hendriks et al. (2017) examined whether the acceptability of stem-cell-based fertility treatments (SCFT) to gynaecologists ($n = 179$) and to a representative sample of the Dutch population ($n = 1250$) depended on the indication for which they were used. The majority of the Dutch population accepted SCFT, once proven safe and effective, for six out of eight possible indications, namely female infertility in young heterosexual couples (94%), male infertility in young heterosexual couples (94%), unexplained infertility in young heterosexual couples (83%), female infertility in single women (69%), lesbian couples (68%) and gay couples (62%). A minority of the general public accepted SCFT for fertile women who want a child that is genetically only her own (27%), and for female infertility in heterosexual couples in which the woman is aged > 50 years (17%). Acceptance of SCFT was positively correlated with attaching low importance to religion, having progressive political preferences, not having a university degree, having experienced infertility, being a woman, being older and not being of European ethnicity. Other studies on the acceptability of IVG have focused almost exclusively on professionals' views (Hendriks et al., 2015).

This study aimed to examine the wider public perspectives on the desirability and acceptability of IVG, including attitudes towards assisted reproductive technology (ART); genetic parenthood; potential human genome editing options; regulation, benefits and risks of IVG; and different IVG scenarios.

Materials and methods

An online survey addressing the research questions was conducted by iVOX, a market research company, for a project by De Maakbare Mens ('The Makeable Human'), a non-

profit-making organization encouraging public dialogue on the societal impact of new medical technologies. There were 20 items on the questionnaire, of which 14 were sociodemographic (age, education, relationship status, parenthood status, etc.). The six items measuring respondents' attitudes were subdivided into 28 questions in total. The survey was held from 10 September to 17 September 2018 using existing panels of potential respondents who had previously agreed to receive survey invitations for which they may be eligible. Participation was voluntary and the questionnaire took an average of 8.5 min to complete. As a modest incentive for participation, iVOX offer a 10 EUR gift card to respondents who complete approximately 15 extensive surveys (or the equivalent thereof, e.g. 20 shorter surveys). A link to the questionnaire was sent out by e-mail to a sample of 3425 Belgian adults (i.e. age ≥ 18 years), stratified by gender, age, region and education, until a total of 1000 participants was reached. Sample results were weighted to match the target population on certain key demographic parameters as a way to compare the sample with the population as a whole (Greenberg and Weiner, 2014). For this weighting, the most recent official adult population target data of the Centre for Information on Media, Brussels were used. These demographic variables were region (Flanders; Brussels; Wallonia), age, gender (man; woman) and education (up to secondary-level education; higher education), with a maximum weight variable of 2.7%. In addition, the weighting was interlaced for the first three parameters, which means that, for example, within the group of women, the sample is representative for gender and region.

The questionnaire started with a brief and neutral explanation of some central concepts (stem cells, gametes, somatic cells, embryo) in laymen's terms (see online supplementary material), and a first general question to examine whether the respondents had ever heard of IVG. The second part of the questionnaire was designed to measure the respondents' attitudes towards ART and genetic parenthood in general, to be scored on a five-point Likert-type scale (totally agree, agree, neutral point, disagree and totally disagree). The respondents were also asked to rank four available options for helping infertile individuals in order of preference: psychological support; IVG; gamete donation; and support for adoption or foster care. This question included the possibility to indicate for each option whether they thought it was (un)acceptable. In the third part, respondents were asked about their perception of and attitudes towards the potential risks and benefits of IVG. Next, they were asked about their attitudes towards animal and embryo research for testing IVG, and five IVG scenarios. These scenarios comprised the use of IVG for: (i) heterosexual couples where the child is related to both parents; (ii) lesbian and (iii) gay couples conceiving a child who shares DNA with both parents; (iv) solo reproduction; and (v) postmenopausal women. A five-point Likert-type scale (from totally important to totally unimportant, and from totally agree to totally disagree) was used for all the statements, apart from a 'no opinion' option positioned next to the scale. The fourth part of the questionnaire measured the respondents' attitudes towards potential human genome editing options, with each statement scored on a five-

point Likert-type scale (totally acceptable, acceptable, neutral point, unacceptable and totally unacceptable), apart from a 'no opinion' option. The 'no opinion' option was included to prevent respondents with poor understanding of the statement from indicating the neutral position or a random answer. The reason why this section was included in the questionnaire was not so much because of the possibility that IVG may pave the way to germline genome editing (for a thorough discussion of this issue, see Segers et al., 2019b), but rather to compare attitudes towards IVG with attitudes towards other controversial hypothetical future ways of reproduction. The final part of the questionnaire measured sociodemographics, including respondents' religion, and whether or not they had children or wished for children. Respondents were also asked whether they had fertility problems and whether they knew significant others with fertility problems. There was no option in the questionnaire to elaborate on the motives for certain responses. The full questionnaire is added in the online supplementary material.

Responses to survey questions were analysed using descriptive statistics (SPSS Version 26; IBM Corp., Armonk, NY, USA). For all statements, all the variables were tested using Cramer's V (for categorical variables) or Kendall's tau (for age as a continuous variable) to analyse the significance of difference of distribution of (totally) agreeing respondents versus the remaining respondents. For categorical distinctions between respondents, percentages are mentioned throughout the manuscript (e.g. 'x% of men agreed, versus y% of women'). This is not the case for differences between respondents of different ages, as age was evaluated as a continuous variable rather than making age categories. Kendall's tau-b score for these correlations can be found in the tables. All correlations mentioned were statistically significant.

This study was approved by the Ethics Committee of Ghent University's Faculty of Arts and Philosophy.

Results

Sociodemographic characteristics

The unweighted characteristics of the 1000 participants are presented in Table 1. The respondents had a mean age of 50 years (range 19–91 years). The majority (61.7%) were Dutch-speaking and did not have a higher education degree (i.e. did not have a Bachelor's or Master's degree) (62.8%). Over half of the respondents (55.6%) indicated that they did not adhere to a denominative religion or life stance. Fifty-seven percent of the respondents indicated that they had genetically related children (57%). The majority of the respondents were heterosexual (93.2%), in a relationship (67.9%), and had no and had no current desire to have (more) children (83.5%). Most respondents (88.4%) did not have fertility problems, but half (49.5%) knew significant others with fertility problems.

The percentage of respondents who chose 'no opinion' as a response to the statements varied between 7.4% and 15.4%. The 'no opinion' responses were not included in the bivariate statistical analysis.

Attitudes towards ART and genetic parenthood

Almost one-third of the respondents (30%) mentioned that they had heard of the possibility to create gametes from stem cells (Table 1). When asked about the best way to assist people who lack viable gametes to have a child, most respondents considered IVG as the best of four options, followed by psychological support and gamete donation. Support for adoption or foster care was indicated as the least desirable option.

The majority (68.5%) of respondents thought that progress in medically assisted reproduction was a positive development, with significantly more women than men sharing this view (71.4% versus 65.5%; $P = 0.044$) (Table 2). Respondents with fertility problems had more positive attitudes towards progress in medically assisted reproduction (77.8%) compared with respondents without fertility problems (67.3%; $P = 0.022$).

One-quarter of the respondents (25.7%) believed that genetic parenthood is necessary for a good parent–child relationship, while approximately half of the respondents (48.4%) did not consider this as a required condition. Men were more inclined to think that genetic parenthood contributes to a good parent–child relationship than women (29.4% versus 22%; $P = 0.007$). Similarly, 29.1% of the respondents with a religious denomination indicated that a genetic relationship is necessary for a good parent–child relationship, compared with 23% of those without a denominative religion or life stance ($P = 0.030$).

Approximately two-thirds of the respondents (64.4%) indicated that a family made with the use of donor sperm or donor eggs is equally valuable as a family in which the child is genetically related to both parents. A significant difference was found between men and women: more women (69.6%) than men (59.1%) agreed that families with donor-conceived children are equally valuable as families with children who are genetically related to both parents ($P = 0.000$). Likewise, respondents with self-reported fertility problems compared with others (75% versus 63.1%; $P = 0.016$), and respondents without a religious denomination compared with those with a denominative religion or life stance (67.3% versus 60.6%; $P = 0.024$) had a more supportive attitude towards donor-conceived families. No significant differences were found for sexual orientation, relationship status and education.

The majority of the respondents (61%) thought it was acceptable for same-sex partners to have and raise a child together. However, 19.3% of respondents disagreed with this statement. Women thought this was acceptable significantly more often than men (72.3% versus 49.2%; $P = 0.000$), and non-heterosexual respondents found this acceptable significantly more often than heterosexual respondents (75% versus 60%; $P = 0.010$). Respondents without a denominative religion or life stance displayed a positive attitude towards same-sex parenthood more often than respondents with a denominative religion (67% versus 53.2%; $P = 0.000$). Younger respondents were more likely to accept this statement than older respondents (continuous variable; $P = 0.000$). Furthermore, a considerably higher proportion of respondents who reported fertility problems accepted

Table 1 Characteristics of the respondents.

Characteristic	Value
Gender	
Male	496 (49.6)
Female	504 (50.4)
Age (years)	50 ± 16.48 (19–91)
Language	
Dutch	617 (61.7)
French	378 (37.8)
Other	5 (0.5)
Education	
Secondary	628 (62.8)
Tertiary	372 (37.2)
Region	
Flanders	579 (57.9)
Wallonia	318 (31.8)
Brussels	103 (10.3)
Religion or life stance	
Religious denomination	444 (44.4)
No denominative religion or life stance	556 (55.6)
Family situation	
No children and no partner	230 (23)
No children and partner	166 (16.6)
Children related to the current partner of the respondent, not to the respondent	34 (3.4)
Children related to the respondent	570 (57)
Wish for children	
No or undetermined	835 (83.5)
Yes	165 (16.5)
Relationship status	
Single	321 (32.1)
In a relationship	679 (67.9)
Sexual orientation	
Heterosexual	932 (93.2)
Non-heterosexual (homosexual, bisexual, lesbian, other)	68 (6.8)
Self-reported infertility	116 (11.6)
Known infertility of significant others	495 (49.5)
Previously heard of IVG	300 (30)

For categorical variables, *n* (%) are presented. For the continuous variable age, mean ± standard deviation (range) is presented. The religion variable was recoded in two groups: 'religious denomination' (Christian, Jewish, Islamic) and 'no denominative religion or life stance' (religious but no specific religion, not religious or secular, those who don't know).

The education variable distinguishes two groups: respondents with a higher education beyond school (tertiary) and those without (secondary).

same-sex parenthood compared with people without fertility problems (75.2% versus 58.9%; $P = 0.001$).

Attitudes towards intervening in the genetic make-up of future children

Of all respondents with an opinion, 81% had a negative attitude towards tailoring physical characteristics (e.g. height or hair colour) of children according to their parents' wishes by adjusting their genes before birth (Table 3). Likewise, a majority (75.5%) rejected adjusting the genes of children before birth to improve other non-medical characteristics such as intelligence, strength or aggressiveness. In contrast, the attitudes of the respondents towards the option of

adjusting the genes of children before birth for health reasons (e.g. to correct disease-causing genetic mutations that would lead to Huntington's disease or Marfan syndrome) were more nuanced: >40% of respondents accepted this possibility while 34.9% did not. Finally, 73.1% of respondents indicated that cloning people who cannot have a genetically related child with their partner was unacceptable.

A significant correlation was found between the overall attitude towards these hypothetical human genome editing options and the respondent's gender. Men were significantly more accepting towards the human genome editing options to modify physical characteristics according to the wishes of future parents (12.1% versus 4.7%; $P = 0.000$), adjusting the genes of children before birth to improve non-medical

Table 2 General attitudes towards assisted reproductive technology and genetic parenthood ($n = 1000$).

	All respondents n (%)			Significant determinants
	(Totally) disagree	Neutral	(Totally) agree	
Progress in medically assisted reproduction is a positive development	92 (9.2)	223 (22.3)	685 (68.5)	Men: 65.5%; women: 71.4% ($P = 0.044$) Dutch: 71.8%; French: 63.8% ($P = 0.011$) Self-reported infertility: 77.8%; no self-reported infertility: 67.3% ($P = 0.022$)
A genetic relationship between parents and child is necessary for a good parent–child relationship	484 (48.4)	260 (26)	257 (25.7)	Men: 29.4%; women: 22% ($P = 0.007$) In a relationship: 27.7%; single: 21.5% ($P = 0.036$) Religious denomination: 29.1%; no denominative religion or life stance: 23% ($P = 0.030$) Age ($s-b = -0.019$, $P = 0.001$)
It is acceptable for same-sex partners to have and raise a child together	193 (19.3)	197 (19.7)	610 (61)	Men: 49.2%; women: 72.3% ($P = 0.000$) Dutch: 66.9%; French: 51.6% ($P = 0.000$) Religious denomination: 53.2%; no denominative religion or life stance: 67% ($P = 0.000$) Heterosexual: 60%; non-heterosexual: 75% ($P = 0.010$) Self-reported infertility: 75.2%; no self-reported infertility: 58.9% ($P = 0.001$) Age ($s-b = 0.192$, $P = 0.000$)
A family made with sperm or egg cells from a donor is equally valuable as a family where the child is genetically related to both parents	125 (12.5)	231 (23.1)	644 (64.4)	Men: 59.1%; women: 69.6% ($P = 0.000$) Dutch: 73.1%; French: 50.4% ($P = 0.000$) Religious denomination: 60.6%; no denominative religion or life stance: 67.3% ($P = 0.024$) Self-reported infertility: 75%; no self-reported infertility: 63.1% ($P = 0.016$) Age ($s-b = 0.076$, $P = 0.002$)

P -value based on Cramer's V (for categorical variables) and Kendall's $s-b$ (for age as a continuous variable) to analyse the significance of difference of distribution of (totally) agreeing respondents versus the remaining respondents. A 'no opinion' option was not included in this part of the questionnaire. The religion variable was recoded in two groups: 'religious denomination' (Christian, Jewish, Islamic) and 'no denominative religion or life stance' (religious but no specific religion, not religious or secular, those who don't know). The number of missing cases varied between 5 (language), 0–1 (sexual orientation), 0–1 (degree) and 0–1 (infertility).

characteristics of the children (e.g. intelligence, strength, aggressiveness, etc.) (17.7% versus 6%; $P = 0.000$), and reproductive cloning for people who cannot have a genetically related child of their own together with their partner (14.8% versus 9.8%; $P = 0.023$).

When compared with heterosexual respondents, considerably more non-heterosexual respondents accepted the option of adjusting the genes of children before birth to modify physical characteristics according to the wishes of future parents (16.9% versus 7.6%; $P = 0.008$), and the option of adjusting the genes of children before birth to improve non-medical characteristics of the child (22% versus 11.1%; $P = 0.026$). Younger respondents were more likely to accept the option of adjusting the genes of children before birth to improve non-medical characteristics of the

child than older respondents (continuous variable; $P = 0.001$).

Potential benefits of IVG

The number of 'no opinion' cases on all the questions regarding attitudes towards the potential benefits of IVG was higher than in other parts of the survey (range 11.0–15.5) (Table 4). The two potential benefits that were judged to be most important were the opportunity to have a genetically related child (important for 75.9%) and a better understanding of human reproduction (74%). Significantly more respondents with a religious denomination compared with those without one (80.6% versus 72.4%; $P = 0.004$) val-

Table 3 General attitudes towards human genome editing options ($n = 1000$).

	All respondents n (%)				Significant determinants
	(Fully) unacceptable	Neutral	(Fully) acceptable	No opinion	
Making children with specific physical characteristics (e.g. hair colour, height, etc.) according to the wishes of future parents by adjusting their genes before birth	750 (81.0)	100 (10.8)	76 (8.2)	74	Men: 12.1%; women: 4.7% ($P = 0.000$) In a relationship: 6.4%; single: 12.1% ($P = 0.004$) Dutch: 6.2%; French: 12% ($P = 0.002$) Heterosexual: 7.6%; non-heterosexual: 16.9% ($P = 0.008$) Age (s-b = 0.073, $P = 0.005$)
Making children with enhanced non-medical characteristics (e.g. more intelligent, stronger, less aggressive, etc.) by adjusting their genes before birth	697 (75.5)	117 (12.7)	109 (11.8)	77	Men: 17.7%; women: 6% ($P = 0.000$) In a relationship: 10.4%; single: 15% ($P = 0.045$) Dutch: 9.2%; French: 16.6% ($P = 0.001$) Heterosexual: 11.1%; non-heterosexual: 22% ($P = 0.026$) Age (s-b = 0.083, $P = 0.001$)
Making healthy children by adjusting their genes before birth	320 (34.9)	201 (21.9)	397 (43.2)	82	Dutch: 45.8%; French: 38.8% ($P = 0.036$)
Cloning people who cannot have a genetically related child together with their partner	667 (73.1)	134 (14.7)	112 (12.3)	88	Men: 14.8%; women: 9.8% ($P = 0.023$) Age (s-b 0.061, $P = 0.019$)

P -value based on Cramer's V (for categorical variables) and Kendall's s - b (for age as a continuous variable) to analyse the significance of difference of distribution of (totally) agreeing respondents versus the remaining respondents.

For statistical analysis, only the respondents with an opinion were included. The number of 'no opinion' cases varied between 74 (7.4) and 88 (8.8).

ued the opportunity to have a genetically related child. Notably, there was no significant difference between men and women, which contrasts with the findings above regarding the importance of a genetic link for a good family relationship and the value judgement of families with donor-conceived children, but is in line with previous findings regarding the importance of genetic parenthood (Gur-mankin et al., 2005; Hendriks et al., 2017, 2019). Another interesting finding is that more respondents without a higher education degree (76.9%) compared with those with a higher education degree (69.4%; $P = 0.015$) appraised the potential of research on IVG to better understand human reproduction.

Over half of the respondents (62.9%) considered it an important potential benefit of IVG that fewer people would have to rely on sperm or egg donation. Being in a relationship ($P = 0.000$) and not holding a higher education degree ($P = 0.032$) were positively correlated with this statement.

More than half of those surveyed (59.9%) judged the prospect of IVG resulting in more oocytes being available for scientific research to be an important advantage. Again, it is remarkable that those without a higher education degree (63.5%) pronounced more interest in scientific research on oocytes that would become available with IVG, compared with the respondents with a higher education degree (54.2%; $P = 0.009$). One hypothesis for why respondents with a college or university degree tended to judge potential benefits overall as less important than those without a college or university degree may be that they are more sceptical towards the potential of IVG to actually reach these goals.

In contrast to the positive attitudes mentioned above, only 31.5% of the respondents indicated that prolonging the reproductive lifespan of women would be an important benefit, while 47% explicitly indicated that this would not be an important benefit.

Table 4 Potential benefits of in-vitro gametogenesis (IVG) (*n* = 1000).

	All respondents				Significant determinants
	(Totally) unimportant	Neutral	(Totally) important	No opinion	
Fewer people would have to rely on sperm or egg donation	115 (13.4)	203 (23.7)	538 (62.9)	144	In a relationship: 66.8%; single: 54% (<i>P</i> = 0.000) Secondary education: 65.7%; higher education: 58.4% (<i>P</i> = 0.032) Age (<i>s-b</i> = -0.063, <i>P</i> = 0.020)
Research on IVG could lead to a better understanding of human reproduction	76 (8.8)	149 (17.2)	639 (74.0)	136	Secondary education: 76.9%; higher education: 69.4% (<i>P</i> = 0.015) Dutch: 76%; French: 69.9% (<i>P</i> = 0.048)
More people would have the opportunity to have a genetically related child	85 (9.6)	129 (14.5)	675 (75.9)	111	Dutch: 78.8%; French: 70.1% (<i>P</i> = 0.005) Religious denomination: 80.6%; no denominative religion or life stance: 72.4% (<i>P</i> = 0.004) Secondary education: 78.3%; higher education: 71.8% (<i>P</i> = 0.023)
Women do not have to hurry to have children before they become infertile	403 (47.0)	184 (21.4)	270 (31.5)	142	In a relationship: 28.9%; single: 37.3% (<i>P</i> = 0.015) Dutch: 23.8%; French: 46.3% (<i>P</i> = 0.000) Age (<i>s-b</i> = 0.057, <i>P</i> = 0.035)
More eggs would become available for scientific research	130 (15.3)	210 (24.8)	508 (59.9)	152	Secondary education: 63.5%; higher education: 54.2% (<i>P</i> = 0.009)

P-value based on Cramer's *V* (for categorical variables) and Kendall's *s-b* (for age as a continuous variable) to analyse the significance of difference of distribution of (totally) agreeing respondents versus the remaining respondents.

For statistical analysis, only the respondents with an opinion were included. The education variable distinguishes between two groups: respondents with a secondary-level education or less and respondents with a higher education. The religion variable was recoded in two groups: 'religious denomination' (Christian, Jewish, Islamic) and 'no denominative religion or life stance' (religious but no specific religion, not religious or secular, those who don't know).

The number of 'no opinion' cases varied between 110 (11.0) and 155 (15.5).

Attitudes towards IVG scenarios

Three in four respondents (77.9%) had a positive attitude towards the use of IVG for heterosexual couples to obtain a child related to both partners, whilst 9.3% of the respondents thought that this was unacceptable (Table 5).

Over half of the respondents had a positive attitude towards lesbian (60.7%) and gay (60.6%) couples conceiving a child who shared DNA with both partners by means of IVG. Almost one-quarter of the respondents judged the use of IVG for same-sex couples to be unacceptable (24.4% for lesbian couples and 25.3% for gay couples). Once more, more female respondents accepted the reproductive use of stem-cell-derived gametes for same-sex couples compared with male respondents (67.2% versus 54% for lesbian couples, *P* = 0.000; 66.2% versus 52.4% for gay couples, *P* = 0.000). Moreover, fewer respondents with a denominative religion or life stance agreed with the use of IVG for same-sex couples compared with those without a denominative religion (55.8% versus 64.4% for lesbian couples, *P* = 0.007; 54.1% versus 63.7% for gay couples, *P* = 0.004). Significantly more non-heterosexual respondents, respondents with fertility problems and younger respondents accepted the use of IVG for same-sex couples.

Half of the respondents (51%) expressed a positive attitude towards solo reproduction by means of IVG where the child is fully related to the parent (who would provide both the egg cell and the sperm cell), whilst one-third (30%) of respondents were not in favour of such a possibility. Female respondents were more likely to accept solo reproduction by means of IVG than male respondents (57.4% versus 44.4%; *P* = 0.000).

The attitudes towards the use of IVG for postmenopausal women differed considerably from the four former scenarios, as the majority of respondents (62.7%) did not accept the possible use of IVG for older women. More female respondents accepted the four former scenarios, while in this scenario, male respondents were remarkably more positive than female respondents (21% versus 15.6%; *P* = 0.031). Interestingly, older respondents were less permissive towards the use of IVG for older women compared with younger respondents (continuous variable, *P* = 0.000). More single respondents accepted the use of IVG for postmenopausal women compared with respondents in a relationship (25% versus 15.2%; *P* = 0.000), and a considerably higher proportion of non-heterosexual respondents accepted the use of IVG for postmenopausal women compared with heterosexual respondents (30.5% versus 17.4%; *P* = 0.007).

Table 5 Attitudes towards in-vitro gametogenesis scenarios ($n = 1000$).

	All respondents				Significant determinants
	(Fully) unacceptable	Neutral	(Fully) acceptable	No opinion	
For heterosexual couples (man and woman) to conceive a child that is genetically related to both partners	86 (9.3)	118 (12.8)	717 (77.9)	79	Dutch: 80.6%; French: 72.2% ($P = 0.010$) Age (s-b = 0.053, $P = 0.042$)
For single persons who want a child without the support of a donor, the child is 100% genetically related to the parent	271 (30.0)	172 (19.0)	461 (51.0)	97	Men: 44.4%; women: 57.4% ($P = 0.000$) Dutch: 54.1%; French: 45.6% ($P = 0.017$)
For lesbian couples to conceive a child that is genetically related to both partners (by converting a body cell of the female partner into a sperm)	222 (24.4)	135 (14.9)	551 (60.7)	92	Men: 54%; women: 67.2% ($P = 0.000$) In a relationship: 58.2%; single: 66% ($P = 0.029$) Dutch: 64.1%; French: 54.4% ($P = 0.005$) Religious denomination: 55.8%; no denominative religion or life stance: 64.6% ($P = 0.007$) Heterosexual: 59.8%; non-heterosexual: 74.6% ($P = 0.038$) Self-reported infertility: 71.6%; no self-reported infertility: 59.3% ($P = 0.019$) Age (s-b = 0.159, $P = 0.000$)
For gay couples to conceive a child that is genetically related to both partners (by converting a body cell of the male partner into an egg)	231 (25.3)	139 (15.2)	554 (60.6)	86	Men: 52.4%; women: 66.2% ($P = 0.000$) In a relationship: 56.7%; single: 65.7% ($P = 0.013$) Dutch: 62.5%; French: 54% ($P = 0.015$) Religious denomination: 54.1%; no denominative religion or life stance: 63.7% ($P = 0.004$) Heterosexual: 58.5%; non-heterosexual: 74.1% ($P = 0.024$) Self-reported infertility: 71.2%; no self-reported infertility: 57.9% ($P = 0.008$) Age (s-b = 0.175, $P = 0.000$)
For older women couples to conceive a genetically related child after menopause	571 (62.7)	173 (19.0)	166 (18.2)	90	Men: 21%; women: 15.6% ($P = 0.031$) In a relationship: 15.2%; single: 25% ($P = 0.000$) Dutch: 15%; French: 23.9% ($P = 0.001$) Heterosexual: 17.4%; non-heterosexual: 30.5% ($P = 0.007$) Age (s-b = 0.139, $P = 0.000$)

P -value based on Cramer's V (for categorical variables) and Kendall's s-b (for age as a continuous variable) to analyse the significance of difference of distribution of (totally) agreeing respondents versus the remaining respondents. For statistical analysis, only the respondents with an opinion were included. The religion variable was recoded in two groups: 'religious denomination' (Christian, Jewish, Islamic) and 'no denominative religion or life stance' (religious but no specific religion, not religious or secular, those who don't know). The number of 'no opinion' cases varied between 74 (7.4) and 98 (9.8).

Attitudes towards regulation, potential risks of IVG, and animal and embryo research for testing IVG

The majority (84.6%) of respondents judged it unacceptable to use IVG when there is a high risk to the future offspring's health (Table 6). Significantly more single respondents compared with those in a relationship (7.5% versus 3%; $P = 0.002$), and more respondents with a higher education degree compared with those with a secondary-level education or less found a higher risk acceptable (6.4% versus 3.4%; $P = 0.035$).

When IVG was the only chance of having a genetically related child, a minority of the respondents (17.5%) found increased risk for the child acceptable, while more than half (58.2%) did not. More men compared with women (20.9% versus 13.9%; $P = 0.080$) thought increased risk for the child was acceptable.

More than one-third of the respondents considered it unacceptable to create human embryos to derive gametes (37.1%) or to investigate the risks of IVG (37.5%). Older respondents were slightly more disapproving compared with younger respondents (continuous variable; $P = 0.000$). In contrast, when questioning the respondents' attitudes towards the use of human embryos that remain after fertility treatment to investigate the risks of IVG, more respondents were in favour (55.8%). Significantly, more respondents with fertility problems compared with those without fertility problems (64.6% versus 54.6%; $P = 0.045$) accepted this, but again, older respondents were more disapproving towards this use of human embryos compared with younger respondents (continuous variable; $P = 0.001$).

Concerning animal research to test IVG, experiments on monkeys were tolerated by fewer people than experiments on mice (30.4% versus 45.3%). Men were twice as likely to accept experiments on monkeys compared with women (40.4% versus 20.4%; $P = 0.000$). Regarding experiments on mice, respondents in a relationship had a more positive attitude compared with single respondents (48.6% versus 38.2%; $P = 0.04$), and more respondents with a higher education degree had a positive attitude compared with respondents without a higher education degree (52% versus 41.3%; $P = 0.020$).

The majority of respondents thought that the government should strictly regulate the application of IVG (85.6%), but at the same time, half of the respondents agreed that the government should invest to make IVG accessible to everyone who needs it (49.8%).

Discussion

In academic literature, one can find several authors explicitly stating that researchers are developing human IVG in response to people's desire to have genetically related offspring (Taelman et al., 2018). This tallies with the present finding that the large majority of the respondents considered offering more people the opportunity to have a genetically related child to be the most important motivation for IVG (75.9%). Also, just over half of the respondents in this study (62.9%) considered it an important potential benefit of IVG that fewer people would have to rely on sperm or egg donation. In itself, these findings do not say anything

about the value that these respondents attached to genetic ties in parent–child relationships, as their attitude may also be based, for instance, on how they evaluated the involvement of a third party in reproductive matters, or on other possible moral concerns regarding gamete donation (e.g. exploitation of egg donors). In this regard, Carter-Walshaw (2019) stated that oocyte donation would only be ethically justifiable in a very limited range of cases if IVG technology for reproductive purposes becomes safe, effective and inexpensive (given the invasiveness of the process of egg harvesting, and the risks and harms involved).

However, the present results regarding attitudes towards ART and genetic parenthood indicate that one-quarter of the respondents (25.7%) believed that genetic parenthood is necessary for a good parent–child relationship. In a recent discrete choice experiment on the relative importance of genetic parenthood (Hendriks et al., 2019), patients indicated that they would switch to a treatment that did not enable genetic parenthood in return for a child health risk reduction of 3.6%, a cost reduction of €3500, an ovarian hyperstimulation risk reduction of 4.6%, a maternal cancer risk reduction of 2.7%, or a pregnancy rate increase of 18%. In line with these results, the extent to which the value of genetic parenthood can be used to advocate for investments in novel treatments such as IVG can be challenged. It should be added that even if many people do actually find genetic ties very important, and even if some of them are willing to use risky and expensive ART to obtain this, this does not entail that this is morally acceptable (Franklin, 2013). Also, in the context of IVG, it is essential to ask about the circumstances in which it is acceptable to help people to have a genetically related child (Segers et al., 2019a). This is also reflected in the opinions assembled in this study, as the majority of respondents did not believe the advantage of a genetic tie would justify significant risks for the future children. While studies in mice indicate that the generation of (seemingly) healthy offspring from IVG is possible, there are several major concerns regarding the genetic and epigenetic integrity of gametes generated by IVG, due to the different manipulations and due to extensive in-vitro culturing. In-vitro-derived mouse oocytes are reported to have a low developmental potential compared with 'in-vivo' gametes, probably due to aberrant gene expression and a high rate of aneuploidy (Hikabe et al., 2016). In-vitro-derived mouse spermatogonial stem cells show aberrant DNA methylation and differences in gene expression (Ishikura et al., 2016). In general, children born after ART treatment are already more likely to have adverse perinatal outcomes compared with spontaneously conceived children, although these risks are widely considered to be within acceptable limits (Berntsen et al., 2019). While some of the additional epigenetic alterations in IVG may be corrected upon fertilization (through DNA demethylation), it remains to be seen whether the 'aggregated' risks due to added manipulations and culturing are still within the range of risks that is deemed acceptable.

Balancing the benefits of IVG against the potential risks and the measures needed to mitigate those risks is complicated by a large diversity of attitudes towards the importance of genetic parenthood on the one hand, and towards the acceptability of embryo and animal research on the other hand. Indeed, perhaps the most striking out-

Table 6 Attitudes towards regulation, potential risks of in-vitro gametogenesis (IVG) and animal and embryo research for testing IVG: do you find it acceptable that... (*n* = 1000).

	All respondents				Significant determinants
	(Fully) unacceptable	Neutral	(Fully) acceptable	No opinion	
Human embryos left over after fertility treatments are used to investigate potential risks of IVG	211 (23.8)	180 (20.3)	494 (55.8)	115	Dutch: 61.2%; French: 45.5% (<i>P</i> = 0.000) Self-reported infertility: 64.6%; no self-reported infertility: 54.6% (<i>P</i> = 0.045) Age (<i>s-b</i> = 0.087, <i>P</i> = 0.001)
Human embryos are made in the laboratory for research into the risks of IVG	332 (37.5)	188 (21.2)	365 (41.2)	115	Men: 45.2%; women: 37.3% (<i>P</i> = 0.020) Religious denomination: 36.6%; no denominative religion or life stance: 44.7% (<i>P</i> = 0.016) Heterosexual: 40.3%; non-heterosexual: 54.4% (<i>P</i> = 0.039) Age (<i>s-b</i> = 0.107, <i>P</i> = 0.000)
Experiments on mice are conducted to investigate potential risks of IVG	295 (32.8)	197 (21.9)	408 (45.3)	100	In a relationship: 48.6%; single: 38.2% (<i>P</i> = 0.040) Dutch: 49.7%; French: 37.9% (<i>P</i> = 0.010) Secondary education: 41.3%; higher education: 52.0% (<i>P</i> = 0.020)
Human embryos are created in the laboratory for deriving gametes	323 (37.1)	216 (24.8)	332 (38.1)	129	Men: 42%; women: 34.4% (<i>P</i> = 0.020) Age (<i>s-b</i> = 0.087, <i>P</i> = 0.001)
The risks of IVG for the child are higher compared with other medical techniques, because IVG is the only possible way of having a genetically related child	492 (58.2)	206 (24.3)	148 (17.5)	154	Men: 20.9%; women: 13.9% (<i>P</i> = 0.080) Dutch: 10.1%; French: 34% (<i>P</i> = 0.000)
The government must strictly regulate the application of IVG	32 (3.5)	100 (10.9)	782 (85.6)	86	Men: 82.5%; women: 88.6% (<i>P</i> = 0.080)
Experiments on monkeys are conducted to investigate potential risks of IVG	404 (44.8)	222 (24.6)	274 (30.4)	99	Men: 40.4%; women: 20.4% (<i>P</i> = 0.000) In a relationship: 33.9%; single: 22.7% (<i>P</i> = 0.001) Heterosexual: 29.7%; non-heterosexual: 42.4% (<i>P</i> = 0.040)
IVG is used if there is a high risk of disorders in the future child	769 (84.6)	100 (11.0)	40 (4.4)	91	In a relationship: 3%; single: 7.5% (<i>P</i> = 0.002) Secondary education: 3.4%; higher education: 6.4% (<i>P</i> = 0.035)
The government must provide money to make IVG accessible to everyone who needs it	231 (25.8)	219 (24.4)	446 (49.8)	104	Dutch: 46.8%; French: 55.6% (<i>P</i> = 0.012) Secondary education: 53.2%; higher education: 43.9% (<i>P</i> = 0.008)

P-value based on Cramer's V (for categorical variables) and Kendall's *s-b* (for age as a continuous variable) to analyse the significance of difference of distribution of (totally) agreeing respondents versus the remaining respondents.

For statistical analysis, only the respondents with an opinion were included. The education variable distinguishes between two groups: respondents with a secondary-level education or less and respondents with a higher education. The religion variable was recoded in two groups: 'religious denomination' (Christian, Jewish, Islamic) and 'no denominative religion or life stance' (religious but no specific religion, not religious or secular, those who don't know).

The number of 'no opinion' cases varied between 85 (8.5) and 155 (15.5).

come from this survey is the practical incompatibility of several findings. First, there is – overall – a positive attitude towards IVG, towards its potential clinical applications and towards government investments to make IVG available, mainly supported by the benefits of establishing a genetic link between parents and children, and furthering insights into human reproduction, which are both deemed important. Second, there is – overall – a negative attitude towards accepting risks for the future children which would exceed the risks of other ART. From these two elements, one would be inclined to conclude that we should invest in preclinical research in order to bring IVG to the clinic in a safe way. Both animal research and embryo research would likely be required to reach that goal (Jans et al., 2018b). More specifically, embryos would need to be created from gametes that were generated *in vitro*, in order to assess whether they are functional and whether they lead to normal embryos. However, such research was deemed unacceptable by a significant proportion of respondents: research on mice and monkeys was considered unacceptable by 32.8% and 44.8% of respondents, respectively, and 37.5% did not accept embryo creation. The large opposition to embryo creation and the use of spare *in vitro* fertilization embryos contrasts with the liberal Belgian law on research on embryos *in vitro*, which allows both types of research on the condition that certain basic requirements are respected, in accordance with a belief in the acceptance of ethical pluralism in society (Pennings, 2003). The present findings suggest a need for public education and dialogue on the topics of embryo and animal research in order to make people reflect on potential incompatibilities between, on the one hand, their attitudes regarding scientific and medical innovation and, on the other hand, their attitudes towards preclinical research. It is also suspected that the public may be unaware that animal experimentation in the field of assisted reproduction generally imposes low degrees of discomfort and suffering (Jans et al., 2018a). Public dialogue and citizen engagement efforts are encouraged on this topic in order to build and maintain trust between scientists and the general public.

Regarding attitudes towards possible future reproductive options for single men and women, these findings indicate a strong discrepancy between the attitudes towards solo genetic parenthood via IVG and the attitudes towards solo parenthood via reproductive cloning in humans. The similarity between both procedures is that both would – in theory – enable someone to generate offspring exclusively from their DNA. The difference is that, in the case of cloning, the resulting child would be genetically identical to the ‘progenitor’, whereas in the case of IVG, the progenitor would provide both egg cell and sperm cell (one ‘natural’, one ‘derived *in vitro*’), resulting in a reshuffling of the genetic code of the progenitor. In the latter case, a man could even become the parent of a daughter, solely from his DNA, if both the sperm cell and egg cell contain the man’s X chromosome. Needless to say, a major concern in the solo IVG scenario (besides the general safety concerns) is that there would be a very high level of homozygosity in the offspring, and thus an increased incidence of recessive disorders. Solo genetic parenthood via IVG was met with

cautious enthusiasm (51% acceptable, 30% unacceptable), while reproductive cloning was condemned (12% acceptable, 73.1% unacceptable), although the arguments and safety concerns to oppose reproductive cloning also hold for solo reproduction via IVG (Segers et al., 2019c). Moreover, the latter holds significant additional risks given the extreme form of inbreeding and the number of additional manipulations. We hypothesize that this discrepancy is linked to ignorance about these additional risks, the fact that people are more inclined to frame IVG in the context of infertility and cloning in the context of dystopian scenarios, and the fact that IVG appears to mimic nature more than cloning. Public education and interaction is important as IVG moves forward.

In the literature, IVG has been lauded as a strategy to ‘democratize reproduction’ as it could generate more equality among people of different sexual orientations in terms of reproductive options (Testa and Harris, 2005). Two-thirds of the respondents in this survey judged the use of IVG for same-sex reproduction to be acceptable. Interestingly, one could also build an argument in favour of reproductive use of IVG for postmenopausal women on such an equality argument (in the sense that it could allow women, like men, to have children up to an advanced age). However, two-thirds of the respondents judged the use of IVG for postmenopausal women to be unacceptable. That said, in both cases (same-sex reproduction and advanced age), this argument is insufficient to conclude that these scenarios are morally acceptable. For instance, both scenarios might imply additional health risks to the future child, such as through additional pregnancy complications, or through epigenetic and imprinting problems when a female gamete is made from a male or vice versa. Two additional comments are warranted here. First, it is suspected that many respondents did not consider the additional requirement of a gestational carrier in the scenario of a male same-sex couple (which may lead to a lower acceptance rate for this application). Second, as the legal age limit for fertility treatment was not mentioned in the survey, respondents may have interpreted ‘postmenopausal women’ as 60-year-old women, rather than 45-year-old women, which means the results cannot be taken to represent an attitude towards the potential practical implementation within the current legal setting.

Discussions about the different groups that might potentially benefit from IVG also include moral questions about who should have access to this technology once it becomes available. In that respect, half of the respondents indicated that the government should invest in making IVG accessible to everyone who needs it. It is of note that the understanding of such a ‘need’ is rather equivocal. If everyone who could benefit from IVG would be eligible for reimbursement, this would create problems for resource allocation. This is reinforced by the observation that with the introduction of IVG, many more people than those who are presently entitled to access infertility treatment may claim access to the technology. In any case, one of the central policy challenges for the future of clinical applications of IVG will be to define coherent criteria to determine who should have

access. In the literature, appropriate oversight structures are called for, and the majority of the respondents in this study also indicated that strict regulation is desirable (Cohen et al., 2017; Mathews et al., 2009).

In conclusion, this study found that the Belgian public has an overall positive attitude towards assisted reproduction and towards the future prospect of in-vitro generation of gametes for infertility treatment. Also, the in-vitro production of gametes for research purposes is evaluated positively. Divergent attitudes regarding the importance of a genetic link between parents and children were found. For a significant minority of the public, sharing genetic ties is a necessary aspect of a good parent–child relationship, while at the same time, families with donor-conceived children were not considered to be inferior to traditional families for the majority of respondents. This has implications that stretch beyond the topic of IVG, and should encourage clinicians in the field of assisted reproduction to explore the importance that couples attach to genetic parenthood when deciding about their optimal treatment. In particular, when risks for the future child need to be balanced against the value of the genetic link, not everyone will draw the line about what is acceptable at the same point. Complicating things further, a significant minority of the public oppose embryo and animal research, while both are important aspects of responsible innovation in assisted reproduction. Of all the potentially controversial applications that were discussed in this survey, the greatest taboos rested on reproductive cloning, germline genome editing and enabling genetic motherhood for postmenopausal women. For all three, significantly more women were opposed than men. At the same time, women tend to adopt a more open attitude towards new ways of family formation, such as shared genetic parenthood for same-sex couples and donor conception. This discrepancy might be explained by: (i) the greater propensity of men to take risks compared with women (explaining why they are more permissive towards risky new technologies); and (ii) the difficulty of aligning cultural beliefs and attitudes around masculinity with the acceptance of non-heteronormative families and the involvement of a third party in family formation (Byrnes et al., 1999; Glick et al., 2007; Plummer, 2016; Inhorn et al., 2009).

This study also found a positive correlation between younger age and a more permissive attitude towards same-sex reproduction, germline genome editing, reproduction by women who are infertile due to their age, and embryo creation for research purposes. This might be explained as a logical consequence of a positive correlation between age and conservatism in general (Truett, 1993). However, it would be interesting to investigate whether young people might be increasingly less inclined to accept infertility and genetic abnormalities as a given part of the human condition, and more inclined to prevent or remedy these unfortunate conditions.

While public consultations and surveys tell us little about the moral acceptability of new technologies, they do offer important insights about taboos, concerns and potential misconceptions that need to be taken into account as science moves forward. The present findings can serve as a starting point for further public engagement on the topic of medically assisted reproduction.

Limitations of this study and suggestions for future research

This study had several limitations. First, the percentage of respondents who chose ‘no opinion’ as a response to the statements presented to them varied between 7.4% and 15.4%. The characteristics of this group of respondents and the impact on the sample’s representativeness need to be taken into consideration. Second, although basic information in laymen’s terms was included in the questionnaire, one cannot expect the respondents to be fully aware of all implications of each option. For example, as noted, respondents may not have considered that same-sex reproduction by two men requires the involvement of a gestational carrier, that the derivation of a male gamete from an XX stem cell line is more likely to entail imprinting problems than the derivation of a female gamete from an XY stem cell line, or that extensive culturing leads to epigenetic defects. Third, and in line with the previous remark, it is suspected that many of the respondents imagine the animal experiments that would be performed in the context of IVG research to be more gruesome than they are in reality. This hypothesis was confirmed when a sample of the respondents ($n = 16$) was invited for a citizen’s forum on the topic of IVG after completing the questionnaire, and were provided with more information on the nature of the envisaged animal experiments, causing many respondents to move to a more permissive position. Finally, the attitudes of the Belgian population cannot be extrapolated to other societies.

In terms of further research, it would be interesting to repeat the same study in other countries to gain richer data on this issue. Qualitative research to further explore and enrich these quantitative data could shed more light on why certain people have certain attitudes, and may explain the differences between different groups within the population. Finally, this survey was limited to a lay public, so it would be interesting to expand the survey to include professionals in the field of medically assisted reproduction and contrast the views of the general population with those of professionals in the field of IVG.

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