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ARTICLE

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BIOGRAPHY

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KEY MESSAGE

A discrete choice experiment showed that genetic parenthood affects the treatment preference of gynaecologists but not that of patients with severe infertility choosing between treatments that varied in safety, effectiveness and costs. This surprising finding challenges the presumed dominant importance of genetic parenthood.

ABSTRACT

Research question: How much do patients with severe infertility and their gynaecologists value genetic parenthood relative to other key treatment characteristics?

Design: A discrete choice experiment included the following treatment characteristics: genetic parenthood, pregnancy rate, curing infertility, maternal health, child health and costs. The questionnaire was disseminated between 2015 and 2016 among Dutch and Belgian patients with severe infertility and their gynaecologists.

Results: The questionnaire was completed by 173 patients and 111 gynaecologists. When choosing between treatments that varied in safety, effectiveness and costs, the treatment's ability to lead to genetic parenthood did not affect the treatment preference of patients with severe infertility (n = 173). Genetic parenthood affected the treatment preference of gynaecologists (n = 111) less than all other treatment characteristics. 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%. Gynaecologists made similar trade-offs.

Conclusions: While awaiting replication of this study in larger populations, these findings challenge the presumed dominant importance of genetic parenthood. This raises questions about whether donor gametes could be presented as a worthy alternative earlier in treatment trajectories and whether investments in novel treatments enabling genetic parenthood, like in-vitro gametogenesis, are proportional to their future clinical effect.

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KEYWORDS

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Genetic parenthood
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INTRODUCTION

Infertile patients prefer genetic over non-genetic parenthood (*Hendriks et al., 2017*). Being a genetic parent requires having physically caused the child's existence by passing on part of one's genetic information (genes) to the child (although some have proposed additional criteria (*Mertes and Pennings, 2007; Piotrowska, 2017; Douglas and Devolder, 2019*). Gynaecologists offer various fertility treatments using patients' own gametes such as IVF. Carriers of genetic disorders are offered preimplantation genetic testing to enable the birth of fully genetically related but unaffected children. Donor gametes, leading to non-genetic parenthood for one or both partners, are only used in a minority (<10%) of fertility treatment cycles (*Kupka et al., 2016*), and are generally only offered if patients do not have viable gametes of their own or if treatments with patients' own gametes have failed (*Hendriks et al., 2016*). The apparent drive to achieve genetic parenthood is further exemplified by a significant amount of biomedical research that aims to develop novel fertility treatments. This includes in-vitro gametogenesis: the generation of gametes from germline stem cells or induced pluripotent stem cells (*Hendriks et al., 2015a; Hikabe et al., 2016; Cohen et al., 2017*) as well as germline genome editing to prevent the transmission of genetic diseases (*NASEM, 2017*). These developments continuously spur ethical and societal debate (*Hendriks et al., 2015b; NASEM, 2017*), in which the value of genetic ties between parents and their children has been flagged as an important open question (*Baylis, 2017; CEG, 2017; Cohen, 2017; Hendriks et al., 2017; Hyun and Osborn, 2017; De Wert et al., 2018*).

As achieving non-genetic parenthood using donor gametes or through adoption is also a possibility, one might question the importance of genetic parenthood relative to other characteristics of fertility treatments. Children born through conception with donor sperm and their families show similar long-term wellbeing and family relationships as fully genetically related families (*Bos and van Balen, 2010*). In addition, the treatment characteristics safety and effectiveness are important to patients and gynaecologists (*Dancet et al., 2013*), and donor gametes perform better in this respect than many fertility treatments with patient's own gametes. For example, for men with non-obstructive azoospermia, the use of donor sperm is safer and more effective than testicular sperm extraction followed by intracytoplasmic sperm injection (ICSI). Strikingly, no study has thus far examined how patients and gynaecologists trade off genetic parenthood against other valued treatment characteristics.

We conducted a discrete choice experiment to assess how patients with severe infertility and their gynaecologists trade off genetic parenthood against other key characteristics of current and future fertility treatment.

MATERIALS AND METHODS

Study design

A discrete choice experiment was designed, according to the ISPOR criteria (*Bridges et al., 2011*) to investigate trade-offs between genetic parenthood and other key characteristics of (current and future) fertility treatments (*Ryan and Farrar, 2000*). In discrete choice experiments, respondents repeatedly choose between two hypothetical options, described by characteristics varying across realistic levels. Conjoint analysis of the responses allows calculating the implicit value of the characteristics and the trade-offs between characteristics.

Ethics committee approval was acquired from the participating Belgian clinic on 22 December 2014 (reference: S57341); the Dutch clinic's ethics committee attested further approval was not required on 16 September 2014 (reference: W14_255).

Development of the discrete choice experiment

Identifying all treatment characteristics valued by patients and gynaecologists

A total of 17 empirical studies were reviewed to identify treatment characteristics that are important to patients (*Owens et al., 1993; Schover et al., 1996; Murray et al., 2004; Bayram et al., 2005; Blennborn et al., 2005; Steures et al., 2005; Pistorius et al., 2006; Newton et al., 2007; Scotland et al., 2007; Twisk et al., 2007; van Weert et al., 2007; Musters et al., 2011; Palumbo et al., 2011; Domar et al., 2012; Sills et al., 2012; van den Wijngaard et al., 2014; Hendriks et al., 2016*). As no empirical studies on gynaecologists could be identified, 10 gynaecologists were interviewed on important characteristics of (current and future) fertility treatments. A total of 13 important treatment characteristics were identified (Supplementary TABLE 1).

Selecting key treatment characteristics

Having the hypothetical treatment options in the discrete choice experiment which differ in thirteen characteristics would make the choices too complex. Therefore, the five treatment characteristics ranked among the most important half of all treatment characteristics by both patients and gynaecologists were selected (Supplementary TABLE 1). More specifically, genetic parenthood, child health, maternal health, pregnancy rate and curing infertility, i.e. the ability to repeatedly establish pregnancy through natural conception after transplantation of precursor germline stem cells to patients' gonads (*Hendriks et al., 2015b*). In addition, costs covered by national healthcare insurance (as fertility treatments are covered in the Netherlands) was included because of its importance to gynaecologists.

Identifying realistic levels for the key treatment characteristics

For each treatment characteristic, two to four levels were defined by an expert panel of gynaecologists and embryologists to realistically represent current fertility treatments, in-vitro gametogenesis and pursuing natural conception (TABLE 1). All levels were expressed per attempt aiming to achieve a pregnancy. For example, for the characteristic risk of major congenital malformations, the following levels were selected: 3% risk representing natural conception, 5% risk representing ICSI, and 10% and 20% representing potential risks of in-vitro gametogenesis (*Bonduelle et al., 2002; CDC, 2008*).

Designing and pilot-testing the questionnaire

The six characteristics and their two to four levels resulted in 864 ($2^1 \times 3^3 \times 4^2$) possible scenarios. A fractional factorial design drew an independent sample of 12 scenarios, while following the principles of efficient design, including level balance, minimal overlap and near orthogonality (*Huber and Zwerina, 1996*). The selected scenarios described two

TABLE 1 KEY TREATMENT CHARACTERISTICS AND LEVELS

Treatment characteristic	*Levels*
Genetic parenthood	Neither of both partners, only fertile partner, both partners
Child health[a]	3%, 5%, 10%, 20%
Maternal health	No risk, 5% risk of severe ovarian hyperstimulation syndrome[b], 5% risk of developing cancer within 15 years
Pregnancy rate	2%, 5%, 20%, 35%
Curing infertility	Single pregnancy as treatment goal, curing infertility as treatment goal, i.e. leading to the ability to autonomously achieve one or more pregnancies
Costs[c]	€0, €4000, €10,000

[a] Specified as risks on major congenital abnormalities that effect functioning, require surgical intervention, or both (*Eurocat, 2014*).

[b] Specified as complication that requires hospitalization.

[c] Specified as costs covered by national health insurance.

hypothetical treatments and, therefore, the 'treatment options' were unlabelled (*de Bekker-Grob et al., 2010*). One of the scenarios from the questionnaire is presented in TABLE 2. The discrete choice experiment questionnaire provided detailed instructions on filling out the choice sets and was identical for patients and gynaecologists. The background questions for patients were different from those for gynaecologists. The phrasing of the questionnaire was adapted in between cognitive interviews with 20 patients, until the questions were properly understood (*Willis, 2004; Reed Johnson et al., 2013*). After a formal pilot of 40 patients and gynaecologists (*Lancsar and Louviere, 2008*), the choice sets for each of the 12 scenarios were reconsidered with the aid of D optimal design using N gene software.

Data collection

Both partners from couples with severe infertility who consulted the fertility clinics of the Leuven University Hospital (Belgium) and the Academic Medical Centre (the Netherlands) between August 2012 and November 2015 were eligible. Couples were defined as severely infertile if the man had non-obstructive azoospermia and underwent a testicular sperm extraction in which no spermatozoa were found, or if the woman was diagnosed with poor ovarian response, defined as the retrieval of three or fewer oocytes or cycle cancellation in at least two subsequent cycles with ovarian stimulation using at least 225 IU of gonadotrophins (*Jayaprakasan et al., 2010*; *Ferraretti et al., 2011*). Eligible couples (174 in the Netherlands, 100 in Belgium) received an invitation letter, two coded questionnaires (one per partner, to be filled out independently) (*Thomson, 1983*), a refusal form and a return envelope via post. Non-responders received two reminders.

TABLE 2 EXAMPLE FROM THE QUESTIONNAIRE DISPLAYING A CHOICE BETWEEN TWO HYPOTHETICAL TREATMENT OPTIONS

	Treatment A	*Treatment B*
Genetic parenthood	Genetic parenthood for both parents	Genetic parenthood for both parents
Risk of a severe birth defect[a]	10%	20%
Risk of severe complications for the prospective mother	None	5% chance of developing cancer within 15 years as a result of the treatment
Chance of getting pregnant (per attempt[b])	2%	20%
Single pregnancy or curing infertility	The goal of this treatment is to achieve a single pregnancy	The goal of this treatment is to cure infertility, after the treatment couples can try to get pregnant at home every month
Costs that are covered by health insurance (per attempt[b])	€0	€4000
I prefer:	☐ A	☐ B

[a] Major birth defect: an abnormality that affects functioning, requires surgical intervention, or both.

[b] An attempt: a medical procedure that leads to a chance of getting pregnant, e.g. an embryo transfer in an IVF procedure.

Gynaecologists who were active in reproductive medicine were eligible. Those who treated patients according to the websites of fertility clinics met this eligibility criterium. The eligible 179 Dutch and 99 Belgian gynaecologists received an invitation letter, a coded questionnaire, a refusal form and a return envelope by post. Non-responders received two reminders by email including a link to an online version of the questionnaire.

Recruitment took place in the winter of 2015–2016. Our a-priori sample size calculation (power = 0.8; $\alpha = 0.05$ [*de Bekker-Grob et al., 2015*]) dictated a minimum sample size of 280 respondents.

Statistical analysis

SPSS 22 (IBM) and R (version 3.1.2) was used for data analyses. Data from patients and from gynaecologists were assessed separately and compared. The probability of respondents' preference in each of the choice sets is assumed to relate to the overall value (utility) of each of the treatment scenarios plus a random error. A main-effects (no interactions) multinomial logit model analysed the importance of each treatment characteristic level (*Hazlewood et al., 2016*). This way the sum of the importance of all its treatment characteristic levels determines the overall value of a treatment. All treatment characteristics were primarily included as categorical variables but subsequently analysed as continuous variables if a linear relationship was confirmed by visual inspection and by comparing the Akanke information criterion between models.

Whether each treatment characteristic significantly affected respondents' hypothetical treatment choice was analysed. The characteristic's coefficient shows the change in benefit for a one-unit, i.e. characteristic levels for

categorical variables and percentages for continuous variables, change in the characteristic. Absolute values of the coefficients, however, have no direct interpretation (*Louviere et al., 2000*).

How much of each treatment characteristic patients and gynaecologists were willing to trade off against genetic parenthood, i.e. genetic parenthood for both partners instead of for neither, was calculated. Therefore, the difference in the importance scores between the highest and lowest treatment characteristic level was divided by the importance of genetic parenthood (marginal rate of substitution [MRS]). Monte Carlo sampling estimated the median and 95% confidence intervals of the MRS (*Berg, 2004*).

The effect of several variables on the stated preference was assessed by including the variables in the model. The following variables were evaluated: all respondents' demographic characteristics, patients' cause and duration of infertility, having pursued third-party reproduction and gynaecologists' work experience, PhD, and whether they worked in an academic clinic.

Latent class analysis investigated preference heterogeneity to uncovered subgroups of respondents with comparable preferences (*Hagenaars and McCutcheon, 2002*). Latent class solutions were fitted with two and three classes by comparing measures of model fit (adjusted Bayesian information criterion and consistent Akanke information criterion) and comparing patterns of importance scores (between models and to the overall multinomial logit model). Respondents were assigned to the latent class for which they had the highest probability. We used logistic regression models to analyse the association between selected respondent characteristics and latent class membership. Univariate statistics (i.e. $P < 0.15$) identified respondent characteristics to be included in the exploratory multivariable models, with a maximum of seven variables to avoid overfitting.

RESULTS

The questionnaire was completed by 173 patients (response rate 32%) and 111 gynaecologists (response rate 40%). The background characteristics are presented in TABLE 3. Thirty-seven per cent of patients had a child, of which around one-half were genetically related to both the respondent and his or her current partner (TABLE 3). Nearly all gynaecologists were parents (96%), and 80% had children that were genetically related to them and their current partner (TABLE 3).

The influence of the treatment characteristics on treatment preference is presented in TABLE 4. All treatment characteristics except for genetic parenthood affected the treatment preference of patients. Genetic parenthood did affect the treatment preference of gynaecologists but had less influence than child health, costs, maternal health and pregnancy rate. Curing infertility did not significantly affect the treatment preference of gynaecologists.

Patients and gynaecologists did not differ in the absolute or relative importance of the six treatment characteristics.

None of the background characteristics, including sex, cause of infertility and having pursued third-party reproduction, were associated with the influence of the treatment characteristics on treatment preferences. Latent class analysis revealed three subgroups of patients and two subgroups of gynaecologists mainly differing in whether genetic parenthood, curing infertility, or both, affected their treatment preferences (Supplementary Table 2).

Patients switched to a treatment that would result in non-genetic parenthood in return for a child health risk reduction of 3.6%, a cost reduction of €3500, an ovarian hyperstimulation syndrome risk reduction of 4.6%, a maternal cancer risk reduction of 2.7% or a pregnancy rate increase of 18% (TABLE 5). The trade-offs of gynaecologists did not differ significantly from those of patients (TABLE 5).

DISCUSSION

This study shows that when choosing between treatments that vary in safety, effectiveness and costs, the treatment's ability to lead to genetic parenthood did not affect treatment preferences of patients with severe infertility. Genetic parenthood affected the treatment preference of gynaecologists less than all other treatment characteristics.

Although philosophers have previously suggested that genetic parenthood may be overvalued (*Rulli, 2016*), our empirical findings are surprising in the light of the limited use of donor gametes in clinical practice (*Kupka et al., 2016*) and of previous studies demonstrating the high importance of genetic parenthood to patients (*Gurmankin et al., 2005; Hendriks et al., 2017*). To the best of our knowledge, the present study is the first to ask patients to weigh the importance of genetic parenthood against that of other treatment characteristics, which they are known to value. Of note, our results do not contrast those of previous studies, indicating patients prefer genetic parenthood 'all else being equal'; rather they suggest that 'all else not being equal', the ability of a treatment to lead to genetic parenthood may not affect decision-making as much as presumed. Men and women did not differ in the importance they attached to genetic parenthood, which corresponds to most previous studies (*Gurmankin et al., 2005; Hendriks et al., 2017*). This remains surprising as men and women have a different medical and physical IVF experience (*Throsby and Gill, 2004*) and as women, in contrast to men, can still be a gestational parent if donor gametes are used (*Ravin et al., 1997*).

To the best of our knowledge, the importance of genetic parenthood to gynaecologists has never been studied. The interviews for developing our questionnaire suggest that gynaecologists value genetic parenthood because they are concerned about the welfare of non-genetically related families, because they think their patients want genetic parenthood and because they consider genetic parenthood 'normal'; some gynaecologists even indicated during the interviews that they considered the desire of patients to use a donor when options for genetic parenthood are available as possibly pathological. The importance of genetic parenthood to gynaecologists can thus be challenged by reassuring data on the welfare of non-genetically related families (*Bos and van Balen, 2010*) and our finding that patients are willing to give up genetic parenthood.

Typical for discrete choice experiments, one could question whether preferences between hypothetical treatments reflect real-life choices. First, our discrete choice experiment did not include all possible treatment characteristics and contextual factors, whereas these may all influence real-life decision-making. Similarly, asking

TABLE 3 BACKGROUND CHARACTERISTICS OF RESPONDENTS

Demographic characteristics		***Patients (n = 173)***	***Gynaecologists (n = 111)***
Sex, *n* (%)	Female Male	94 (54) 79 (46)	53 (48) 58 (52)
Age (mean ± SD in years)		37 ± 6	49 ± 9
Ethnic background, *n* (%)	Western Non-Western	153 (89) 18 (11)[a]	105 (95) 6 (5)
Country, *n* (%)	Belgium the Netherlands	71 (41) 102 (59)	35 (32) 76 (68)
Education, *n* (%)	University degree No university degree	108 (62) 65 (38)	111 (100) 0 (0)
Income, *n* (%)	Higher than modal (>€38,800) Equal or less than modal (≤€38,800) No response	127 (73) 23 (13) 23 (13)	93 (84) 4 (4) 14 (13)
Social status, *n* (%)	Upper class Higher middle class Lower middle, working, or lower class	51 (29) 91 (53) 31 (18)	111 (100) 0 (0) 0 (0)
Having children with, *n* (%)	Genetic link to respondent and his or her current partner Genetic link to respondent, not his or her current partner Genetic link to current partner but not to respondent No genetic link to respondent or his/her current partner No parenthood	30 (18) 19 (11) 12 (7) 2 (1) 108 (63)[a]	86 (80) 16 (15) 1 (1) 1 (1) 4 (4%)[a]
Medical background of patients			
Cause of infertility, *n* (%)	Male (non-obstructive azoospermia) Female (poor ovarian response) Male and female Unknown	109 (64) 28 (16) 19 (11) 15 (9)[a]	NA
Duration active wish for a child (mean ± SD in years)		4.4 ± 2.7	NA
Attempted alternatives, *n* (%)	Third-party reproduction Adoption or foster care None of the above	57 (33) 7 (4) 112 (65)[b]	NA
Time since last treatment (mean ± SD in years)		1.0 ± 1.1	NA
Currently in treatment, *n* (%)	Yes No No response	35 (20) 130 (75) 8 (5)	NA
Professional background of gynaecologists			
Undergone fertility treatment(s), *n* (%)	Yes No	NA	13 (12) 96 (88)[a]
Working experience in reproductive medicine (mean ± SD in years)		NA	18 ± 10
Obtained a PhD, *n* (%)	Yes No	NA	64 (58) 46 (42)[a]
Type of hospital, *n* (%)	Academic Non-academic	NA	32 (29) 78 (71)[a]

[a] Data for this question were missing in fewer than five respondents.

[b] Three respondents attempted third-party reproduction and adoption or foster care. NA, not applicable.

patients to choose between two options may not fully capture real-life decision-making in which patients choose for a treatment trajectory, e.g. first attempting testicular sperm extraction followed by ICSI, opting for donor sperm if that fails. Second, the levels of the characteristics representing treatments that do not yet exist were based on assumptions rather than data (which are not yet available). Third, one may doubt whether hypothetical preferences reflect real-life choices as they may, for example, not incite emotions involved, such as abstaining from pursuing genetic parenthood to the same extent. Another discrete choice experiment in the same patient population relieves some of these doubts as hypothetical preferences between fertility clinics corresponded to reported reasons for changing fertility clinic (*van Empel et al., 2011*). Furthermore, we conducted our survey in the Netherlands and Belgium. Although scholars refer to a Euro-American kinship discourse (*Schneider, 1980; Freeman et al., 2014*), our results might not reflect the importance of genetic parenthood in other cultures. Fourth, we included patients with severe infertility, as, in the future, this group will likely be offered innovative techniques like in-vitro gametogenesis first. It is possible, and perhaps likely, that this group differs from patients with other diagnoses or in other treatment stages, e.g. at the time of the initial diagnosis. On the one hand, our sample may value genetic parenthood more, as they have undergone the most interventional therapies available (multiple IVF cycles or testicular sperm extraction) to pursue genetic parenthood. On the other hand, our sample may value genetic

TABLE 4 RESULTS OF MULTINOMIAL REGRESSION: IMPORTANCE OF TREATMENT CHARACTERISTICS

Treatment characteristic Levels	*Coefficient patients (95% CI)*	*Coefficient gynaecologists (95% CI)*
Child health (linear)		
Per percent increase in risks	−0.20[b] (−0.33 to −0.06)	−0.29[a] (−0.29 to −0.09)
For maximal increase in risks (3 – 20%)[c]	−3.32[b] (−5.30 to −1.34)	−4.93[b] (−8.20 to −1.66)
Costs		
Increase from €0–€4.000	−0.87[a] (−1.29 to −0.45)	−1.61[a] (−1.95 to −1.27)
Increase from €0–€10.000	−1.66[a] (−2.41 to −0.91)	−2.23[a] (−2.69 to −1.77)
Maternal health		
Increase from no to 5% risk of severe ovarian hyperstimulation syndrome	−0.77[a] (−1.03 to −0.41)	−0.38[a] −0.74 to −0.02
Increase from no to 5% risk of cancer	−1.26[a] (−1.84 to −0.68)	−1.32[a] (−1.60 to −1.01)
Pregnancy rates (linear)		
Per percent increase	0.02[a] (0.01 to 0.04)	0.03[a] (0.01 to 0.05)
For maximal increase (2–35%)[a]	0.69[b] (0.38 to 1.08)	0.98[b] (0.42 to 1.39)
Genetic parenthood		
For fertile partner, instead of no partner	0.19 (−0.21 to 0.60)	0.31[a] (0.11 to 0.51)
For both partners, instead of no partner	0.70 (−0.35 to 1.75)	0.73[a] (0.36 to 1.10)
Curing infertility		
Curing infertility instead of a single pregnancy	0.41[a] (0.21 to 0.59)	0.08 (−0.17 to 0.33)

Model parameters for patients: log-likelihood = −1987.13; pseudo R^2 = 0.18; model parameters for gynaecologists: log-likelihood = −2203.77; pseudo R^2 = 0.21.

[a] Significant at $P < 0.05$.

[b] Significant at $P < 0.001$.

[c] A translation of the linear variable.

parenthood less as they may have become accustomed to the idea of to being unlikely to attain it (*Indekeu et al., 2014*) and as they may have received additional counselling in third-party reproduction. Surprisingly, among our sample, having pursued third-party reproduction was not associated with the value attached to genetic parenthood. Whether and how the duration of infertility, the specific diagnosis, and chosen treatments or other options to pursue parenthood affect the value of genetic parenthood should be examined further. Finally, the response rates were low, which is common among physicians (*Asch et al., 1997*), and which, among patients, could relate to the topic's sensitivity and limited ongoing contact with their treating physician (*Edwards et al., 2002*).

TABLE 5 THE CHANGE IN OTHER TREATMENT CHARACTERISTICS FOR WHICH RESPONDENTS ARE WILLING TO TRADE GENETIC PARENTHOOD FOR NON-GENETIC PARENTHOOD

Treatment characteristic	*Trade off (95% CI[a])*	
	Patients	*Gynaecologists*
Child risks	−3.6% (−5.3% to 1.4%)	−2.8% (−4.3% to −1.3%)
Costs	€−3500 (€-5550 to €1450)	€−2400 (€−4850 to €−950)
Maternal risks		
Severe ovarian hyperstimulation syndrome	−4.6% (−6.3% to −2.9%)	−4.3% (−6.4% to −2.2%)
Developing cancer	−2.7% (−5.3% to −0.6%)	−2.8% (−4.6% to −1.0%)
Pregnancy rate	+18% (8% to 28%)	+19% (7% to 31%)

Genetic parenthood for both parents is compared with genetic parenthood for neither of both parents

[a] Confidence interval based on the Krinsky Robb method adjusted for class probabilities.

The treatment trajectories currently taken by patients and gynaecologists seem to be discrepant with our findings. For example, most couples with non-obstructive azoospermia attempt testicular sperm extraction before using donor sperm insemination (*Hendriks et al., 2016*). Testicular sperm extraction followed by three cycles of ICSI has about a 29% chance of a live birth, i.e. sperm is retrieved in 56% of extractions and three subsequent ICSI cycles result in a live birth in 52% (*Dabaja and Schlegel, 2012; Vloeberghs et al., 2015*). In contrast, 12 months of treatment with donor sperm insemination has a 59% chance of a live birth (*Botchan et al., 2001*). According to our findings, the advantage of genetic parenthood is worth less than a 20% decrease in pregnancy rate, and thus one would expect patients to prefer donor sperm insemination over testicular sperm extraction followed by ICSI. This discrepancy between the treatment trajectories currently taken by patients and gynaecologists and our findings on their treatment preferences might be explained by the habit to only offer donor gametes at the end stages of treatment trajectories, making 'autopilot' decisions instead of explicitly weighing all treatment characteristics, e.g. donor gametes are being presented early on but only as an afterthought (*Townes et al., 1974; Daniluk, 2001*); the motivation of preventing anticipatory regret (*Hendriks et al., 2017*) outweighing other values, e.g. safety, initially in a multiple-treatment trajectory; the societal pressure to achieve genetic parenthood (*Stoebel-Richter et al., 2012*); and contextual factors such as a scarcity in donor gametes.

Further research is needed to corroborate the preferences found in this study in a larger, more culturally and diagnostically diverse population. If these preferences hold, follow-up studies should elucidate which of the above-mentioned potential explanations

causes the discrepancy between patients' preferences and current clinical decision-making, as this discrepancy raises important ethical questions.

In relation to clinical practice, these include what are the appropriate standards for informed consent, whether motivations should be considered in justifying the allocation of scarce healthcare recourses, and whether investments are needed to address the challenges with donor gametes, e.g. acquiring donors and setting-up donor registries. For example, the former could include randomizing patients considering testicular sperm extraction between current decision-making practices and a more extended procedure, assisted by a decision aid with all treatment options and their characteristics.

Regarding new therapies, the results challenge the extent to which the value of genetic parenthood can be used to advocate for developing novel treatments, such as in-vitro gametogenesis and germline genome editing (*Hendriks et al., 2015b; NASEM 2017*). If our finding that genetic parenthood was only worth a limited amount of additional risks, lower pregnancy rates and higher costs hold true in larger populations, the demand for novel treatments, with seemingly inevitable health risks and costs, may be limited. This raises questions about whether the time and resource consuming development of novel treatments aimed at establishing genetic parenthood is proportional to their future clinical impact. Finally, our findings are relevant as input for ethical and societal debates weighing the merits of possible future treatments, such as in-vitro gametogenesis and germline genome editing.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2019.02.008.

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