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Hendriks, S.; Dancet, E.A.F.; Vliegenthart, R.; Repping, S.

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The acceptability of stem cell-based fertility treatments for different indications

S. Hendriks¹, E.A.F. Dancet¹,²,³, R. Vliegenthart⁴, and S. Repping¹,*

¹Center for Reproductive Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands ²Research Foundation Flanders, Brussel, Belgium ³Leuven University Fertility Clinic, Department of Development and Regeneration, KU Leuven-University of Leuven, Herestraat 49, 3000 Leuven, Belgium ⁴Amsterdam School of Communications Research, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands

*Correspondence address. Center for Reproductive Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail: S.Repping@amc.nl

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STUDY QUESTION: What is the acceptability of using stem cell-based fertility treatments (SCFT) for different indications according to gynaecologists and the general public?

SUMMARY ANSWER: The majority of gynaecologists and the general public accept SCFT for the indications female or male infertility in young heterosexual couples, and female infertility in single women and same-sex couples.

WHAT IS KNOWN ALREADY: SCFT could result in genetic parenthood for intended parents with indications that cannot be treated using currently available methods, such as being in a same-sex relationship or female post-menopausal age. It is unclear whether the acceptability of SCFT differs between indications for treatment and whether gynaecologists and the general public differ in their assessments.

STUDY DESIGN SIZE, DURATION: In November 2015, a cross-sectional survey was disseminated among 179 gynaecologists and a panel of 1250 respondents comprising a representative sample of the Dutch general public.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The potential indications for future SCFT to achieve genetic parenthood were identified by literature review. A questionnaire was developed, reviewed by experts from different disciplines and tested among the general public. The questionnaire asked whether treating eight groups of intended parents with SCFT was acceptable or not. Regression analysis examined whether demographic characteristics influenced choices and whether the general public and gynaecologists differed in opinion.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 82 (46%) gynaecologists and 772 (62%) members of the general public completed the survey. The acceptability of using SCFT varied according to both gynaecologists and the general public between the eight groups of intended parents (P < 0.001). The majority of the Dutch general public accepts SCFT 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%). The majority of gynaecologists also found treating these groups acceptable, except for the indication of unexplained infertility, which was only accepted by a minority of gynaecologists (43%). A minority of both the general public and gynaecologists accepted SCFT for fertile women who want a child that is genetically only her own (27 and 6%, respectively) and for female infertility in heterosexual couples in which the woman is over 50 years of age (17% and 26%, respectively). 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 were positively associated with considering using SCFT acceptable for one or multiple indications.

LARGE SCALE DATA: N/A.

LIMITATIONS REASONS FOR CAUTION: The generalizability of our findings to future decades or other countries might be limited as opinions about novel technologies change over time and might vary across cultures. Support among gynaecologists and the general public is interesting but not proof of ethical acceptability.

WIDER IMPLICATIONS OF THE FINDINGS: Once proven safe and effective, fear of limited acceptability by the general public is unwarranted, and thus should not stop gynaecologists from offering SCFT to single infertile women and same-sex couples in addition to young infertile heterosexual couples.
Introduction

Involuntary childlessness can result from the inability of a person and/or their partner to conceive and/or carry a pregnancy. Having a same-sex relationship or being single can also cause involuntary childlessness.

Current fertility treatments have limited effectiveness. First, only 70% of infertile heterosexual couples achieve parenthood (Pinborg et al., 2009). Second, we lack fertility treatments that can achieve genetic parenthood for both parents of same-sex couples and heterosexual couples without functional gametes. Therefore, researchers are currently developing stem cell-based fertility treatments (SCFT) (Hendriks et al., 2015a; Boiani, 2017; Cohen et al., 2017). These are fertility treatments that involve creating gametes by manipulation of pluripotent or germline stem cells of the infertile patient. If successful and safe in the future, these treatments may enable all individuals (who have someone to carry the pregnancy) to attempt to achieve genetic parenthood irrespective of their fertility problem, relational status or sexual orientation (Hendriks et al., 2015b).

The acceptability of currently available fertility treatments to the general public and fertility clinic staff differs depending on the indication for which they are used (Kovacs et al., 2003; Sperling and Simon, 2010). Acceptability to the general public was, for example, more likely for the indication of infertility among heterosexual couples than for treating lesbian couples or singles with donor gametes (Kovacs et al., 2003; Heikkila et al., 2004, 2006). Professional’s opinion papers on the clinical application of SCFT positively appraised the ability to treat infertility in young heterosexual couples while the ability to allow genetic parenthood for unconventional intended parents, such as same-sex couples, singles and post-menopausal women was flagged for further reflection (Hendriks et al., 2015b). Limited public support for SCFT has been expected, especially for treating unconventional intended parents (Smajdor, 2008; Lovell-Badge, 2012). No study has thus far, however, questioned a group of professionals, let alone the general public, on the acceptability of using SCFT for different indications.

To allow responsible decision-making on the clinical application of SCFT, the perspective of different stakeholders on who should be treated is relevant. Questioning gynaecologists is relevant as they traditionally decide on treatment indications and on the clinical application of novel techniques. The perspective of the general public is relevant as they represent the group of intended parents and their unborn children, and as they will be affected by the broader societal implications of the indications for which SCFT are used. Although SCFT are yet to be applied clinically, reflecting on their applications now allows developing policies in which stakeholders’ values are represented (Hinxton, 2008).

This study aimed to examine whether the acceptability of SCFT to gynaecologists and the general public depends on the indication for which they are used.

Materials and Methods

The questionnaire

A questionnaire was developed in four phases. First, a literature review identified the potential indications for SCFT (Hendriks et al., 2015b). Second, a questionnaire operationalizing the indications by describing eight potential groups of intended parents who could attempt to achieve genetic parenthood with SCFT was developed. Third, nine independent experts in communication, ethics, law and medicine, as well as patient representatives reviewed the questionnaire and confirmed that the phrasing was non-directive (Molewijk et al., 2003; McMillan and Hope, 2008). Fourth, the questionnaire was pilot tested in cognitive interviews with 18 members of the general public. The questionnaire was adjusted based on the interviews, which involved inviting participants to think out-loud as well as verbal probing techniques, until six subsequent interviewees indicated all questions were comprehensible (Patton, 1990; Willis, 2004).

The final questionnaire questioned the acceptability of using SCFT for each of the eight groups of intended parents, as exemplified in Figure 1 (see Supplementary Data I). Short cases were described, which included information about the type of couple (e.g. man and women in their 30s), the cause of their involuntary childlessness (e.g. unexplained infertility), their ability to achieve genetic parenthood through other means, and how future SCFT could possibly be applied to them. Respondents could select the response options ‘acceptable under certain conditions’, ‘not acceptable’ and ‘no opinion’. The questionnaire was preceded by an information folder which introduced the basic biomedical principles and experimental nature of SCFT (see Supplementary Data II); a questionnaire including demographic questions, which additionally questioned gynaecologists about their professional role; and a part of a questionnaire for another study which informed on all previously described potential advantages and disadvantages of using these treatments (Hendriks et al., 2015b) (see Supplementary Data III).

Data collection

Data were collected with the same questionnaire among gynaecologists and the general public. The ethics committee of the Academic Medical Center of Amsterdam attested approval was not required (W15_191).

All 179 gynaecologists working in Dutch fertility clinics were eligible. An invitation letter, coded questionnaire, refusal form and return envelope were sent by postal mail. Non-responders received two reminders including a link to the digital questionnaire by email.

A sample of 1250 respondents, matching the Dutch adult population in several demographic characteristics (i.e. sex, age, education, household size and region), was drawn from an actively recruited panel of members of the general public (Couper and Miller, 2008). The questionnaire was disseminated online by a certified research company.

Statistical analysis

Data were analysed with the Statistical Package for Social Sciences SPSS 22.0 Inc. for Mac (IBM, Chicago, IL, USA).
The proportion of gynaecologists and of the general public expressing an opinion on acceptability was described by indication. All subsequent analyses focussed on the respondents expressing an opinion.

By indication, we described the likeliness for the general public and the gynaecologists to accept the use of SCFT.

Whether or not the indication defined the likeliness of acceptance by gynaecologists or members of the general public was analysed with a generalized estimating equation.

For each of the indications, whether the gynaecologists and the general public differed in likeliness of acceptance was first analysed with Chi-square tests. Second, the same analyses compared gynaecologists to the subgroup of the general public that matched them for three characteristics, which inherently came with their profession (≥30 years of age, University education and upper social class).

We conducted a multivariate binary logistic regression analysis to allow predicting the acceptability of SCFT based on all the questioned background characteristics. Adjusted, rather than crude, odds ratios (ORs) were chosen as we expected correlations between the characteristics based on previous research (CBS, 2015; Olson et al., 2006).

### Results

#### Respondents

A total of 854 respondents completed the survey, including 82 gynaecologists (response rate = 46%) and 772 members of the general public (response rate = 62%). The general public represented the Dutch adult population regarding several demographic characteristics (i.e. gender, age, education, household size and region).

The characteristics of the responding gynaecologists and members of the general public are described in Table I. About half of the respondents were men, and one-third had a university degree. Most respondents were between 43 and 64 years old, were European, had children and were in heterosexual partner relationships. About 15% had experienced infertility. The majority of the respondents reported being religious (mostly Christian) while most also reported attributing little importance to religion. Respondents reported having moderate to progressive political preferences.

The gynaecologists had worked within the field of reproductive medicine for 18 years, on average. Most had obtained a PhD and worked in clinics which were non-academic and/or did not have an IVF laboratory.

### Having an opinion on acceptability

Depending on the indication for offering SCFT, 4–17% of the gynaecologists and 17–26% of the general public, indicated having 'no opinion' on acceptability.

### Acceptance by indication

The likeliness for gynaecologists (P < 0.001) and the general public (P < 0.001) to accept SCFT differed by indication.

For five of the eight indications, SCFT were considered acceptable by the majority (≥50%) of both the general public and the gynaecologists (Table II). These indications included (in order of likeliness to be accepted): female infertility in young heterosexual couples, male infertility in young heterosexual couples, female infertility in single women (also using a sperm donor), lesbian couples and gay couples. The two groups of respondents only differed significantly in the likeliness to accept SCFT for female infertility in single women (P < 0.001), with gynaecologists being more willing to accept them.

Using SCFT for unexplained infertility in young heterosexual couples was accepted by the majority of the members of the general public but only by a minority of gynaecologists (P < 0.001; Table II).

A minority of the general public and of the gynaecologists considered using SCFT for fertile women who want a child that is genetically only her own to be acceptable, although the general public found this more acceptable than gynaecologists (P < 0.001; Table II). A minority of both the general public and the gynaecologists also found SCFT acceptable for female infertility in heterosexual couples in which the woman is of post-menopausal age (≥50 years of age; Table II). The two groups did not differ significantly (P = 0.06).

### Appraising the differences between gynaecologists and the general public

As detailed above and in Table II, the responding gynaecologists differed from the demographically representative sample of the general public in their likeliness to accept SCFT for three of the eight indications. More specifically, gynaecologists were more likely than the general public to accept treating infertile single women, whereas gynaecologists were less likely than the general public to accept treating unexplained infertility in young heterosexual couples or fertile women who want a child that is genetically only her own.
These three differences remained significant (P ≤ 0.01) if gynaecologists were compared to the subgroup of the general public (n = 94) that matched them in the three characteristics which inherently came with their profession (≥30 years of age, University education and upper social class; Table II).
likelihood of accepting SCFT for at least one of the eight indications (Table III).

Expressing progressive political preferences and attaching less importance to religion were associated with acceptance for all but one indication (n = 7/8). The exceptions were unexplained infertility in young heterosexual couples and female infertility in heterosexual couples in which the woman is of post-menopausal age. Women were more likely than men to accept SCFT for female infertility in single women and lesbian couples. Not having a European ethnicity was associated with acceptance of the use of SCFT for female infertility in single women and female infertility in heterosexual couples in which the woman is of post-menopausal age. Not having a University degree was associated with being more likely to accept SCFT for lesbian couples. Increased age was associated with accepting the use of SCFT for fertile women who want a child that is genetically only her own.

The six background characteristics not associated with acceptance of SCFT for any of the eight indications were: type of religion, social status, having children, heterosexual orientation, being in a committed relationship and having experienced infertility.

**Discussion**

This is, to the best of our knowledge, the first study questioning the general public on their acceptance of SCFT for various indications. Our results contradict the assumed, but never tested, limited public support for SCFT (Smajdor, 2008; Lovell-Badge, 2012) as the majority of the Dutch general public accepts SCFT for six out of eight indications. This study also shows that the majority of gynaecologists agree on the acceptability of SCFT for five of these six indications. In contrast to the majority of the general public, only a minority of gynaecologists accepted treating unexplained infertility in young heterosexual couples. Only a minority of both the general public and gynaecologists accepted SCFT for fertile women who want a child that is genetically only her own and for female infertility in heterosexual couples in which the woman is over 50 years of age.

The information on SCFT preceding the questionnaire and the simultaneous dissemination of a questionnaire on the importance of all advantages and disadvantages of SCFT might have influenced the perspective of responders. Therefore, it is important to note that we relied on an independent expert panel and pilot interviews to ensure ending up with a non-directive, understandable questionnaire. The questioned SCFT are not yet implemented into clinical care, making our study timely. Gathering insights for setting up a flexible regulatory framework before clinical implementation is deemed important (Schatten, 2002; Winston and Hardy, 2002; Hinoux, 2008). The sample of the general public was representative for several demographic characteristics, but people of non-European ethnicities and/or religions other than Christianity regrettably remained under-represented. The generalizability of our findings is limited as opinions about novel technologies differ across cultures and change over time (Kovacs et al., 2003). It should be noted that our findings represent the acceptability to those deciding to express an opinion. There may have been multiple reasons for not expressing an opinion, of which one may be the difficulty of knowing what is required for parents to guarantee the future
welfare of their child (De Geyter et al., 2010). It should also be noted that our response option for considering treatment acceptable was ‘acceptable under conditions’. Our findings should, therefore, be interpreted under these, unspecified, conditions, which may relate, for example, to the safety of SCFT. Finally, support among gynaecologists and the general public is interesting but is not proof of ethical acceptability (Sulmasy and Sugarman, 2001).

It is difficult to compare our data on the acceptability of treating various groups of intended parents with SCFT to previous data on the acceptability of current fertility treatments for these groups, as acceptability might change over time, might vary across cultures, might depend on the local accessibility to fertility treatments and availability and protection of gamete donors (Kovacs et al., 2003; Pennings et al., 2008; Billari et al., 2011). Nevertheless, we did not identify a level of acceptability of SCFT, which was considerably lower than the acceptability of current fertility treatments. This is surprising as SCFT are more interventional, less conventional and would drastically extend the biological boundaries of reproduction. The high level of acceptance of SCFT despite these issues may be explained by a preference for genetic parenthood and for preventing the ethical and practical concerns resulting from having to rely on donor gametes, but this should be examined further.

Finding most support for SCFT in young heterosexual couples with male or female infertility corresponds to this group receiving most support for current fertility treatments (Stern et al., 2002; Kovacs et al., 2003; Heikkila et al., 2004, 2006; Dempsey, 2010; Hostiuc, 2013; Wanggren et al., 2013). The few opponents of fertility treatments for young infertile heterosexual couples might not have reservations about the intended parents, but rather have deontological objections against fertility treatments and/or object to interfering with nature (Dempsey, 2010). On the one hand the support for SCFT for female infertility in single women (69–91%) is surprising as this application was flagged for further reflection in opinion papers from professionals (reviewed in Hendriks et al., 2015a, 2015b). On the other hand, it is in line with the acceptance of current fertility treatments for this group reported by previous studies (38–96%) (Stern et al., 2002; Kovacs et al., 2003; Kaplan et al., 2004; Gurmkin et al., 2005; Heikkila et al., 2004, 2006; Lawrence et al., 2010; Sperling and Simon, 2010; Wanggren et al., 2013). Reasons to accept this group of intended parents are likely to be similar for SCFT and current fertility treatments. More specifically, these reasons are the right to reproduce, equality, the unlikeliness that single-parent families are more likely to be psychologically harmful to children and the economic benefits of treating more patients (Crowe, 1985; Stern et al., 2002; Hunfeld et al., 2004; Master, 2006; Smajdor, 2008; Zachia et al., 2011). Gynaecologists being more accepting of treating female infertility in single women may relate to them already treating these women with currently available fertility treatments.

SCFT for same-sex couples were also flagged for further reflection in opinion papers from professionals (reviewed in Hendriks et al., 2015a, 2015b), but were in fact supported by the majority of our responding gynaecologists and members of the general public (50–68%). The support for current fertility treatments for same-sex

Table III Background characteristics determining the acceptability of SCFT by indication among the general public.

<table>
<thead>
<tr>
<th>Group of intended parents</th>
<th>Multivariate analysis</th>
<th>Significantly associated characteristics*</th>
<th>Adjusted OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young heterosexual couple with female infertility</td>
<td>Importance of religion</td>
<td>0.84</td>
<td>0.75–0.95</td>
<td></td>
</tr>
<tr>
<td>Young heterosexual couple with male infertility</td>
<td>Importance of religion</td>
<td>0.84</td>
<td>0.74–0.95</td>
<td></td>
</tr>
<tr>
<td>Young heterosexual couple with unexplained infertility</td>
<td>Importance of religion</td>
<td>0.92</td>
<td>0.85–0.99</td>
<td></td>
</tr>
<tr>
<td>Single woman with female infertility (also using a sperm donor)</td>
<td>Female gender</td>
<td>1.53</td>
<td>1.01–2.30</td>
<td></td>
</tr>
<tr>
<td>Lesbian couple</td>
<td>University education</td>
<td>0.61</td>
<td>0.38–0.99</td>
<td></td>
</tr>
<tr>
<td>Gay couple (also using a surrogate)</td>
<td>Importance of religion</td>
<td>0.86</td>
<td>0.80–0.92</td>
<td></td>
</tr>
<tr>
<td>Fertile woman who wants a child that is genetically only her own</td>
<td>Importance of religion</td>
<td>0.92</td>
<td>0.85–0.99</td>
<td></td>
</tr>
<tr>
<td>Heterosexual couple in which the woman is of post-menopausal age (50 years)</td>
<td>Importance of religion</td>
<td>0.88</td>
<td>0.82–0.94</td>
<td></td>
</tr>
</tbody>
</table>

*Listed background characteristics were significant at P > 0.05. Tested background characteristics: gender, age, European ethnicity, education, type of religion, importance of religion, political preference (conservative–progressive), social status, having children, heterosexual orientation, being in a relationship and having experience with infertility. OR, odds ratio.
couples varied a lot between studies (7–97%) (Miall, 1993; Stern et al., 2002; Kovacs et al., 2003; Kaplan et al., 2004; Gurmankin et al., 2005; Heikkila et al., 2004, 2006; Dempsey, 2010, Lawrence et al., 2010; Sperling and Simon, 2010; Zachia et al., 2011). The arguments against and in favour of current fertility treatment for same-sex couples are likely to also apply to SCFT. More specifically, the arguments against include: concerns for the well-being of children raised by same-sex couples, deontological objections, no medical condition to justify a medical intervention, possible effects of this new type of families on the parental roles in society, the need for a surrogate in case of gay couples, and general objections against homosexuality (Miall, 1993; Weiss, 2003; Hunfeld et al., 2004; Testa and Harris, 2004, 2005; Newson and Smajdor, 2005; Croker, 2006; Heikkila et al., 2006; Whittaker, 2007; Dempsey, 2010; Lawrence et al., 2010; Mertes and Pennings, 2010; Zachia et al., 2011). The arguments in favour of treating same-sex couples include: reproductive rights, equality, the proven well-being of children raised by same-sex couples, genetic parenthood presumably leading to better well-being of the children than adoption or conception with donor gametes and the economic benefits of treating more patients (Crowe, 1985; Stern et al., 2002; Testa and Harris, 2004, 2005; Master, 2006; Whittaker, 2007; Smajdor, 2008; Mertes and Pennings, 2010). In addition, two counterarguments might apply more to SCFT: the potentially increased risks of abnormalities when creating gametes of the opposite sex, and the implications for the biological relevance of males (Weiss, 2003, Mertes and Pennings, 2010).

Interestingly, the acceptability of using SCFT in case of unexplained infertility and the inherent presence of other options to attempt achieving genetic parenthood was low among gynaecologists but high among the general public (82% versus 43%, respectively). Gynaecologists might consider treating unexplained infertility an ‘off-label’ application as no cause to be treated has been identified. The general public might want to treat involuntary childlessness rather than a cause of infertility. The acceptance of other SCFT among the general public is also known to depend on the severity of the disorder treated (Evans and Kelley, 2011).

The limited likelihood of acceptance of SCFT in fertile women who want a child that is genetically only her own (by generating male gametes from her stem cells and then using these to fertilize her own oocytes, 6–27%) corresponds to the low acceptability of reproductive cloning (2–13%) (Woolacott, 1997; Stern et al., 2002; Sperling and Simon, 2010; Evans and Kelley, 2011; Hostiuc, 2013). Professionals have expressed concerns about increased risks of recessive diseases for the child and about transcending too far from natural reproduction (Stern et al., 2002; Cohen, 2005; Newson and Smajdor, 2005; Mertes and Pennings, 2007; Whittaker, 2007; Skene, 2008). Gynaecologists being less accepting of this indication may also relate to their knowledge of recessive diseases and resulting safety concerns.

The limited likelihood of acceptance of SCFT in heterosexual couples in which the women are over 50 years of age (17–26%) is comparable to the limited acceptance of this group of intended parents for current fertility treatments (10–50%) (Stern et al., 2002; Heikkila et al., 2004, 2006; Maheshwari et al., 2008; Lawrence et al., 2010; Sperling and Simon, 2010; Billari et al., 2011). Two main arguments against current fertility treatments for older women also apply to SCFT: the increased risks of obstetric complications and concerns about older parents’ ability to raise a child (Letherby, 1999; Mertes and Pennings, 2010; Billari et al., 2011; Luyten et al., 2015). The argument against current fertility treatments in older women that does not apply to SCFT is the concern about the increased risks of chromosomal anomalies (Billari et al., 2011). Gynaecologists being more accepting than the general public of treating older women might be related to gynaecologists being more likely to be exposed to, and thereby empathize with, this group of intended parents, and/or their knowledge that data on child outcomes from being raised by older parents shows benefits rather than harms (Stein and Susser, 2000; Kalmijn and Kraaykamp, 2005; Billari et al., 2011).

Two of the six respondent characteristics associated with being more likely to accept SCFT were not surprising in the light of the literature on the acceptability of current fertility treatments. Higher age (Lawrence et al., 2010) and attaching low importance to religion (Chliaoutakis et al., 2002; Papaharitou et al., 2007; Lawrence et al., 2010, Evans and Kelley, 2011), were also associated with being more likely to accept current fertility treatment for certain groups of intended parents. The other four characteristics associated with the likeliness to accept SCFT were more surprising. Our finding that respondents with a University degree were less likely to accept SCFT contrast with the positive association between having a University degree and the acceptance of other reproductive technologies and other SCFT (Miall, 1993; Evans and Kelley, 2011). Our finding that a progressive political preference was associated with more acceptance is surprising in the light of the lack of an association between political preferences and the acceptance of gamete donation (Chliaoutakis et al., 2002) but matches its association found with other stem cell treatments (Evans and Kelley, 2011). Previous studies report contrasting results relating to women or men being more accepting of assisted reproduction (Miall, 1993; Lawrence et al., 2010). Our finding that having an ethnicity other than European was associated with being more likely to accept SCFT for certain indications is interesting, as the relation between ethnicity and acceptability of reproductive technologies has rarely been studied (Hudson et al., 2009).

It is important to note that SCFT are yet to be applied clinically. Nevertheless, recent biomedical breakthroughs have shortened the time to clinical implementation (Hikabe et al., 2016; Zhou et al., 2016; Boiani, 2017; Cohen et al., 2017). Once proven safe and effective, a fear of limited acceptability by the general public should not keep gynaecologists from offering SCFT (in research settings) to single infertile women and same-sex couples as well as to young infertile heterosexual couples. Future research into the acceptability of SCFT should focus on the exact conditions under which SCFT would be acceptable (e.g. maximal rate of congenital anomalies). This could, for example, include investigating how respondents trade-off advantages (e.g. genetic parenthood) and disadvantages (e.g. safety) of SCFT. Additionally, qualitative studies may examine the underlying motivations explaining differences in acceptability of treating different patient groups with these treatments. Such an in-depth analysis of conditions for implementation would add to the insights gathered here. Furthermore, the reasons why some respondents did not express an opinion could be explored. It would also be interesting to directly compare the acceptability of SCFT with current fertility treatments, and to examine cultural and temporal differences in acceptability.

Supplementary data

Supplementary data are available at Molecular Human Reproduction online.
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Authors’ roles

S.H. contributed to the study design, data collection, analysis, manuscript drafting and critical discussion. E.A.F.D. contributed to the study design, analysis, manuscript drafting and critical discussion. S.R. and R.V. contributed to the study design and critical discussion.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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