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ORIGINAL ARTICLE *Infertility*

International consensus: ovarian tissue cryopreservation in young Turner syndrome patients: outcomes of an ethical Delphi study including 55 experts from 16 different countries

M.J. Schleedoorn[1,*], B.H. Mulder[1], D.D.M. Braat[1], C.C.M. Beerendonk[1], R. Peek[1], W.L.D.M. Nelen[1], E. Van Leeuwen[2], A.A.E.M. Van der Velden[3], and K. Fleischer[1], on behalf of the Turner Fertility expert panel[†]

[1]Obstetrics and Gynaecology, Radboud University Medical Centre, Nijmegen, The Netherlands, [2]Medical Ethics, Radboud University Medical Centre, Nijmegen, The Netherlands, and [3]Paediatric Endocrinology, Radboud University Medical Centre Amalia Children's Hospital, Nijmegen, The Netherlands

*Correspondence address. Department of Obstetrics and Gynaecology (route 791), Radboud University Medical Center P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; E-mail: myra.schleedoorn@radboudumc.nl

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STUDY QUESTION: What is the standpoint of an international expert panel on ovarian tissue cryopreservation (OTC) in young females with Turner syndrome (TS)?

SUMMARY ANSWER: The expert panel states that OTC should be offered to young females with TS, but under strict conditions only.

WHAT IS KNOWN ALREADY: OTC is already an option for preserving the fertility of young females at risk of iatrogenic primary ovarian insufficiency (POI). Offering OTC to females with a genetic cause of POI could be the next step. One of the most common genetic disorders related to POI is TS. Due to an early depletion of the ovarian reserve, most females with TS are confronted with infertility before reaching adulthood. However, before offering OTC as an experimental fertility preservation option to young females with TS, medical and ethical concerns need to be addressed.

STUDY DESIGN, SIZE, DURATION: A three-round ethical Delphi study was conducted to systematically discuss whether the expected benefits exceed the expected negative consequences of OTC in young females with TS. The aim was to reach group consensus and form an international standpoint based on selected key statements. The study took place between February and December 2018.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Anonymous panel selection was based on expertise in TS, fertility preservation or medical ethics. A mixed panel of 12 gynaecologists, 13 (paediatric) endocrinologists, 10 medical ethicists and 20 patient representatives from 16 different countries gave consent to participate in this international Delphi study. In the first two rounds, experts were asked to rate and rank 38 statements regarding OTC in females with TS. Participants were offered the possibility to adjust their opinions after repetitive feedback. The selection of key statements was based on strict inclusion criteria.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 46 participants completed the first Delphi round (response rate 84%). Based on strict selection criteria, six key statements were selected, and 13 statements were discarded. The remaining 19 statements and two additional statements submitted by the expert panel were re-evaluated in the second round by 41 participants (response rate 75%). The analysis of the second survey resulted in the inclusion of two additional key statements. After the approval of these eight key statements, the majority of the expert panel (96%) believed that OTC should be offered to young females with TS, but in a safe and controlled research setting first, with proper counselling and informed consent procedures, before offering this procedure in routine care. The remaining participants (4%) did not object but did not respond despite several reminders.

LIMITATIONS, REASONS FOR CAUTION: The anonymous nature of this study may have led to lack of accountability. The selection of experts was based on their willingness to participate. The fact that not all panellists took part in all rounds may have resulted in selection bias.

[†]Members of the TurnerFertility expert panel are listed in the acknowledgements.

WIDER IMPLICATIONS OF THE FINDINGS: This international standpoint is the first step in the global acceptance of OTC in females with TS. Future collaborative research with a focus on efficacy and safety and long-term follow-up is urgently needed. Furthermore, we recommend an international register for fertility preservation procedures in females with TS.

STUDY FUNDING/COMPETING INTEREST(S): Unconditional funding (A16-1395) was received from Merck B.V., The Netherlands. The authors declare that they have no conflict of interest.

Key words: Turner syndrome / fertility preservation / ovarian tissue cryopreservation / Delphi study / ethics / primary ovarian insufficiency / international statement / paediatrics / endocrinology—disorders of sex development

Introduction

Removal of one of the two ovaries for cryopreservation followed by autotransplantation of ovarian cortex fragments in the future (i.e. ovarian tissue cryopreservation: OTC) is already an option for preserving the fertility of young females at risk of iatrogenic primary ovarian insufficiency (POI) (Jensen *et al*., 2015; 'Netherlands Network of Fertility Preservation (NNF),' 2016; 'Oncoline,' 2016; Van der Ven *et al*., 2016). Offering OTC to females with a genetic cause of POI could be the next step. One of the most common genetic conditions related to POI is Turner syndrome (TS), affecting 25–50 per 100 000 live-born girls (Gravholt *et al*., 2017).

TS is caused by the partial or complete absence of one of the sex chromosomes. Missing an X or Y chromosome affects foetal development. Signs and symptoms vary greatly among females with TS but are mostly related to the patient's karyotype. Monosomy 45,X is associated with a more severe lymphatic and skeletal phenotype, while the dysmorphic features of patients with a mosaic karyotype can be very mild, depending on the level of mosaicism. No association was found between karyotype and cardio-aortic malformations (Noordman *et al*., 2018). The majority of females with TS are diagnosed before the age of 12 years because of growth retardation (Massa *et al*., 2005). TS may be diagnosed prenatally by chorionic villus sampling or amniocentesis in cases of foetal cystic hygroma, intra-uterine growth retardation, cardiovascular malformations or advanced maternal age, or shortly after birth because of dysmorphic signs such as neck webbing, cubitus valgus and lymphoedema. In a few cases, TS is diagnosed in adolescence because of delayed puberty or primary or secondary amenorrhea.

Females with TS are known to have a shorter reproductive lifespan due to an accelerated loss of germ cells. This process starts during meiosis I of the foetal oocyte and continues until the point when the ovarian reserve is completely exhausted (Weiss, 1971; Reynaud *et al*., 2004). In most females with TS, this point is reached during childhood or early adolescence (Reynaud *et al*., 2004). Up to 33% have some pubertal development and 10–15% experience one or more spontaneous menstruation cycles (Pasquino *et al*., 1997; da Silva Negreiros *et al*., 2014; Tanaka *et al*., 2015). Hence, spontaneous pregnancies in adult females with TS are rare, occurring in ~2.0–7.6% of cases (Hovatta, 1999; Birkebaek *et al*., 2002; Bryman *et al*., 2011; Hadnott *et al*., 2011; Bernard *et al*., 2016).

As the majority of females with TS are unable to conceive a child naturally, most of them depend on alternative parenting options such as adoption, foster care or oocyte donation. However, like most women, females with TS prefer a genetically related child above other forms of parenting, as adoption, foster care or oocyte donation have their own limitations (Hallebone, 1991; Bracewell-Milnes *et al*., 2016). The inability to bear biological children is the most prevalent and painful challenge experienced by most females with TS, especially at the moment that their family and friends begin to procreate (Sylven *et al*., 1993; Sutton *et al*., 2005). In an interview study with 97 females with TS aged 7–59 years and 21 parents, uncertainty about their fertility started at a young age and was a major concern for both groups (Sutton *et al*., 2005). In females with other causes of POI, uncertainty about fertility and the inability to have biological offspring was associated with a reduction of quality of life and serious psychosocial disorders (Nilsson, 2014).

It is, therefore, unsurprising that physicians are increasingly being asked about fertility preservation (FP) options for females with TS (Grynberg *et al*., 2016), especially as research shows that oocytes can still be found in the ovaries of some girls with TS (Hreinsson *et al*., 2002; Huang *et al*., 2008; Kavoussi *et al*., 2008; Borgstrom *et al*., 2009; Lau *et al*., 2009; Balen *et al*., 2010; El-Shawarby *et al*., 2010; Oktay *et al*., 2010; Oktay & Bedoschi, 2014; Balkenende *et al*., 2015; von Wolff *et al*., 2015; Finlayson *et al*., 2017; Jensen *et al*., 2017; Mamsen *et al*., 2019; Talaulikar *et al*., 2019).

FP is the process of safeguarding the patient's own gametes so that these can be used to have biological children in the future. In single females, FP can be performed by either the vitrification of mature oocytes or by cryopreserving ovarian tissue containing primordial follicles. Vitrification of mature oocytes (oocyte cryopreservation, OC) is the most established FP approach but is limited to a small percentage of females with TS only, i.e. those with a spontaneous menstrual cycle during adolescence or adulthood (Oktay *et al*., 2015). Furthermore, females interested in OC have to be emotionally mature enough to undergo the procedure, which involves a period of at least 2 weeks with daily hormone injections, frequent ultrasonographic monitoring, and transvaginal oocyte retrieval (Oktay *et al*., 2015). In view of these limitations, OTC appears to be a more promising technique to preserve the fertility of females with TS, as it can be performed regardless of the patient's age or ovarian activity. This procedure may offer more females with TS the possibility to store a number of primordial follicles before their disappearance (Borgstrom *et al*., 2009).

Since 2002, OTC procedures have been performed experimentally in more than 100 young females with TS (Hreinsson *et al*., 2002; Huang *et al*., 2008; Borgstrom *et al*., 2009; Balen *et al*., 2010; von Wolff *et al*., 2015; Finlayson *et al*., 2017; Jensen *et al*., 2017; Mamsen *et al*., 2019) [ClinicalTrials.gov: NCT01410045]. Unfortunately, optimal discriminative markers for the presence or absence of follicles are lacking, but there is a general agreement that the mosaic karyotype is the most likely group to have ovarian follicles and to benefit from FP (Borgstrom *et al*., 2009; Oktay *et al*., 2015; Grynberg *et al*., 2016; Mamsen *et al*., 2019).

Thus far, there are no published records of girls with TS who have returned for autotransplantation of cryopreserved ovarian tissue. Hence, the efficacy of OTC in females with TS remains unknown. In other patient groups, the occurrence of pregnancy and live birth after autotransplantation of cryopreserved ovarian tissue is highly correlated with the number of functional primordial follicles found in the ovarian tissue (Donnez, 2011). However, even in these patient groups there is limited data regarding the efficacy of the procedure when OTC is performed at a very young age (Demeestere *et al*., 2015). Autotransplantation of ovarian cortex fragments with a decreased follicular density combined with the risk of re-initiation of accelerated follicle apoptosis might be less effective. Possibly, *in vitro* activation (IVA) of residual dormant follicles (Kawamura *et al*., 2013; Suzuki *et al*., 2015; Kawamura *et al*., 2016; Zhai *et al*., 2016) prior to autotransplantation might be helpful in females with TS to optimize their fertility chances. However, no cases of IVA in patients with TS have been reported thus far. The isolation and IVM of primordial follicles from cryopreserved ovarian tissue could become an effective alternative to autotransplantation in the future (McLaughlin *et al*., 2018). However, this method is still experimental and not yet available in the clinic. Hence, females with TS who are currently undergoing OTC are still depending on autotransplantation.

Even if the follicular density is normal or slightly decreased, it remains questionable if autotransplantation of cryopreserved ovarian tissue in females with TS will lead to healthy offspring, as females with TS females who conceived spontaneously are known to have an increased risk of miscarriages and chromosomal abnormalities among their offspring (Bernard *et al*., 2016). Whether these increased risks are related to the quality and functional integrity, or the chromosome profile, of the follicular cells remains unclear.

Hence, offering OTC in routine clinical care could give false hope and psychological harm in the future. Young patients might not be able to fully understand the possible risks and benefits of the procedure (Di Pietro *et al*., 2012; McDougall, 2015; Wallace *et al*., 2016), and thus, parents will be burdened with this decision (Hreinsson & Fridstrom, 2004).

Another concern that should be taken into account is that OTC requires laparoscopic surgery under general anaesthesia with a possible risk of complications (Jansen *et al*., 1997). Furthermore, removing half of the ovarian reserve in females with TS might impact their chances for spontaneous puberty, menstruation and pregnancy. The short-term and long-term effects of the surgical removal of one ovary in females with TS are currently unknown, but recent studies (Bellati, 2014; Geomini, 2014; Khan, 2014; Lass, 1999) have shown that the surgical removal of one ovary in females with a normal ovarian reserve does not affect the patient's menstrual cycle, or their chance for spontaneous pregnancies in the future (Coccia *et al*., 2011). However, the procedure could lead to early menopause, of up to 3 years earlier in comparison to a woman who still has both ovaries (Bjelland *et al*., 2014).

Lastly, one should consider that pregnancies in females with TS show more foetal and maternal complications compared to pregnancies in healthy females. Pregnant females with TS have an increased risk of intra-uterine growth restriction and preterm labour (Hewitt *et al*., 2013). Thyroid dysfunction, diabetes, obesity, hypertension and pre-eclampsia occur in ~40% of pregnant women with TS (Hewitt *et al*., 2013). In the past, women with TS were advised to avoid pregnancy due to the risk of mortality. Recent studies have shown that the risk for aorta dissection and maternal mortality associated with pregnancy have decreased from 2.0 to 0.5% due to increased awareness of cardiovascular complications, stringent preconception screening and cardiovascular follow up during pregnancy (Gravholt *et al*., 2017; van Hagen *et al*., 2017). Pregnancies in females with TS should be strictly monitored by a multidisciplinary team including high-care obstetricians, and cardiologists and anaesthesiologists with expertise in maternal heart disease and/or disease of the aorta. If this care is unavailable, pregnancies in females with TS might be contraindicated because of an increased risk of complications.

For the above mentioned reasons, FP in females with TS remains a controversial topic for clinicians (Borini & Coticchio, 2019). However, patient organizations are optimistic and demand equal access to FP options worldwide (Borgstrom *et al*., 2009; Di Pietro *et al*., 2012). To further explore the opinion of international professionals and patient representatives, we conducted a three-stage ethical Delphi study to systematically discuss the advantages and disadvantages of OTC in females with TS. The aim of this study was to reach group consensus and to form an internationally accepted standpoint as to whether OTC should be offered to females with TS, or not.

Materials and Methods

The RAND/UCLA Delphi procedure (Dalkey, 1969; Fitch *et al*., 2001; Boulkedid *et al*., 2011) was used to combine scientific evidence with the expertise and opinion of different international experts within the field of TS, OTC or medical ethics. The Delphi procedure is a well-accepted method for attaining group consensus. It is a structured process that uses a series of questionnaires or rounds to gather information from different experts anonymously. Rounds are held until group consensus is reached according to predetermined defined consensus rules. In medical research, the Delphi procedure is commonly used to reach consensus on key recommendations (Schleedoorn *et al*., 2016), quality indicators (Campbell *et al*., 2003) or key statements (Carley *et al*., 1999).

In this study, the Delphi procedure was used to determine whether the expected benefits exceed the expected negative consequences of OTC in TS (Brook *et al*., 1986; Boulkedid *et al*., 2011). The outcome of this study was an international standpoint for or against OTC in females with TS, supported by a set of key statements.

Two questionnaire rounds and one agreement round were performed. Panel members were polled individually and anonymously. Participants were offered the possibility to adjust their opinions after repetitive feedback after each round, thus avoiding the negative social influences associated with face-to-face discussion (Fitch *et al*., 2001). Questionnaires were conducted by electronic data capture, using *CastorEDC*® (Castor, George Westinghousestraat 2, 1097 BA, Amsterdam, The Netherlands). Possibilities to add new statements or comments were provided in each questionnaire. Invitations and reminders were sent via *CastorEDC*®. All scores were listed in a database created with IBM SPSS Statistics version 25.0 (IBM Netherlands, Johan Huizingalaan 765, P.O. Box 9999, 1066 VH Amsterdam, Netherlands). The consensus procedure took place between February and December 2018.

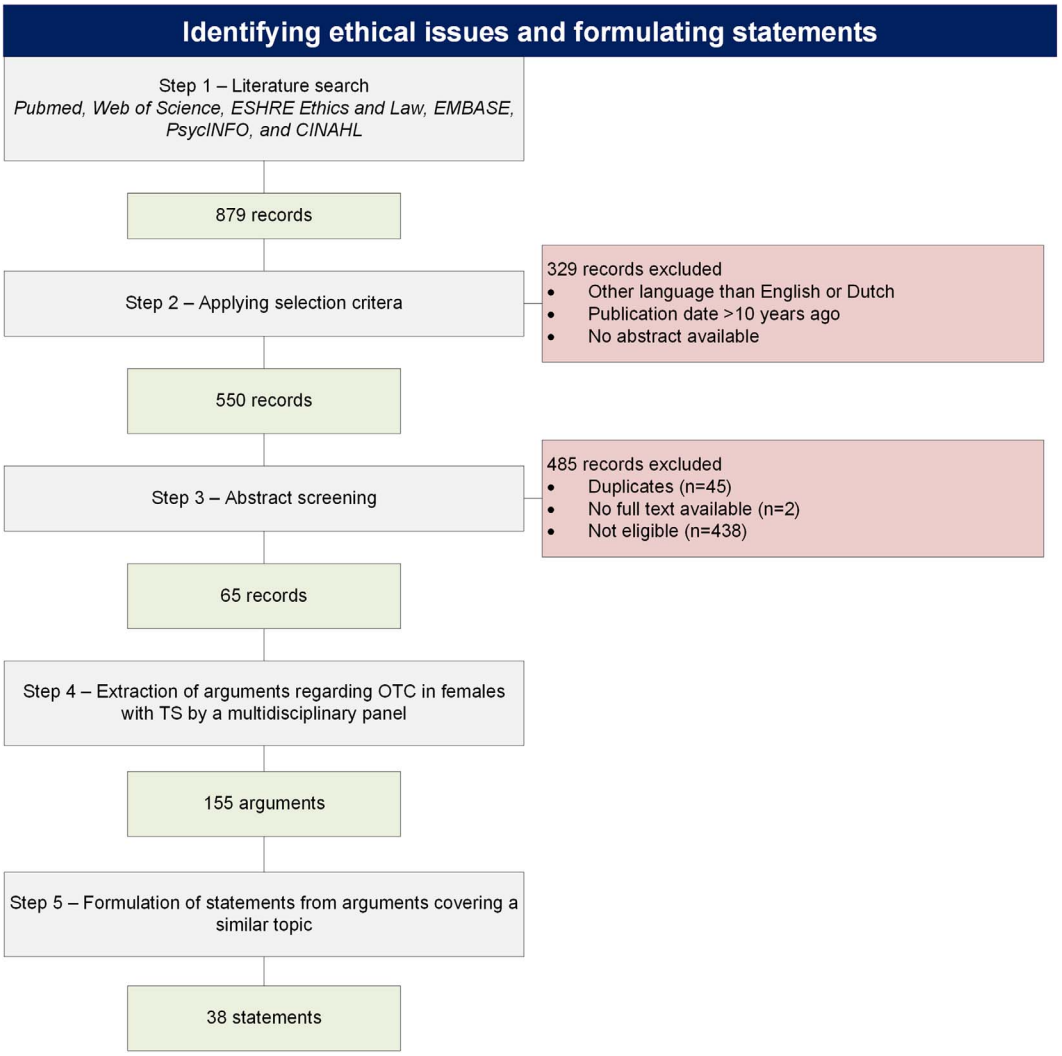

Figure 1 Identifying ethical issues and formulating statements concerning potential use of ovarian tissue cryopreservation in young females with Turner syndrome. The figure provides a detailed description of the comprehensive literature search, extraction of arguments and formulation of statements. OTC: ovarian tissue cryopreservation, TS: Turner syndrome.

Identifying ethical issues and formulating statements

A total number of 65 articles were screened for arguments both for and against OTC in TS after a comprehensive literature search (Fig. 1). Each article was screened independently by two researchers from a multidisciplinary research group (i.e. two gynaecologists (n = K.F., C.B.), one paediatric endocrinologist (n = A.v.d.V.), one medical ethicist (E.v.L.), one senior scientist in reproductive biology (n = R.P.) and one physician in reproductive medicine (M.S.) for arguments regarding OTC in females with TS. None of these researchers participated in the Delphi selection procedure. Arguments were extracted if both independent researchers agreed.

This selection procedure resulted in a total number of 155 arguments regarding OTC in TS. Arguments focusing on a similar topic were grouped and brought together into a framework of 38 statements (Supplementary Table SI). These statements were divided over the four basic ethical domains (Gillon, 1994), i.e. beneficence (n = 18), autonomy (n = 5), non-maleficence (n = 8) and justice (n = 7). Each statement highlighted a specific ethical concern regarding OTC in females with TS. The original 155 arguments are presented as additional information below each statement.

Selection of key statements and formulation of a common stand

Step 1: Composition of the expert panel

To enhance the acceptance of this international standpoint in clinical practice, the expert panel consisted of a representative diversity of international professionals and patient representatives. Sufficient English language proficiency was an admission requirement for all experts.

Invitations for the Delphi study were sent out by e-mail to 59 international professionals (female professionals n = 37, male professionals

$n = 22$) with expertise in the field of FP, TS and/or medical ethics. Eligible experts were gynaecologists ($n = 18$) and (paediatric-) endocrinologists ($n = 17$) with either a prominent role in one or more international expert groups (i.e. ESHRE Special Interest Group for Fertility Preservation, DSD-Life, Oncofertility, FertiPROTEKT or Turner Syndrome Guideline Group) and/or an author of one or more key publications regarding FP in females with TS. Medical ethicists ($n = 24$) were recruited by the ESHRE Task Force Ethics & Law and the personal network of the senior research team members (K.F., A.v.d.V., E.v.L., W.N., C.B., R.P., D.B.). Patient representatives should have had a prominent role in one of the international TS patient organizations. Therefore, a request for patient representatives (i.e. patients and/or parents of patients) was sent out to 17 patient organizations in 15 different countries. Contact data from 38 patient representatives were obtained, and invitations were sent out to them by e-mail.

Step 2: First Delphi round

In the first Delphi round, the panel was asked to rate the 38 statements on a 9-point Likert scale ranging from 1 (extremely irrelevant) to 9 (extremely relevant). Relevance was graded by the experts in response to the following question: *'To what extent is the following statement an important determinant to offer/discourage OTC in young females with TS?'*. Participants were encouraged to read the original arguments and were provided with supporting evidence and background information. By the end of the questionnaire, participants were asked to create a top 5 of their most relevant statements to promote discrimination between recommendations with a high Likert score. In addition, they were given the option to add comments and new statements. Participants were given 4 weeks to complete the first round. Reminders were sent after 2 and 3 weeks.

The results of the first round were analysed using predefined consensus criteria based on Campbell's criteria (Campbell *et al*., 2000). These criteria include a median score of 8 or higher without panel disagreement. Panel disagreement was defined as the case in which 25% or more of the individual scores was in the lowest tertile of the scale (Likert score 1–3). Previous studies (Mourad *et al*., 2007; van den Boogaard *et al*., 2010; Stienen *et al*., 2011; Uphoff *et al*., 2012; Dancet *et al*., 2013; den Breejen, 2013; Luitjes *et al*., 2013; Woiski *et al*., 2015) have shown that Campbell's criteria alone are often not discriminative enough. Therefore, a third criterion was added, which is commonly used in Delphi studies, namely a top 5 score (Mourad *et al*., 2007; van den Boogaard *et al*., 2010; Stienen *et al*., 2011; Uphoff *et al*., 2012; Dancet *et al*., 2013; Luitjes *et al*., 2013; Woiski *et al*., 2015). Recommendations should have at least a top 5 score of 35 points or higher. Points were awarded to each top-five ranking position, with number 1 position = 5 points, number 2 position = 4 points, number 3 position = 3 points, number 4 position = 2 points and number 5 position = 1 point. The authors combined the three criteria as described above and converted them into three possible outcomes 'selected', 'rejected', or 'no consensus'. Recommendations that met all three criteria were classified as 'selected', those who met none of the criteria as 'rejected' and the remaining recommendations as 'no consensus'. The 'no consensus' recommendations were again discussed in the second questionnaire round.

Step 3: Second Delphi round

The second round started with an overview of the selected, rejected and 'no consensus' recommendations. First, the experts were asked for their approval of the key statements that have been selected in the first round. Second, the expert panel was asked to revise their opinion for the 'no consensus' recommendations in light of the replies of the other panel members. The overall median score, the median score of each subgroup, the total top 5 score and their own previous rating were shown for each statement. When experts were not able to participate in the first Delphi round ($n = 9$), but wanted to participate in the second Delphi round, the overall median score, the median score of each subgroup and the total top 5 score were shown for each statement. Participants were asked once again to score the 'no consensus' recommendations on the same 9-point Likert scale as used in the first Delphi round (ranging from 1 (extremely irrelevant) to 9 (extremely relevant)). By the end of the questionnaire, the recommendations that they scored with 8 or higher were shown, and participants were asked to select up to three additional statements.

Participants were given 3 weeks to complete the second round. Reminders were sent after 1 week and after 2 weeks.

The selection of additional key statements during the second round was based on two predefined criteria that were used during the first round (i.e. a median score of 8 or higher and panel disagreement below 25%). Furthermore, additional key statements should be selected by at least 30% of the experts. These three criteria were combined and converted into two possible outcomes: 'selected' or 'rejected'. Recommendations that met all criteria were classified as 'selected' and the remaining recommendations as 'rejected'.

After having discussed the medical and ethical aspects of OTC in females with TS, the expert panel was asked to form a current standpoint if OTC should be offered to young females with TS or not.

Step 4: Final approval

An overview of the selected key statements and the current expert panel's standpoint was sent out by e-mail to all 55 experts who initially gave consent for study participation, as 14 out of the 55 experts (25%) did not participate in the second Delphi round. They were provided with a last opportunity to make remarks and asked for their approval of the final set of key statements and the expert panel's standpoint in order to reach international consensus.

Results

Selection of key statements and formulation of a common stand

Step 1: Composition of the expert panel

A total number of 12 gynaecologists, 13 (paediatric) endocrinologists, 10 medical ethicists and 20 patient representatives (patients $n = 7$, parents $n = 13$) from 16 different countries gave consent to participate in this study, forming an international expert panel of 55 members (Fig. 2). The composition of the expert panel for each Delphi round has been visualized in Supplementary Figure S1.

All professionals, except one of the (paediatric) endocrinologists, were employed in academic hospitals or were working in an academic setting. Most of them were females ($n = 23$), and about one-third of them were male professionals ($n = 12$).

Gynaecologists had an average work experience of 23 years (range 9–40 years), (paediatric) endocrinologists had an average work experience of 21.4 years (range 7–40 years) and medical ethicists had an average work experience of 22 years (range 9–38 years).

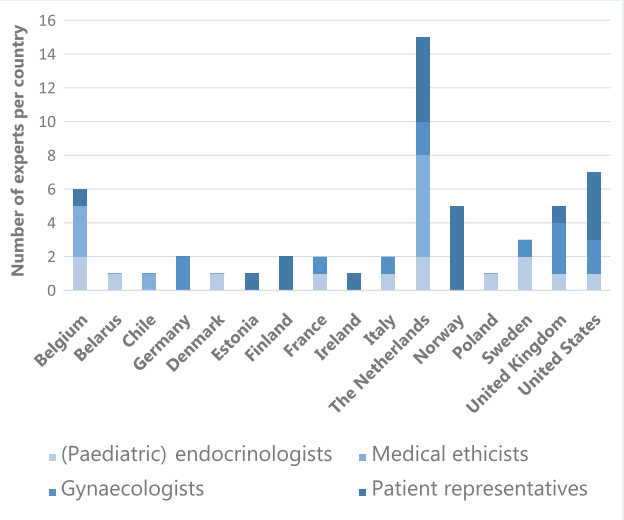

Figure 2 Members of the TurnerFertility expert panel (*n* = 55) divided by country. (Paediatric) endocrinologists: (*n* = 13) representing 10 countries: Belgium (*n* = 2), Belarus (*n* = 1), Denmark (*n* = 1), France (*n* = 1), Italy (*n* = 1), The Netherlands (*n* = 2), Poland (*n* = 1), Sweden (*n* = 2), UK (*n* = 1), USA (*n* = 1). Medical ethicists (n = 10) representing three countries: Belgium (n = 3), The Netherlands (n = 6), Chile (n = 1). Gynaecologists: (*n* = 12) representing seven countries: Germany (*n* = 2), France (*n* = 1), Italy (*n* = 1), The Netherlands (*n* = 2), Sweden (*n* = 1), UK (*n* = 3), USA (*n* = 2). Patient representatives: (*n* = 20) (7 patients with TS and 13 parents) representing eight countries: Belgium (*n* = 1), Estonia (*n* = 1), Finland (*n* = 2), Ireland (*n* = 1), The Netherlands (*n* = 5), Norway (*n* = 5), UK (*n* = 1), USA (*n* = 4).

Most of the professionals (77%) had children themselves, and most of them conceived spontaneously. Two professionals conceived using ART, and one professional adopted a child.

The remaining panel consisted of 20 patient representatives, 7 females with TS and 13 parents of patients with TS. The average age for patients was 32 years (range 18–50) and for parents 45 years (range 36–55).

Most patient representatives were highly educated, with at least an associate degree (*n* = 15), while the remaining five patient representatives finished at least high school. None of the women with TS had children themselves, but all except one expressed a desire to have children in the near future. None of them had tried ART. One woman with TS tried to adopt a child but was rejected for unknown reasons. One of the parents adopted a child, and the others conceived spontaneously.

Step 2: First Delphi round

A total number of 46 participants completed the first Delphi round (response rate 84%). Reasons for not participating were concerns about privacy (*n* = 1), not enough time (*n* = 4), not feeling sufficiently involved with the subject (*n* = 2), a conflict of interest (*n* = 1) and software problems (*n* = 1). The average time for completing the first survey was 30 min.

Based on the predefined selection criteria, 6 of the 38 statements were selected as key statements (Fig. 3). These six key statements were divided over the four ethical domains (beneficence (*n* = 2), autonomy (*n* = 1), non-maleficence (*n* = 2) and justice (*n* = 1)). In the first round, 13 statements could be discarded, and 19 statements remained undetermined. In addition, two new statements submitted by the expert panel, were added to the second Delphi round (Supplementary Table SI).

Step 3: Second Delphi round

The remaining 19 statements and the two additional statements submitted by participants were re-evaluated in the second round by 41 participants (response rate 75%). Time investment was reported as the main reason for not participating. The average time for completing the second survey was 10 min.

The analysis of the second survey resulted in the inclusion of two additional key statements (Fig. 3). The other 19 statements could be discarded.

By the end of the second Delphi round, 30 experts (75%) believed that OTC should be offered to young females with TS in a safe and controlled research setting, one participant voted against (2%) and 10 experts chose to remain neutral (24%).

Step 4: Final approval

The final set of eight key statements (Fig. 3) and the current expert panel's standpoint were approved by 53 out of 55 participants (response rate 96%). All experts, including those who voted against, remained neutral or did not respond in the second Delphi round, now agreed that OTC should be offered to young females with TS, but under strict conditions only. The expert panel suggested a research setting, with proper counselling and informed consent procedures, and a long-term follow-up to study the efficacy of OTC in young females with TS first, before offering this procedure in routine care.

Two experts (4%), one gynaecologist and one medical ethicist, did not respond despite several reminders.

The detailed process of study enrolment and response rates by Delphi round is shown in Figure 4. A process description of the key statement selection by Delphi round can be found in Supplementary Figure S2.

Differences in scoring behaviour between experts

In the first Delphi round, patient representatives mainly highlighted arguments focusing on the psychological harm of infertility, and one of the key statements was selected by the patient representatives despite a moderate popularity among the professionals. This statement focused on the impact of infertility on the quality of life. Medical ethicists were more concerned about creating false hope resulting in psychological harm in the future. Gynaecologists and (paediatric-) endocrinologists underlined statements regarding non-maleficence. The fact that young TS patients might be too immature to give informed consent was considered a major issue for both patient representatives and (paediatric) endocrinologists but was not recognized by the gynaecologists and medical ethicists. Younger participants (<25 years old) expressed the importance of including all patients in the consent process, regardless of their age. The statement that 'infertility leads to psychological harm' was selected twice as frequently by participants without children compared to participants with children. Male

KEY STATEMENTS	Delphi round	Median total	Median (paediatric) endocrinologists	Median medical ethicists	Median gynaecologists	Median patient representatives	Panel disagreement	Top 5 score	Selection percentage
Theme 1: Beneficence									
1. Infertility in women with Turner syndrome leads to psychological harm.	1	8	8	8	8	7.5	2.2%	46	-
2. Patients with Turner syndrome rate their own infertility as their primary concern.	1	8	8	8	7	8	4.3%	65	-
3. There are other ways to become a parent besides having genetically own children.	2	8	7.5	7	8	7.5	4.9%	-	30.5%
Theme 2: Autonomy									
4. Regardless their age, girls with Turner syndrome should be included in the consent process.	1	8	8	8	8	7.5	4.3%	38	-
Theme 3: Non-maleficence									
5. Pregnancies in women with Turner syndrome are associated with higher rates of maternal complications.	1	8	8	7	9	8	6.5%	52	-
6. Pregnant women with Turner syndrome are at risk of severe cardiac complications and mortality.	1	8	8	6	8	8	6.5%	60	-
Theme 4: Justice									
7. Patients at risk of premature ovarian insufficiency should have equal access to counselling and fertility preservation options.	1	8	8	8	9	8	6.5%	70	-
Additional statements									
8. Each girl with TS interested in OTC, should be discussed within a multidisciplinary expert team, after psychosocial and cardiologic screening have taken place.	2	8	8	7	9	7.5	7.3%	-	44.4%

Figure 3 The final set of eight key statements divided among the four basic ethical themes (beneficence, autonomy, non-maleficence and justice). Inclusion was based on predetermined selection criteria (i.e. a median score of 8 or higher AND panel disagreement below 25%) AND a top 5 score of 35 points or higher (first Delphi round) OR a selection percentage of 30% or more (second Delphi round).

participants were more concerned about pregnancy-related complications, whereas the female participants highlighted the psychological harm of infertility. Religion, age and the availability of OTC in the participant's country did not influence the scoring behaviour between participants in the first Delphi round.

Differences in scoring behaviour between the various experts were only seen in the first Delphi round and disappeared in the following two rounds when opinions were exchanged.

Discussion

In this Delphi study, we demonstrated that an international expert panel of both professionals and patient representatives agreed that OTC in patients with TS should be offered, but in a safe and controlled research setting only. The expert panel's standpoint was supported by eight key statements (Fig. 3). The first two statements highlighted that infertility leads to psychological harm, and that patients with TS

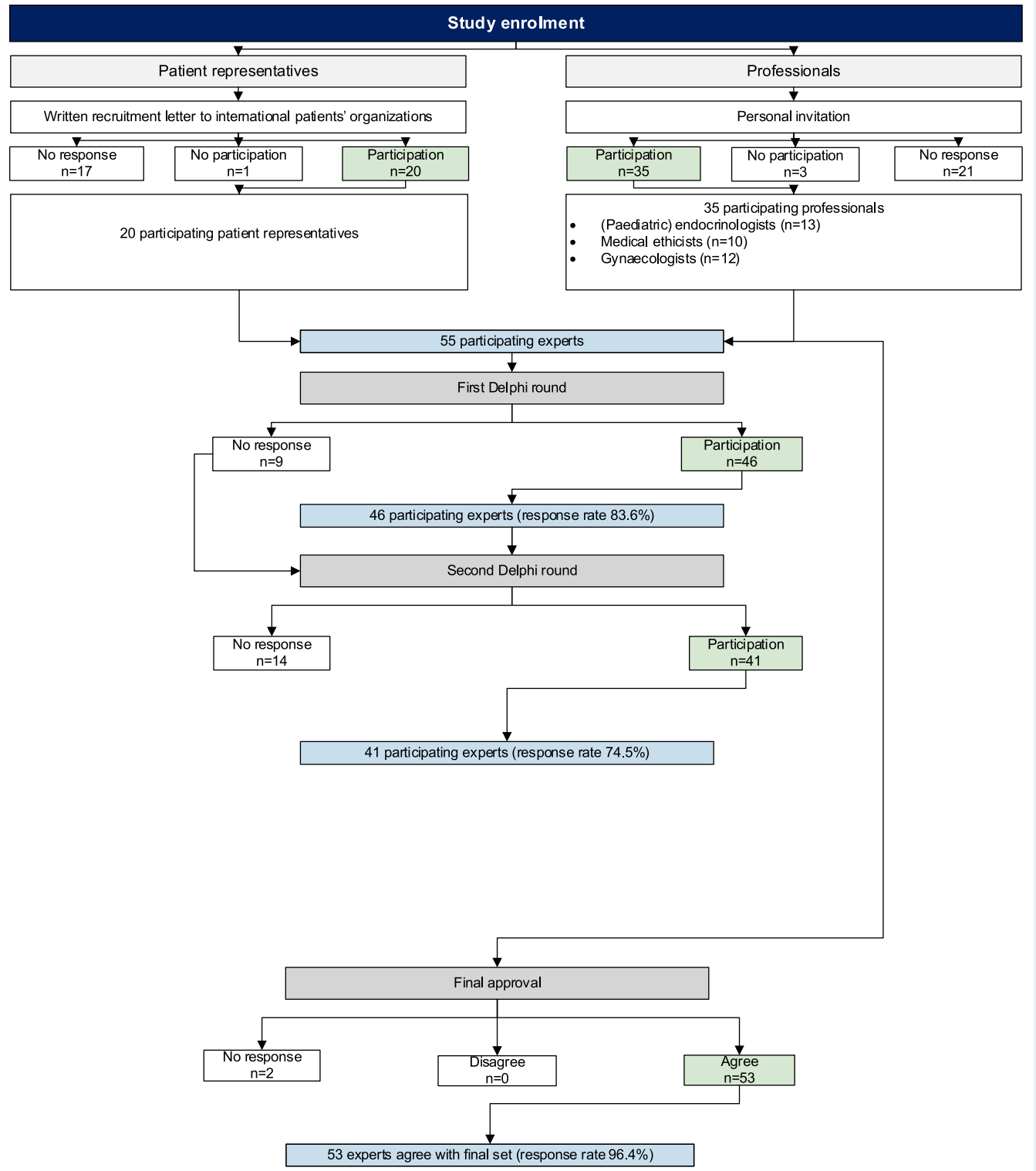

Figure 4 **Detailed process of study enrolment and response rates by Delphi round.**

consider this their main concern (key statements 1 and 2). In addition, patients with TS should have equal access to FP options, in line with other patient groups (e.g. patients awaiting cancer treatments) (key statement 7). However, there were concerns about the increased risk of maternal morbidity and mortality associated with TS during a future pregnancy (key statements 5 and 6). Patients with TS should be counselled about the alternative options for future parenthood (i.e. adoption, fostering and oocyte donation) (key statement 3).

Furthermore, the option of voluntary childlessness should be discussed. All patients with TS interested in OTC should undergo psychosocial and cardiac screening and should be discussed by a multidisciplinary expert team (key statement 8). Great caution and restrictive (i.e. more negative, or even discouraging) counselling are recommended if laparoscopic surgery or pregnancy is contraindicated (i.e. in patients with severe cardiac comorbidity).

In addition, patients with TS should always be included in the consent process, regardless of their age (key statement 4).

To our knowledge, this is the first international standpoint regarding OTC in females with TS. To reach international group consensus we used the RAND/UCLA Delphi procedure, which is a well-accepted method to perform Delphi studies. A key strength of this study was the combination of evidence and expert opinion, involving both professionals and patient representatives from 16 different countries. Furthermore, our expert panel represented a robust sample of the most important stakeholders to ensure that all the medical and ethical aspects of OTC in females with TS were discussed. The literature shows that a diversity of expert panel members leads to the inclusion of different perspectives, in turn leading to better overall performance (Murphy *et al*., 1998). This diversity provided a suitable set of key statements and consensus on a final standpoint, which should support broad acceptance in daily practice internationally. Remarkably, ours was one of the few studies where a combined panel of medical professionals and patient representatives was involved in defining a standpoint regarding the indication for medical treatment for a specific patient group. It is well known that patient input is invaluable when it comes to clinical practice guideline development (Dancet *et al*., 2013; den Breejen, 2013; Pohontsch *et al*., 2015). Essentially, patients are the ultimate experts in patient-centeredness of care (Grol, 2001; Epstein & Street, 2011), which is possibly the dominant paradigm in modern healthcare systems. The final set of key statements, and thus the outcome of this Delphi study, could have been different if only professionals had been involved in the selection procedure (Krahn & Naglie, 2008; Aarts *et al*., 2011; van Empel *et al*., 2011; Uphoff *et al*., 2012; den Breejen, 2013; Kotter *et al*., 2013). In the first Delphi round, patient representatives mainly highlighted arguments focusing on the psychological harm of infertility, whereas medical ethicists were more concerned about creating false hope resulting in psychological harm in the future. Gynaecologists and (paediatric-) endocrinologists underlined statements regarding non-maleficence. This is in line with previous studies reporting that professionals underestimate 'softer' dimensions of healthcare (e.g. quality of life) and overestimate the importance of biomedical outcomes compared to patients (Laine *et al*., 1996; Rothwell *et al*., 1997; Mack *et al*., 2005; Wessels *et al*., 2010; van Empel *et al*., 2011).

However, differences in scoring behaviour between the various experts were only seen in the first Delphi round and disappeared in the following two rounds when opinions were exchanged. Only one of the key statements (*Infertility in women with TS leads to psychological harm*) was selected by the patient representatives, despite having a moderate popularity among the professionals.

Although we considered the expert panel to be representative because of their diverse backgrounds (Hermens *et al*., 2006; Ouwens *et al*., 2010; Kesmodel & Jolving, 2011; Kotter *et al*., 2013), the recruitment of professionals and patient representatives based on their expertise, having a leading role in one of the Turner patient's organizations, and willingness to participate may have led to selection bias. As a result, panel members with a prominent opinion regarding OTC in females with TS might have been preferentially motivated to participate in this Delphi study. Furthermore, as not all panel members took part in all three rounds, there might be some response bias (Sica, 2006) because of time constraints or technical problems. Therefore, the final set of key statements and the expert panel's standpoint might reflect the opinion of the most motivated panel members (Sica, 2006). However, we tried to overcome this by inviting all 55 experts who initially agreed to participate in this Delphi study to participate in the final approval round.

The anonymous nature of this study was both a strength and a weakness. The purpose of anonymity in a Delphi study is to allow a safe exchange of opinions, without the bias of the more influential responders dominating the discussion. External influences are eliminated, as participants do not have to worry about their reputation. However, it might encourage hasty decision-making and a lack of accountability for their answers.

This study described the systematic selection of key statements and the formulation of a final standpoint regarding use of OTC in females with TS by an international panel of patient representatives and professionals. International group consensus was reached after three rounds. The approval to perform OTC in a safe and controlled research setting is the first step in the global acceptance of this FP option in females with TS. The eight supporting key statements will contribute to the implementation of and patients' access to this new treatment method. Our results reinforce the importance of involving patient representatives in decision-making and guideline development.

Future collaborative research with a focus on the efficacy and safety of OTC in females with TS is urgently needed before OTC is performed in females with TS in routine care. Therefore, we recommend an international prospective cohort study with long-term follow-up with a research protocol based on the eight selected key statements. Furthermore, we recommend an international register for FP procedures in females with TS.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

M.S., W.N., E.v.L., A.v.d.V. and K.F. designed the research project. R.P., C.B., M.S., W.N., E.v.L., A.v.d.V. and K.F. obtained all arguments from the literature and brought them together into a framework. M.S. and B.M. composed the expert panel, conducted the surveys, led data collection, performed data analysis and wrote this manuscript. R.P., C.B., D.B., M.S., W.N., E.v.L., A.v.d.V. and K.F. contributed substantially to data interpretation and manuscript revisions. All authors read and approved the final manuscript.

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Conflict of interest

The authors and members of the expert panel declare that they have no conflict of interest in this procedure.

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