Preservation of ovarian cortex tissue in girls with Turner syndrome: A multicenter exploratory intervention study

Published: 10-10-2017
Last updated: 16-11-2024

To investigate the occurrence of live birth in women with TS after ovarian tissue cryopreservation in childhood followed by auto transplantation in adulthood.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON47177

Source
ToetsingOnline

Brief title
TurnerFertility

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Endocrine disorders of gonadal function
- Congenital reproductive tract and breast disorders

Synonym
Turner syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cryopreservation of ovarian tissue, Fertility preservation, Premature ovarian insuffiency, Turner syndrome

Outcome measures

Primary outcome

Live birth after auto transplantation of cryopreserved-thawed ovarian cortical

tissue (i.e. live birth rate or LBR)

proximate: The number of primordial follicles found in the ovarian tissue

Secondary outcome

Secondary study parameters/endpoints

• The association between patient*s age at cryopreservation and LBR

• The association between patient*s genotype and LBR

• The association between patient*s AMH level at cryopreservation and LBR

• The association between patient*s FSH level at cryopreservation and LBR

Tertiary study parameters/endpoints

• The willingness of patients to perform a unilateral oophorectomy for

fertility preservation (i.e. the study participation rate)

• The number of eligible patients

• The age of the participant

• The incidence of somatic mosaicism (buccal cells, urinecells and peripheral

lymphocytes)

• The incidence of germ cell mosaicism (oocytes versus somatic cells)

• Serum hormone levels (i.e. FSH, LH, AMH, E2, inhibin B)

• The number of complications related to the laparoscopic procedure

• The incidence of spontaneous puberty and/or spontaneous menarche after laparoscopic oophorectomy

• The incidence of spontaneous pregnancies after laparoscopic oophorectomy

• The incidence of menstruation cycle recovery after auto transplantation of cryopreserved-thawed ovarian tissue in the future

• The incidence of pregnancies after auto transplantation of cryopreserved-thawed ovarian tissue in the future

• The number of ongoing pregnancies after auto transplantation of cryopreserved-thawed ovarian tissue in the future

• The number of miscarriages after auto transplantation of cryopreserved-thawed ovarian tissue in the future

• Time to pregnancy after auto transplantation of cryopreserved-thawed ovarian tissue in the future

• Time to live birth after auto transplantation of cryopreserved-thawed ovarian tissue in the future

Study description

Background summary

**Every once in a while, you know, when you*re holding a kid and they*re snuggling up to your neck, I really thought: I wish I could have kids. I wish I

had the choice.** (31-year-old female diagnosed with Turner syndrome) (Sutton et al., 2005). Infertility caused by premature ovarian insuffiency (POI) or failure (POF) is a major concern for patients with Turner syndrome (TS) and their parents (Sutton et al., 2005). Due to an accelerated loss of germ cells, most girls with TS undergo ovarian failure at a very early age, starting as early as 18 weeks fetal age. The timeline at which this occurs is less clear, and may be different for each patient with TS. Spontaneous pregnancies are rare, and occur in approximately 2-5% of women with TS (Bernard et al., 2016; Bryman et al., 2011; Hadnott, Gould, Gharib, & Bondy, 2011). However, up to 30% of females with TS have some pubertal development and up to 10% experience spontaneous menarche (Pasquino, Passeri, Pucarelli, Segni, & Municchi, 1997). A Swedish study group reported that primordial follicles can be found in the ovaries of both mosaic and non-mosaic girls with TS up to 17 years of age (Hreinsson et al., 2002). Due to this new insight, physicians are often asked by patients with TS and their parents about the options of fertility preservation (Grynberg et al., 2016). Fertility preservation includes the cryopreservation of the patient*s own gametes, either by preserving mature oocytes or ovarian tissue containing primordial follicles. Cryopreservation of mature oocytes can be performed only in post pubertal females, since oocyte maturation requires ovarian stimulation with exogenous FSH administration followed by transvaginal ultrasound-guided oocyte retrieval (Oktay et al., 2015). Ovarian tissue cryopreservation, however, appears to be a promising technique to preserve the fertility of younger girls with TS and provides the possibility to store a larger number of primordial follicles before their disappearance (Borgstrom et al., 2009). Although still experimental, cryopreservation of ovarian tissue has been well described in girls and young women undergoing gonadotoxic cancer treatments, and over the past decades, several clinical guidelines have been developed (Font-Gonzales et al., 2016; Jakes et al. 2014). Retransplantation of cryopreserved-thawed ovarian cortical tissue in cancer survivors has resulted in restoration of ovarian function and follicular development (Oktay & Karlikaya, 2000; Radford et al., 2001), and at present, more than 60 live births have been reported (Van der Ven et al., 2016; Jensen et al., 2014; Andersen et al., 2014.; Demeestere et al., 2015; Dittrich, Hackl, Lotz, Hoffmann, & Beckmann, 2015; Donnez et al., 2004; Donnez et al., 2013; Meirow et al., 2005). Unfortunately, there are currently no recommendations on fertility preservation in patients with TS. Although both preservation procedures have been performed experimentally in girls and adolescents with TS (Balen, Harris, Chambers, & Picton, 2010; Borgstrom et al., 2009; Hreinsson et al., 2002; Huang et al., 2008), the promise of fertility preservation is at present hypothetical, given that no girl with TS who has undertaken these approaches thus far has returned for autotransplantation or IVF. Further research is needed to provide supporting evidence for the efficiency of both fertility preservation techniques in this specific patient group. Furthermore, there is a need for reliable markers to assess the ovarian reserve in girls with TS to offer fertility preservation services to those patients who would benefit most.

Study objective

To investigate the occurrence of live birth in women with TS after ovarian tissue cryopreservation in childhood followed by auto transplantation in adulthood.

Study design

A multicenter exploratory intervention study

Intervention

1)Laparoscopic unilateral oophorectomy
2)Buccal Swab and one urine sample
3)1 Extra blood sample of 3.5mL will be collected during yearly blood check. Hence, there will be no extra venipuncture performed.

Study burden and risks

It is important that the participant and her parents weigh the possible pros and cons before participating in this research.

Benefits
The fertility of the participant could be saved with this procedure. In addition, participation in this study will give her and her parents more information about her fertility. The participant may also not benefit from participation in this research. For example, if no follicles are found in her ovary. Her participation contributes to more knowledge for other girls about TS and (in)fertility.

Risks
A disadvantage of participating in this study is the potential risk of complications related to the laparoscopic unilateral oophorectomy. and/or the unknown effect on future fertility of these girls. Moreover, the procedure might raise false hope in patients (and/or parents) about the chance of getting pregnant after auto transplantation of cryopreserved-thawed ovarian tissue in the future. However, we attempt to overcome this by extensive and honest information provision by both written materials and face to face counseling.

Burden
Participation in this study also means:
- participation in this study takes time
- 3 additional hospital visits and 1 additional hospitalization
- (extra) controls;
- that the participant and her parents have appointments to which they must comply

Due to a lack of evidence, it is not possible to predict the outcome for each individual participant. All patients and their parents will be counseled about the 3 possible scenario*s before participating in this study regarding their benefit:

1) The participant belongs to the largest group of patients (95-98%) who are infertile at the end of adolescence. OTC could be successfully performed (e.g. follicles where found in the cortex strips).
Due to early menopause, this patient does not have any spontaneous chances of getting pregnant. The removal of one ovary will not reduce her spontaneous pregnancy chances (0% 0%). Her fertility might be saved for later.

2) The participant belongs to the largest group of patients (95-98%) who are infertile at the end of adolescence. OTC was not successful (e.g. no follicles where found in the cortex strips).
Due to early menopause, this patient does not have any spontaneous chances of getting pregnant. The removal of one ovary will not reduce her spontaneous pregnancy chances (0% -> 0%). Unfortunately, her fertility could not be saved. The intervention does not have a personal benefit for this participant.

3) The participant belongs to the smallest group of patients (2-5%) who may become spontaneously pregnant in the future. OTC could be successfully performed (e.g. follicles where found in the cortex strips).
Due to a solid ovarian reserve in her remaining ovary, this participant still has a chance of spontaneously becoming pregnant. Her fertility might be saved for later if needed.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein 10
NIJMEGEN 6525 GA
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein 10
NIJMEGEN 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

• Girls and young females with classic Turner (i.e. 45X monosomy) or Turner variants (e.g. 45X/46XX mosaicism, ring X mosaicism, isochromosome X),
• Aged 2 through 18 years,
• who completed the diagnostic workup phase of TS including routine cardiac screening*,
• whose agreement to participate in this study has been signed by the parents (girls 2-11 years old),
• whose agreement to participate in this study has been signed by the patient and her parents (girls 12-17 years old),
• whose agreement to participate in this study has been signed by the patient (adolescents of 18 years old).

Exclusion criteria

• Contra-indications for laparoscopic unilateral oophorectomy under general anaesthia (e.g. severe cardiovascular comorbidity and/or BMI >40 kg/m2)*,
• Contra-indications for cryopreservation (i.e. active HIV, hepatitis-B or hepatitis-C infection);*Based on the international Cincinatti Turner Guideline Concensus Meeting, July 2016 and consultation of Dutch cardiologists, paediatric-cardiologists and anaesthesists between 2016-2017 there are no absolute cardiovascular contra-indications for surgical intervention and/or pregnancy. Advice against surgical intervention and/or pregnancy should be based on the patient-specific cardiovascular risk profile. The 2% mortality risk due to acute aortic dissection is based on one survey and literature review study (Karnis et al. 2003) that reported the outcomes of 101 pregnancies in patients with TS after oocyte donation. Only 50% of the patients were screened by a cardiologist before entering the oocyte donation

programme. Therefore, all girls who want to participate in this study should have completed the diagnostic work up phase of TS including routine cardiac screening and will be screened by a paediatric anaesthesist. Exclusion will be based on the patient specific risk profile.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-02-2018
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	10-10-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-09-2019
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-07-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL57738.000.16