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Khattak, Hajra; Gallos, Ioannis; Coomarasamy, Arri; Topping, Anne

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BMJ Open

Why are women considering ovarian tissue cryopreservation to preserve reproductive and hormonal ovarian function? A qualitative study protocol

Hajra Khattak ,[1] Ioannis Gallos,[1] Arri Coomarasamy,[1] AE Topping [2]

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[1]Tommy's National Centre for Miscarriage Research, Institute of Metabolism and Systems Research, University of Birmingham College of Medical and Dental Sciences, Birmingham, UK
[2]Institute of Clinical Sciences, School of Nursing, University Hospitals Birmingham NHS Foundation Trust, University of Birmingham, Birmingham, UK

Correspondence to
Dr Hajra Khattak;
hajra.khattak@nhs.net

ABSTRACT

Introduction Current fertility preservation options available to women are oocyte cryopreservation (egg freezing) or embryo cryopreservation. A newer procedure, ovarian tissue cryopreservation (OTC), has become available in some centres, which offers another option for women and girls considering fertility preservation. These procedures are commonly offered to women about to undergo treatments for cancer. OTC involves removing sections of ovarian tissue and cryopreserving it for future reimplantation, often several years later. OTC offers girls and women who may become infertile with optionality and the possibility of pregnancy. OTC has potential for other applications, including restoring ovarian endocrine function beyond biological menopause. This is not without controversy but has led to some women considering undergoing the procedure for purposes of ovarian hormonal preservation (conservation of ovarian endocrine function). OTC is invasive, involves two surgical procedures with concomitant risks and can be costly. Understanding why women may consider and ultimately undergo OTC is timely, so that evidence-based and women-centred care can be provided.

Methods A pragmatic narrative qualitative design will be used. A purposive sample of women aged 18–45 who are considering, or have sought, OTC will be recruited over 1-year period. Potential participants will be approached via a clinic that offers OTC on a private basis or via social media.

Analysis Participant interviews will be audio and, if consented, video recorded. These will be conducted face-to-face or virtually. The recordings will be transcribed verbatim and analysed using a thematic analysis approach supported by NVivo software.

Ethics and dissemination Ethical approval has been granted by the Institutional Ethical Review ERN_19–1578A. We expect to disseminate the findings of this study through journal articles, conference presentations and multimedia to public.

Strengths and limitations of this study

- This study seeks to provide an in-depth understanding of the decision-making process in women in relation to fertility or hormonal preservation.
- A rigorous study design has been developed to explore any concerns women express seeking individual control over temporal aspects of loss of fertility and menopause.
- Use of purposive sampling will include recruitment of women from different backgrounds facilitating a diverse and broad sample.
- Sample may not be representative given recruitment from only one clinic.
- Social media recruitment excludes the views of women who do not use such platforms.

INTRODUCTION

A consequence of advances in anticancer therapies is that the number of young women surviving cancer has increased; however, the treatment may leave some subfertile or infertile. Fertility preservation is an approach often offered to young women before commencement of cancer treatment to future proof fertility post-treatment and improve the quality of life for these women. Advances in fertility preservation techniques have increased the potential for women to seek these techniques for reasons other than cancer, what could be termed as social reasons. The average age of women having their first child has increased in the recent decades.[1 2] Various reasons have been offered, including lack of partner, increased access to education, employment and career progression, access to contraception and financial considerations, which have provided women with greater choice and control over their fertility.[1 3 4] Oocyte and embryo freezing are established fertility preservation methods,[5–7] several centres worldwide are offering a newer procedure that involves cryopreserving ovarian tissue.[8–11] The availability of cryopreservation of ovarian tissue has increased since its introduction two decades ago, but access remains limited.[12 13] For women who are planned to undergo cancer therapy, the processes involved in oocyte freezing can be lengthy involving a period of controlled

ovarian stimulation that can cause delays to planned treatment. Ovarian tissue cryopreservation (OTC) is an alternative approach that has been used by many women worldwide.[9 14–16] The availability of this procedure is limited in the UK with only a handful of centres offering this service on the national health service (NHS).[17–22] In the UK, the OTC procedure is normally only offered to women with a cancer diagnosis prior to commencing fertility ablating treatment. Globally, some centres are now offering OTC not only for the preservation of fertility largely to women with cancer but also for social reasons.[23 24] This interest for social reasons is linked with the evidence that reimplanted previously frozen ovarian tissue can produce a return of hormonal function, hence could be used for preserving hormonal function for longer.[25–29] OTC and transplantation procedures have also been used with women who are at risk of developing premature ovarian insufficiency (POI), including non-cancer indications such as oophorectomy, benign ovarian tumours, Turner syndrome and benign haematological conditions.[30–33] This technique, therefore, offers patients with a wide variety of illnesses, a chance to have biological children and experience motherhood, in addition to preserving their hormonal function. Prior to wider adoption; however, it is crucial that alongside the clinical evidence of benefit, we understand patient experience associated with this procedure. This will inform the provision of best care to these patients.

OTC has largely been used as a fertility preservation method in women treated for cancer. The consequences of gonadotoxic therapies (eg, chemotherapeutic agents) not only affect reproductive outcomes but also cause iatrogenic menopause. Fertility preservation methods are also offered to healthy women who may wish to delay pregnancy. Age-related oocyte preservation is now gaining greater acceptability as a strategy for controlling timing of pregnancy for social reasons.[34 35] The technique does not preserve ovarian hormonal function in women with normal ovarian hormonal function but offers the potential for extended preservation, hence, the need to explore the reasoning underpinning the decision to seek OTC for hormonal purposes. It is important to note that given the experimental nature of this procedure, OTC for social reasons is not widely available or even allowed in some countries.

Women are now living longer and almost of half their life in a menopausal state.[36] This can impact on the physical health of women, incurring increased cardiovascular risk and osteoporosis, and for some impact on mental well-being.[37 38] Although pharmacological interventions are available, OTC has the potential to provide physiological hormonal production and delay menopause.[25 26 39] One explanation for social interest in OTC is the notion of future proofing, as it offers the potential of hormonal 'insurance'. Menopause is increasingly portrayed as a negative life event in both the medical literature and popular media.[40–42] Some evidence suggests that how a woman experiences menopause is largely based on her sociocultural background and/or their female family members' experience with menopause.[43] Furthermore, postmenopausal women reportedly held more positive perceptions of menopause compared with those in a perimenopausal or premenopausal stage.[44] This may provide some explanation of why some young girls and women may wish to preserve tissue that could extend their ovarian hormonal function. Women may be pre-empting the biographical disruption that results from the changes they perceive they will experience during menopause.[45] What is unknown is whether anticipatory concern is based on personal experience and/or information they have gathered from the media, news or healthcare professionals or indeed a combination.

Biographical disruption in relation to menopause

Biographical disruption, a term that was first coined in 1982 by Michael Bury, to describe how events or occurrences such as illness cause a profound change that affects how the individual understands themselves. Normally applied in relation to long-term illness where the individual may feel that the illness has created a major disruption to their self-identity, causing them to redefine their 'biography'.[45] This concept could be applied to women experiencing negative effects of menopause, or for women who will ultimately become menopausal, by framing menopause as a state, which women may feel challenged to redefine their identity. A qualitative study conducted by de Salis *et al* examined the experiences of menopause in women and identified three main explanatory narratives. Menopause was defined either as a normal process where no transition occurs in the women or in her societal interactions; as a struggle, associated with loss of identity and distress and/or menopause as release from the messy business of menstruation and, therefore, a liberating experience.[38] In the literature, menopause has been associated with ageing and related risks such as osteoporosis and cardiovascular disease unless hormone replacement therapy (HRT) is prescribed.[46] HRT is not an unproblematic solution and issues with HRT are well known.[47] This presents some women with decisions balancing acceptability and risks of life-long hormone replacement.

Anticipation of the biographical disruption engendered by menopause, therefore, may worry some women in their younger years. Awareness of the symptoms of menopause has gained greater profile in recent years possibly fuelled by media interest, and whether this influences women to seek out and, in some cases, opt for a procedure that can potentially delay or even reverse menopause remains unknown. Women who seek to preserve their fertility or hormonal function may have many reasons, and this study aims to explore these phenomena. Through this study, we intend to explore how menopause is seen by these women and examine if anticipation of a biographical disruption pre-empts women to bank their ovarian tissue for future use.

Theoretical framework

The philosophy of Pragmatism alongside decision-making theory, as described by Kahneman's System 1 and 2 thinking, will be used to frame this study.[48]

Pragmatist theory

Pragmatism can be defined as a link between 'human knowing' and 'human action'[49] and how beliefs are held and shared. Pragmatism recognises that although two individuals may experience the same situation, their worldviews of the situation may not be the same. The extent to which the experience is similar depends on the degree of shared view. This phenomenon provides a unique individual, as well as a shared, view of the experience.[49 50] Through interviewing a wide range of women (age range 18–45), we believe we will collate a unique account of the views and experiences of women who consider or choose fertility and hormonal preservation using OTC. Furthermore, as per the pragmatist position, meaning of actions and beliefs is found in consequences.[50] In the context of this study, this relates to the decisions participants make after they have had an initial consultation where they are being assessed for eligibility for the OTC procedure. For participants recruited via social media, these theoretical assumptions will help illuminate the thinking employed by women when deciding whether or not to opt for this procedure based on their current knowledge. Their responses will be analysed alongside their demographics such as age, occupation, relationship status, whether they already have children or if they have an interest in becoming a parent later in life, and employment. As actions are 'fluidly' linked to consequences such that they are open to change, if the situation pertaining to action changes, so would the consequence of the action, even though the action remains unchanged.[49 50] Based on this assumption, we aim to understand what women decide when and if their circumstances change (such as being ineligible for OTC after the initial consultation).

A pragmatist approach to qualitative inquiry involves using multiple resources as well as multiple methods of data collection. Data analysis can involve using various qualitative approaches.[51] Recruitment from a clinic that offers this procedure in addition to worldwide recruitment from social media will help us understand the views, motivations and expectations of women regarding OTC procedure in a wide variety of settings.

Thinking fast and slow (in relation to decision-making)

In behavioural psychology, two systems of thinking are described; 'system 1' and 'system 2' that ultimately influence the decisions we make. 'System 1' is fast, influenced by emotions and intuitive. This system enables humans to differentiate between danger and safety.[48] In comparison, 'system 2' is slower and functions through reasoning. It is used as a backup and often difficult to actuate. While 'system 1' operates automatically, normally 'system 2' remains in the background. Often these two systems interact with each other rather than operate independently, System 2 overriding system 1 (if it is intermittently over-ruled). The crucial point is when system 1 does not allow for system 2 to take over.[52] This concept of fast and slow thinking potentially could be applied to how women may make decisions when considering OTC to preserve their fertility or hormonal function. The proposition is that although women may use system 1 when seeking information and attending an initial consultation about the procedure, whereas system 2 may come into play when a more considered decision is required when finally deciding whether to undergo the procedure. It is envisaged that understanding women's decision-making will influence the quality of information and care provided to these women and better manage expectations.

AIMS AND OBJECTIVES

Aim

To explore the participants' perceptions, concerns, expectations and reasoning behind considering OTC.

Objectives

The objectives of this study are to interview women who have considered OTC as a method of fertility and hormonal preservation and gain an insight into:

1. What motivates women to seek OTC?
2. What women understand about OTC?
3. Gain an in-depth understanding of the decision-making process in women who have considered having OTC and may or may not have undergone initial assessment about eligibility for OTC.
4. The impact of their decision-making and meaning of fertility or hormonal preservation.

METHODS AND ANALYSIS

Study design

Pragmatic qualitative descriptive design.

Data collection

This study will use qualitative enquiry to explore decision-making process associated with seeking OTC for preserving fertility and hormonal function. The data will be collected using semistructured interviews. A topic guide will be used to frame the interviews but will not drive the enquiry (online supplemental file), as these will take the form of 'a conversation with a purpose'.[53] The interviews will be conducted by the lead researcher, following confirmation of consent and will be audio and/or video conferencing recorded. Participants will be given the option to be interviewed in person (subject to COVID-19 restrictions) or using telecommunication such as telephone or video teleconferencing. The interviews will be supplemented with clinical and demographic information provided as part of their clinical care and will be extracted from their clinical records. This will include age and investigations such as blood tests and ultrasound scan performed to ascertain suitability for OTC.

Data analysis

All interviews irrespective of mode, or participant, will be audio-recorded, downloaded and saved as sound files to a secure server prior to transcription. Transcription will be undertaken by a trusted supplier bound by a secure data transfer agreement through a password-protected server. Following transcription anonymisation will seek to remove any identifiable information and each transcript will be allocated a unique identifier.

All transcribed interview data will be analysed using thematic analysis.[54] Themes generated from the interview data will be divided into groups based on participants' reasoning for considering OTC (medical or social). Transcripts will first be imported into NVivo software to facilitate data management.[55] After familiarisation, reading and rereading each transcript and checking against sound file, coding will be undertaken. Sections of text will be named, and these will ultimately form a series of codes. These codes will be organised into tentative groupings (themes), and through an iterative process of sorting, resorting and reallocation form a tentative thematic map. This thematic schema may undergo numerous stages of refinement ultimately surfacing an analysis of the women's accounts irrespective of whether they ultimately underwent the procedure or not. This study is designed and will be reported in line with the Consolidated Criteria for Reporting Qualitative Studies.[56]

Study setting

The study will take place in a clinic that currently offers this technique on a private healthcare basis (in a non-NHS setting). Study information will also be shared on social media platforms. Due to restrictions as a result of COVID-19 pandemic, participants will be interviewed over the phone and/or video telecommunication if not possible to be interviewed in person.

Sample and recruitment

All women who book a consultation to discuss OTC within the study period will be approached by a member of the clinical team. For recruitment from the internet, participants will contact the study coordinator themselves.

Inclusion criteria

- Women.
- Ability to provide informed consent.
- Aged 18–45 years.
- Considering OTC.

Exclusion criteria

Women who have already made a decision to opt for other methods of fertility preservation such as oocyte and embryo freezing will be excluded.

Sampling

The sampling will be purposive in nature based on the following categories (across full age range of 18–45):

1. Women who have heard of OTC and have considered it as a fertility or hormonal preservation method.
2. Women seeking OTC who are deemed eligible by the clinician based on ultrasound scan and blood tests and decide to proceed with the procedure.
3. Women who are deemed eligible for OTC by the clinician but decide to not go for OTC.
4. Women who are deemed ineligible for OTC based on their tests but are still keen to preserve their reproductive and endocrine function.
5. Women suffering from cancer, seeking OTC as a mean of fertility preservation or having already had the consultation or procedure.

Recruitment

Based on comparable studies, it is anticipated that a sample size of 12–24 women who are considering OTC will be adequate to answer the study questions, covering the age range and categories specified. Recruitment and sampling, however, will continue until data saturation point is reached, estimated at 24 participants.[57]

Prospective recruitment

Women who are interested in ovarian tissue freezing contact a central office. Once an appointment is booked for consultation, they are normally sent written information regarding the procedure. Alongside this information, they will be sent a participant information sheet (PIS) for this study (either via email or in post) by clinic staff. Furthermore, women coming for consultation will also be provided with a PIS by the clinic staff if not received prior. For prospective recruitment, women will be approached by the consulting clinician or other clinical staff they meet for their initial appointment to discuss ovarian tissue freezing, to ascertain if they are interested in participating in the study. Should the woman express a willingness to participate and agrees to be interviewed following their OTC consultation, the lead researcher will speak to the patient. This will provide participants with an opportunity to ask questions. If the woman agrees to take part, the lead researcher will provide informed consent. Furthermore, any healthcare professional involved in the care of the participant, named on the delegation log and trained in line with Good Clinical Practice (GCP) will also be able to take consent and recruit women to the study.[58] Participants agreeing to take part on the day will be given the option of conducting a face-to-face interview. If they prefer, they can also be interviewed remotely using audio and/or telecommunication at a later date. For online recruitment, study details and invitation to take part will be posted on social media platforms and forums. The participants who are interested will be encouraged to approach the researcher via email, who will then share the study documents (participant information leaflet and consent form).

Retrospective recruitment

Women who have previously attended the clinic and have already had their consultation to discuss and/or undergo OTC will be contacted by a member of clinic

staff via telephone, email or postproviding them with information about the study. This information will also provide an invitation to participate in the study, a PIS and consent form that will include contact details of the lead researcher. Patients can then contact the lead researcher via email if interested in participating, to ask questions and if they wish to proceed and organise an interview. Participants can opt for a virtual interview using audio and or video telecommunication or be interviewed in person (depending on restriction related to COVID-19 pandemic). Participants will be given the option of completing the electronic consent form using an electronic signature or returning it via post. For those with virtual interviews, and not having returned a completed consent form prior, the consent process will be undertaken at the beginning of the interview, audio-recorded and signed by the researcher conducting the interview.

Sample identification

The participants will be identified by the lead researcher, associated clinicians, healthcare professionals trained in GCP and research nurses. This will be done when patients enquire about the ovarian tissue freezing service from the central office (via email, by telephone or post). Posters explaining the study will be displayed, and information leaflets, will also be available in clinics. For online recruitment, the lead researcher will post on various social media platforms such as Facebook, Twitter and Instagram. Participants interested in the study will approach the researcher independently. Participants will then be selected according to the inclusion criteria.

Consent

Informed consent will be obtained by the lead researcher or healthcare staff involved in the care of the woman who are GCP trained, prior to participants recruited or being interviewed. Participants will be provided with written information such as leaflets and consent form that explains the study usually a few weeks before their consultation with care provider. The study information will be sent along with all other clinical information. Participants will ideally be given 24 hours from reviewing study information before they can participate. For those who have not received this information before their consultation will be given the patient information sheet and consent form on the day of their consultation. Participants can agree to take part in the study directly after their consultation (ie, less than 24 hours) if it means it is less burden on them in terms of time commitment. These women will also be given the chance to go away and think about the interviews if they required time, in which case interviews will be held remotely. For patients who have already had their consultation will be sent details about the study. The clinical care provider will advise the patient to contact the researcher if they are interested. If these women agree to participate, the consent form will be sent to them via email or post. The consent form can be returned via email using an electronic signature or via post. Participants will also be given the option of being able to complete the consent form prior to their interview (it will be audio-recorded and consent form signed by the lead researcher). For participants recruited via the internet, study documents will be sent over email or social media messaging. All patients will be assessed for capacity and only those deemed capable will be recruited to the study. Participants will be encouraged to ask questions. Participants will be informed that they can withdraw at any time up to 14 days following the interview, without giving any reason. However, they should withdraw more than 14 days after the interview, the data collected about them will be retained. This will be explained in the PIS and consent form. Participants recruited via the clinic will also be assured that this will not affect their medical care in any way.

Research governance

Assessment and management of risk

Women accessing this clinic are normally self-referrals and only a minority may have been referred by another clinician. Preserving fertility and hormonal sufficiency can be an emotive subject, and this may be compounded if a woman is already experiencing a condition such as cancer, or may believe they have or will discover through the assessment process to identify eligibility for OTC, signs of early menopause. The ethical implications of interviewing women whose fertility may be in doubt or challenged (due to cancer treatment or other conditions) have been discussed during the development of this study. The well-being of women accessing this procedure, and agreeing to participate, is paramount and takes precedence over any knowledge to be gained. Should a woman become emotionally distressed during an interview,and does not wish to continue, the interview will be terminated. As the interviewer is a clinician, with advanced communication skills and a trained interviewer, any immediate distress will be managed. The participant will be signposted to relevant support services such as the Daisy Network who provide support for women with POI or back to the care of their General Practitioner (GP). If during the process of being investigated for the procedure, participants unexpectedly found that they were experiencing early menopause diagnosed through clinical history and investigations, they will be referred to the relevant healthcare professionals and support groups.[59] If these women wish to continue to take part in the study, they will be given the option of interview at a later date when they feel comfortable and ready.

Regulatory review and Compliance

This study will take place in a clinic of non-NHS healthcare provider. Before any research activities commence, the research team will obtain the approval of the relevant research and ethics committees. Arrangements will be put in place with the study site provider organisation for issuing permission to conduct the study. For any amendments to the study, an application form will be completed

and submitted to the University of Birmingham Research Ethics. Amendments will only be implemented once approved.

Protocol compliance

Serious deviations from the study protocol will be reported without delay by the doctoral researcher to the chief investigator and sponsor and onwards as appropriate. The chief investigator will ensure that such deviations are investigated and appropriate actions taken. The responsible research and ethics committee will be notified as soon as possible of any serious breach that could undermine public confidence in the research. Procedures for recording and reporting serious adverse events will be clearly documented in the site file.

Data protection and patient confidentiality

All participants will be allocated an identifier, and this will be linked to all data. All identifiable study information will be held securely on an encrypted and password-protected computers at the University of Birmingham and separately from data. Data files will only be accessible by members of the research team and regulatory bodies. The face-to-face and telephone interviews will be undertaken using a password-protected recorder, and those using n video conferencing will be recorded using the record programme function using a password-protected PC. All sound files will be downloaded to a study-specific secure server at the University of Birmingham and recording deleted from the device and programme. Each sound file (with identifier) will be transferred securely to an agreed transcription service with confidentially agreements in place. Following transcription, every effort will be made to remove any recognisable information to anonymise the transcripts. Participants will be informed that anonymous verbatim quotations may be included in any manuscripts generated from audio-recordings and/or transcripts to report study findings.

All study researchers, clinicians and nurses will uphold the principles and comply with the requirements of the EU General Data Protection Regulation 2016/679 and Data Protection Act 2018 in the collection, storage, processing and disclosure of personal information. All study researchers, clinicians, nurses and midwives will also maintain up to date GCP training. The data protection measures of this study will adhere to relevant policies and procedures of the University of Birmingham. All study data collected on paper will be held securely, in a locked room or locked cabinet at the university that is accessible only to the research team and relevant regulatory authorities. All study data collected or otherwise generated in electronic form will be held securely on encrypted and password protected in university-owned computers or University of Birmingham's research data stores and drives, which will also provide data backup. Any audio recordings to be externally transcribed will be released only to a specialist transcription supplier and subject to a Confidentiality Agreement to prevent disclosure of any personally identifiable information to third parties. The audio recordings will be transferred via a secure server with user identifiers and passwords. Subsequently, any personally identifiable data within transcripts will be removed by the research team and substituted by anonymised unique identification references. All study data will be held securely in the custody of the chief investigator for 10 years after first publication of the results, in accordance with the University of Birmingham Research Data Management Policy.

ETHICS AND DISSEMINATION

Study findings will be owned by the University of Birmingham and disseminated in order to contribute to understanding of the experience of, and motives and expectations of women seeking ovarian tissue freezing. Study findings may be used to inform the development of future funding proposals, facilitate the continuous professional development of healthcare practitioners and development of referral pathways and guidelines.

The participants will be informed of the outcomes and provided with a lay summary on request. Study findings will be reported in the form of a doctoral research thesis and academic manuscript/s, to be supplemented by presentation/s and relevant conferences and report to interested charities and appropriate women's support networks. The manuscript/s will be also made openly available via a dedicated online repository hosted by the University of Birmingham for this purpose.

Patient and public involvement

It was not possible to involve patients or the public in the design, or conduct, or reporting or dissemination plans of our research.

Limitations of the study

Because recruitment is to take place from only one clinic, the sample may not be representative. Furthermore, participants may be restricted in access to the clinic due to restrictions because of the pandemic and this may affect recruitment. Finally, social media recruitment excludes the views of women who do not use such platforms.

Contributors HK is a doctoral student, also training in Obstetrics and Gynaecology and is supervised by a team that is experienced in conducting qualitative research. AC is her lead supervisor, with AET and IG being co-supervisors. The lead researcher (HK) has received training to conduct the interviews. AC is the principal investigator. All the authors were involved in designing this study. HK and AET have contributed to gaining ethical approvals and drafting the initial version of this manuscript. All authors approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs
Hajra Khattak http://orcid.org/0000-0002-7330-3825
AE Topping http://orcid.org/0000-0002-0111-2341

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