The impact of age and parity on the experience of relief and regret in women who have undergone hysterectomy for benign disease.

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Background:

Hysterectomy may be undertaken in women with benign gynaecological conditions such as pelvic pain, heavy menstrual bleeding and prolapse. Those conditions can cause significant distress and reduction in quality of life [1, 2]. Treatment of pelvic pain and heavy menstrual bleeding is dependent on the underlying cause and initially may include medical and hormonal therapies and fertility conserving surgery. In some cases, when more conservative treatments have failed to adequately relieve symptoms, hysterectomy is suggested by the patient or the treating doctor [3]. Removing the uterus is an irreversible surgery after which the woman is not able to carry a pregnancy. A variety of factors including both age and parity may impact on a woman's experience of relief and regret following hysterectomy. To evaluate the impact of age and parity as well as identify other factors that may contribute to relief and regret after undergoing hysterectomy for benign disease would be of great value to women and their clinicians considering this option. It may help identify women who could benefit from psychological assessment and support prior to undertaking hysterectomy and aid in counselling about the long term impact of hysterectomy.

Very few studies report on the long-term experience of women who have undergone elective hysterectomy at a young age. One study showed an increase in postoperative stress in young women who had undergone emergency hysterectomy if they had a persisting wish for fertility [4]. Another small study described a sense of loss of femininity [5].

There is however a large body of literature examining regret after non-hysterectomy female sterilisation (e.g., tubal ligation). A 1 year prospective trial demonstrated pre-operative depression as a significant predictor of regret [6]. An Australian retrospective study found that young age (less than 30 years) had the most pronounced effect on strong regret and subsequent request for in-vitro fertilisation to carry a pregnancy [7]. Becner et al conducted a retrospective questionnaire-based study assessing 308 women who underwent sterilisation. They used the Zung Self-Rating Depression Scale as part of the questionnaire and found very low rates of regret overall; however, women who would not choose sterilization again had significantly higher scores on the depressive scale 1-5 years after their procedure [8]. A systematic review of 19 articles evaluated

risk factors for regret following female sterilisation and demonstrated a consistent inverse relationship between women's age at sterilization and their likelihood of regretting having had the procedure [9]. In addition to age, less information about the procedure and knowledge of other options was also associated with regret [10].

Unlike other female sterilisation where the options to attempt either reversal of the procedure or in-vitro fertilisation to conceive exist, hysterectomy is definitive. However, hysterectomy is usually undertaken not for sterilisation but to relieve significant symptoms impacting on quality of life. Other factors might influence a patient's reflections after hysterectomy. A qualitative study that was performed in the United States assessed four different ethnic groups as well as homosexual women [11]. They found that while most of the women who had a hysterectomy were satisfied with the outcome of surgery, decision-making patterns differed amongst groups. Other studies have also found cultural and ethnic-specific differences in women's reflections on uterus removal [12]. A small qualitative study has demonstrated that for some women, hysterectomy was associated with loss of femininity [13].

Neuroticism is one of the higher-order personality traits, associated with negative affectivity. It is associated with higher reporting of subjective distress and worse self-perceived health, although is not necessarily correlated to actual physical health status [14]. Neuroticism also predisposes individuals to the development of depression [15]. It is therefore important to take neuroticism into account when individuals are asked to subjectively reflect on their health experience and symptoms.

Fertility declines gradually throughout reproductive life. There is a higher rate of loss of ovarian reserve after the age of 35, and infertility definitions and management change after this age [16]. Hence, undergoing sterilisation under the age of 36 is considered 'young' by most clinicians.

Our rationale for this study is that as clinicians who are regularly consulted by young women considering hysterectomy, we do not know if they experience relief following symptom resolution, regret due to the irreversible nature of this procedure and possible incomplete symptom relief, or both. We do not know if age will result in a different experience for women undergoing elective hysterectomy, or if parity and desire for future fertility at the time of decision making has a larger impact than age itself. This

question is very frequently raised in our weekly clinical meeting where candidates for surgery are discussed. Due to paucity of empirical literature, we are unable to provide evidence-based advice to our patients.

We are not aware of previous studies that have assessed the long-term experience of relief and regret in women with benign conditions such as endometriosis, fibroids or prolapse who have elected to undergo hysterectomy. Determining factors that impact of regret and relief will help guide patients and clinicians considering this option.

Primary Outcome:

To investigate the relationship between age and parity on the experience of relief and regret following hysterectomy for benign disease.

The experience of relief and regret as well as other measures below will be assessed as per the questions in the attached questionnaire. We are not using an existing quality of life or other questionnaire, as there is not one that is appropriate to the aims of this study.

Secondary Outcomes:

- To report the extent to which women who have undergone elective hysterectomy for benign disease experience relief and regret
- To report on the indications and the rate of symptom resolution in women undergoing hysterectomy for benign disease
- To investigate the relationship between other factors that may impact on the experience of regret and relief following hysterectomy for benign disease including: current levels of psychological morbidity, neuroticism, resolution of symptoms following hysterectomy, desire for future fertility at time of hysterectomy, previous medical and psychological history and indication for hysterectomy.
    - Depression, anxiety and stress will be measured with the relevant subscales of the Depression Anxiety Stress Scale Short Form (DASS-21,

[17]). The DASS-21 is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress. Participants are asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state *over the past week*. Higher scores on this 21-item instrument indicate greater symptom burden. Internal consistency and concurrent validity of the DASS-21 have been confirmed [17, 18].

- Neuroticism will be measured with the 10-item Neuroticism subscale of the International Personality Item Pool (IPIP-NEO) [19]. The IPIP-NEO has been shown to be reliable [20] and valid [21].

Study null hypotheses:

Primary outcome:

Younger and nulliparous women are no more likely to experience regret compared to older and parous women.

Secondary outcomes:

- Women who undergo hysterectomy for benign disease experience equal rates of relief and regret
- Factors likely to contribute to the experience of relief are: past history of proven endometriosis, heavy menstrual bleeding and prolapse and symptom resolution following hysterectomy
- Factors likely to contribute to the experience of regret are desire for future fertility, incomplete symptom resolution, neuroticism and past history or current depression/anxiety.

  Women reporting regret following hysterectomy are more likely to currently have higher levels of psychological morbidity and neuroticism

Study design: Cross sectional survey of a cohort.

Study Units: All general gynaecological units at the Royal Women's Hospital performing elective hysterectomy for benign conditions (Gynaecology Units 1, 2 and 3)

Inclusion criteria:

- All women who have undergone elective hysterectomy for benign disease in a general gynaecology unit at the Royal Women's Hospital (Gynaecology Units 1, 2 and 3)
- Age <51 at time of surgery (this will include a range of ages for whom fertility is a possible issue and for whom fertility is not an issue and will target a mostly pre-menopausal population. With the exception of prolapse surgery the reasons for which hysterectomy is undertaken and pathologies detected differ in a menopausal group)
- Any type of hysterectomy included (total/subtotal; vaginal/ abdominal/ laparoscopic)
- Hysterectomy performed from 01/01/2008 – 31/07/2015 inclusive (as we want to allow at least 3 years of time from surgery to allow for long-term reflection on the decision)

Exclusion criteria:

- Indication for hysterectomy was malignancy or suspected malignancy including endometrial hyperplasia
- Hysterectomy performed as unplanned/emergency procedure
- Caesarean hysterectomy
- Non-English speaking

Patient identification, recruitment and informed consent:

Eligible patients will be identified via a search from medical records using coding for hysterectomy performed as a procedure during admission from 01/01/2008 – 31/07/2015 (inclusive) and filtering for age during admission as < 51 years and admitting unit as Gynaecology Unit 1, 2 or 3. Their UR numbers will be compared to a list of patients with a diagnosis of endometrial cancer and endometrial hyperplasia and anyone with these diagnoses will be excluded. Patients eligible for inclusion will be approached via mail with a general letter from the Gynaecology Unit 2 Head of Unit. This letter will be an invitation to receive information about a study they can be part of

which will not state that the study is about hysterectomy (see attached "Invitation letter to participants").

Interested participants are directed either to proceed directly to the survey monkey website, where they can read the Patient Information and Consent Form (PICF), consent if they wish and proceed to complete the questionnaire, or return an expression of interest form via reply paid post informing us how they prefer to be contacted. A member of the research team will contact the interested participant as follows:

1. Participant indicates they prefer to be contacted via email – email sent with information and link to survey monkey website (see attached "Email to interested participants")
2. Participant indicates they prefer to be contacted via SMS – SMS sent with link to survey monkey website (see attached "SMS to interested participants")
3. Participant indicates they prefer to be contacted via phone call – member of research team to call patient and discuss the study on the phone. If participant agreeable they will be forwarded on the PICF and questionnaire via preferred method
4. Participant indicates they prefer to be contacted via post – letter sent with information (see attached "Post letter to interested participants") along with hard copy of PICF and questionnaire and reply paid envelope

Invited participants will be allocated a unique study number to use in on their questionnaire so that their name need not be used in their response.

Participants not interested in the study are advised to register their non-interest and wish not to be contacted again by email or returning a "please do not contact" slip via reply paid post. Non-interested participants will not be contacted further.

We will contact non-respondents with a follow up phone call 4 weeks after the invitation has been sent.

Consenting participants will have the option to tick that they consent to being contacted in the future by the researches with a view to participating in a semi-structured interview.

Distress protocol

We recognise that for some patients receiving an invitation to participate in this study or completing the questionnaire may cause distress. Therefore, we will take the following actions:

1. In the invitation letter, the PICF and the questionnaire participants will be directed to contact a member of the research team (Dr Charlotte Reddington) if they identify that they are experiencing distress as a result of the invitation to participate or actual participation in the study. The contact for Lifeline is also provided in these documents.
2. This member of the research team will make contact with the patient to identify the nature and severity of the distress and will determine further action(s) which may include:
    a. Review in the gynaecology clinic with a consultant gynaecologist
    b. Referral to psychology/psychiatry services at the Women's or in the local community, as appropriate
    c. Linking the participant with the hospital consumer advocate
    d. Acute mental health assessment by the CAT team

Should participants score anywhere above 'moderate' on the relevant subscales of the DASS-21 Dr Charlotte Reddington will contact the participant to discuss referral options.

Should participants who have experienced or are experiencing assault or abuse indicate in question 26 that they would like to receive support Dr Charlotte Reddington will contact the participant to discuss referral options.

Sample size and power calculation:

1362 women aged <51 years underwent hysterectomy from 2008 – 2015 inclusive under the three general gynaecology units at the Royal Women's Hospital. Of the 1362 women 110 were aged <36 at the time of hysterectomy. Once those with diagnoses of endometrial hyperplasia and endometrial cancer are excluded there will approximately 1250 women eligible to participate. The mean age of those eligible to participate in this

study is 43 years, with standard deviation of 4.87. Using STATA V15 a sample size of 128 participants is required to detect a 2.5 year difference (half a standard deviation) in mean age between those who do and don't report regret regarding hysterectomy with power=0.8 and alpha=0.05. While 128 is the minimum number to assess a 2.5 year difference in age in those who regret vs don't we would also like to be able to assess the associations and interactions of other confounders such as: age, parity, neuroticism, psychological morbidity, history of abuse, indication for hysterectomy, desire for future fertility and symptom resolution following hysterectomy using logistic regression. Using a conservative estimate that 50 observations (or participants) are required per variable examined in the logistic regression [22], a sample size of 450 participants will allow us to examine at least 9 variables for their association and interaction(s) with relief and regret. We therefore aim for a sample size of 450 participants, with 128 minimum for assessment of the primary outcome of age and regret.

Study schedule:

Eligible participants will be identified and contacted using the methods described above. We will invite all 110 women who were aged <36 years at time of hysterectomy to participate to ensure that we will capture as much information about this 'young' group of women as possible. We will then randomly select other eligible participants aged 36-50 at time of hysterectomy in batches of 100 to participate. We will invite 100 women per fortnight to participate and continue inviting 100 randomly selected eligible participants each fortnight until we either have 450 consenting participants or until we run out of eligible participants to contact.

We therefore predict recruitment to take approximately 6-7 months. Once informed consent has been obtained, each participant will be allocated a trial number. All the information collected will be de-identified and securely stored in a password-protected database, from which analysis will take place. Data entry will occur concurrently with recruitment and we expect data entry to be finalised 1-2 months after recruitment has completed.

Statistical analysis:

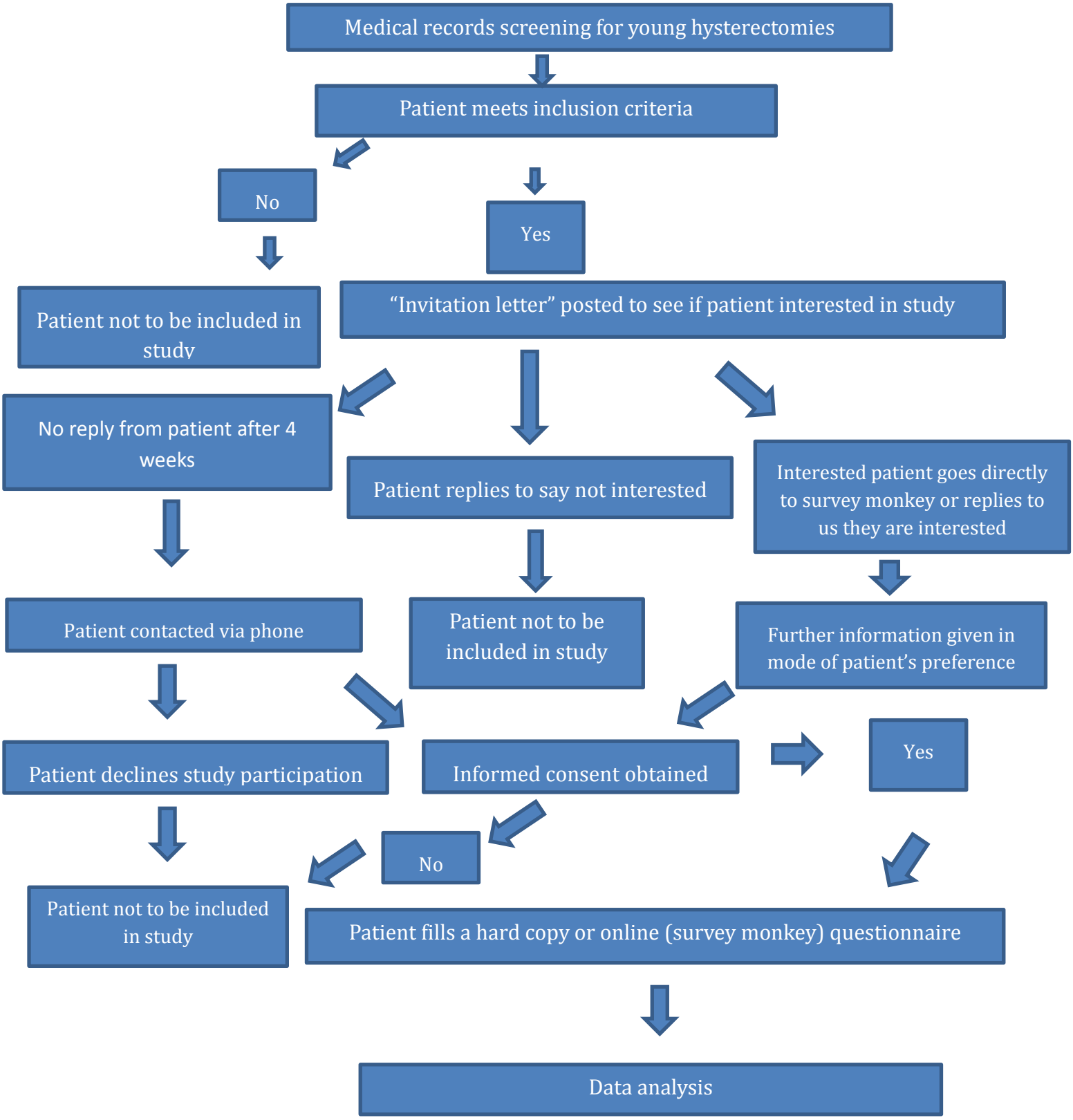
At completion of the study analysis will involve comparing categorical outcomes such as presence of previous general and gynaecological conditions using Chi squared tests and comparing continuous variables such as parity and various scales in the questionnaire measures using t-tests. If the data does not have a normal distribution then a non-parametric tests such as the Mann Whitney U test will be used. We will use ordinal logistic regression modelling to assess the effects of age and parity on relief and regret in this cohort. We will use regression modelling to assess the interactions of potential variables of interest associated with relief or regret (such as neuroticism, depression, indication for hysterectomy, fertility plans, experience of abuse and symptom response to surgery). P value of <0.05 will be considered significant.

Funding

This is a low cost study. All costs will be covered by the investigators. Grants to aid in administrative costs have been applied for, awaiting response.

Conflict of interest: None

Study flow:


Medical records screening for young hysterectomies
Patient meets inclusion criteria
No
Yes
Patient not to be included in study
"Invitation letter" posted to see if patient interested in study
No reply from patient after 4 weeks
Patient replies to say not interested
Interested patient goes directly to survey monkey or replies to us they are interested
Patient contacted via phone
Patient not to be included in study
Further information given in mode of patient's preference
Patient declines study participation
Informed consent obtained
Yes
No
Patient not to be included in study
Patient fills a hard copy or online (survey monkey) questionnaire
Data analysis

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