

Study protocol- HOPPSA

Hysterectomy and OPPortunistic SALpingectomy

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1. Background

In 2004 Shih and Kurman first proposed that high grade serous ovarian cancer, the most fatal subtype, originates in the transformation zone between tubal and peritoneal epithelium in the fimbriae of the Fallopian tubes (1). Data supporting this theory has accumulated and is now commonly accepted. Recently it is suggested that endometrial and clear cell ovarian cancer might also to a great extent originate in the tubal epithelium by metaplasia of cells of Müllerian origin (2). This has led to the idea of opportunistic salpingectomy as a way of decreasing the risk of epithelial ovarian cancer.

Recent observational epidemiological studies from Sweden and Denmark suggest a relative 35-42% ovarian cancer risk reduction after salpingectomy (removal of pathological tubes) compared with no surgery (3,4). Concern has been raised regarding the surgical safety of performing bilateral salpingectomy at the time of hysterectomy. One observational study indicates an increased surgical time (16 min) but no increase in the need for blood transfusions or hospital readmissions (5). Abdominal as well as laparoscopic and vaginal surgical approaches were evaluated. Neither did Vorwerk nor Morelli and colleagues find any increase in surgical complications in their retrospective cohort studies (6,7). Another concern of performing bilateral salpingectomy at the time of hysterectomy is the potential negative effects on ovarian function. This has so far been evaluated with surrogate measures (Anti-Müllerian Hormone (AMH), Follicle Stimulating Hormone, Antral Follicle Count, mean ovarian diameters and Peak Systolic Velocity) with no finding of negative impact (7). In a small randomized pilot study (n=30), ovarian function (AMH after three months) was preserved and there was no increase in surgical complications (8). Long term effects of estrogen deficit, such as cardiovascular disease and osteoporosis related fractures, have not been studied in relation to salpingectomy and hysterectomy.

A Swedish HTA (Health Technology Assessment)-report from 2016 has identified important knowledge gaps (9):

1. uncertainty about the effect size of salpingectomy on subsequent ovarian cancer incidence, since the available observational studies are based on non-opportunistic salpingectomy and the adequate comparison; salpingectomy vs no salpingectomy at the time of hysterectomy, has not been studied
2. sufficient safety data (surgical complication and long term effect on ovarian function) is lacking

While there is ample theoretical evidence and limited observational data for the benefit of opportunistic bilateral salpingectomy, there have been no prospective randomized trials confirming a reduced risk of ovarian cancer. Furthermore, the evidence for the safety of bilateral salpingectomy at the time of hysterectomy for benign reasons is also only observational and short-term, and no previous study has evaluated symptoms of ovarian failure as an endpoint.

2. Objectives

In a register based randomized controlled trial (R-RCT), examine if opportunistic salpingectomy compared with no salpingectomy, at the time of hysterectomy for a benign reason

- has no increased risk of complications
- has no negative side effects on ovarian function and subsequent cardiovascular disease or incidence of fractures
- implies reduced risk of subsequent ovarian cancer

2.1 Primary objectives

Short term

To examine if opportunistic salpingectomy

- has no increased risk of complications up to eight weeks after surgery, assessed according to the Clavien-Dindo classification (10) and the existing questions on complications in GynOp (The Swedish National Quality Register of Gynecological Surgery)

Intermediate term

To examine if opportunistic salpingectomy

- has no negative side effects on ovarian function, assessed with a validated scale for menopausal symptoms at baseline, one and five years after surgery ("MRS – Menopause Rating Scale") (11)

Long term

To examine if opportunistic salpingectomy

- implies reduced risk of subsequent ovarian cancer (including subsets of the different histopathological diagnoses) and primary tubal and peritoneal cancer, assessed through the national registers, and at long term follow-up (10-30 years)

2.2 Secondary objectives

Short term

To examine if opportunistic salpingectomy

- increases operative time
- increases length of hospital stay
- increases perioperative bleeding

Intermediate and long term

To examine if opportunistic salpingectomy

- reduces the occurrence of subsequent adnexal surgery, assessed through GynOp at one year and through The Patient Register up to ten years after surgery
- implies no increased use of hormone replacement therapy (HRT), assessed through GynOp at one year and through The National Drug Register up to ten years after surgery
- implies no increased change in AMH measured at baseline and one year after surgery
- affects the risk for cardiovascular disease and osteoporosis related fractures, as an extension of the outcome ovarian function and a potentially earlier menopause

3. Endpoints

3.1 Primary endpoints

Short term

- Complications according to the Clavien-Dindo classification and the existing questions on complications in GynOp, assessed during surgery and hospital stay and at eight weeks post-operatively.

Intermediate term

- Change in menopausal symptom score measured from baseline to one year follow-up, assessed with "MRS – Menopause Rating Scale"

Long term

- Epithelial ovarian cancer including histopathological types and grade, primary tubal and peritoneal cancer, as well as clinical stage according to FIGO, assessed through The Swedish Cancer Register, The Swedish Quality Register for Gynaecological Cancer, The Swedish Cause of Death Register and The Swedish Population Register and at long term follow-up (10-30 years)

3.2 Secondary endpoints

Short term

- Operative time
- Length of hospital stay
- Perioperative blood loss
- Conversion to other surgical route
- Failure rate of salpingectomy at planned vaginal hysterectomy

Intermediate and long term

- Prevalence of menopausal symptoms of at least moderate level according to "MRS – Menopause Rating Scale", assessed at one and five years
- Ovarian function, measured as change in anti-Müllerian hormone (AMH) serum level, from baseline to follow-up at one year in a subset of patients
- Subsequent adnexal surgery, including all surgery engaging salpinges and/or ovaries, assessed through GynOp at one year and through The Patient register up to ten years after surgery
- Use of HRT, defined by the ATC register including the drugs classified as GO3B-F (androgens, estrogens, progestogens or combination of those), assessed through GynOp at one year and through The National Drug Register up to ten years after surgery
- Cardiovascular disease, assessed through The Patient Register and national quality registers (such as Riksstroke and Swedeheart) if applicable, at 10-30 years
- Fractures (primarily radial, vertebral and hip fractures), assessed through The Patient Register and national quality registers (such as The Swedish Fracture Register) if applicable, at 10-30 years

4. Study design

4.1 Generally

The study is conducted within The Swedish National Quality Register of Gynecological Surgery (GynOp) and comprises the majority of gynaecological departments in Sweden. All gynaecological departments reporting data to the register (70%) will be included in the study. Data from the other Swedish gynaecological register for gynaecological surgery (GKR), will be included if variables are interchangeable.

4.2 Study design

The study is a national R-RCT. Patients not willing to be randomized will have the option to choose procedure (salpingectomy or not). The study has a non-inferiority design regarding the primary outcomes at short and intermediate term. A superiority design is applicable for the long term outcome ovarian cancer.

4.3 Randomization procedure

The randomization to the two groups (salpingectomy or no salpingectomy) will be performed within the GynOp register in a dedicated randomization module. The randomization will be performed in a ratio 1:1, i.e. half of the patients will undergo salpingectomy and half of the patients will not. The randomization procedure will be stratified for the variables center, age and intended operative route (abdominal, laparoscopic and vaginal). The vaginal route will be included only for those clinics that already perform bilateral salpingectomy vaginally. The randomization program will control that an even distribution between randomization groups occurs over time, either by applying variable block sizes or optimal allocation, including the stratification variables. Timing of randomization will be as close as possible to the time of surgery, i.e. at the pre-operative visit, closest to the day of surgery or on the day of surgery, depending on local practical circumstances. The randomization will be performed by the examining/operating gynaecologist, or assistant personnel.

Emergency randomization (in case of problems with on-line connection), can be achieved through telephone contact with the Gynop register office (090 785 04 64).

4.4 Blinding.

The intention is to blind patients for the surgical procedure until one year after surgery (after the evaluation of post-menopausal symptoms). Patients will be able to read their medical records on-line. The blinding period will thus extend from the time of randomization until at least past the surgical procedure. Surgeons will not be blinded for practical reasons.

5. Patients

5.1 Selection of patients

All patients planned for hysterectomy due to a benign indication, will be screened for eligibility in an automatic manner within GynOp after the pre-operative health questionnaire has been registered. The register will signal for potentially eligible patients. Patients who fill out their pre-operative questionnaire on-line receive written information about the study directly on the screen. Others will receive written information by ordinary mail, when scheduled for surgery. Preferably, patients will receive study information also at the consultation when the decision on hysterectomy is taken. Informed consent can be

given either on-line within GynOp or by signing a paper document at any time point before randomization.

5.2 Number of patients. Sample size calculation

Approximately 700 women <55 years of age who undergo abdominal or laparoscopic hysterectomy without a concomitant salpingectomy are registered in GynOp per year (2014-2015). Opportunistic salpingectomy has increased during the two past years and an additional 900 hysterectomies with concomitant bilateral salpingectomy was performed during 2015. Thus, approximately 1600 patients would be eligible for screening in GynOp per year. A non-inferiority design with sequential analyses of the short and the intermediate term primary outcomes is planned; Complications at eight weeks post-operatively and Menopausal symptoms one year after surgery.

5.2.1. Short term outcome - Complications at eight weeks (non-inferiority)

Total complication rate (mild and severe) was 30% during 2015. If non-inferiority is defined as an increased complication rate of up to 8% (i.e. an increase from 30% to 38 % is considered as of non-significant clinical relevance), the upper limit of the two-sided 95% confidence interval (CI) for the difference between groups shall not exceed 8% with a probability of 80% ($\beta=80\%$), and an estimation of up to 3% more complications in the salpingectomy group, 1280 patients per randomization group is needed to show non-inferiority. For protection against a 10% loss to follow-up, approximately 2850 patients are needed for recruitment, to have 2560 patients evaluable for analysis. The sample size target will include the laparoscopic and the abdominal route. The vaginal route is likely to have a high failure rate and will not be included in the targeted sample size.

If all clinics that register in GynOp participate and 90% of eligible patients ($n=1440$ per year) consent to randomization, recruitment will require two years. Correspondingly, if 50% (800 patients per year) consent, recruitment will take 3.5 years.

5.2.2. Intermediate term outcome - Change in menopausal symptoms at one year (non-inferiority)

The Menopause Rating Scale (MRS) gives a rating of 0-4 in 11 items, resulting in a total range of 0-44. An increase in MRS from baseline to one year is expected in both groups, based on a negative effect of hysterectomy on ovarian function (12) and also on increasing age. A clinically relevant difference is defined as 5 points on MRS (13). This difference can be applied both as a clinically relevant change within groups as well as a clinically relevant difference in change between groups. If non-inferiority is defined as 4 points on MRS, the upper limit of the two-sided 95% confidence interval for the difference in change between the two groups shall not exceed 4 points (standard deviation (SD) for change 6.9) with a probability of 80% ($\beta=80\%$), and an estimation of up to 3 points higher rating in the salpingectomy group, 749 patients per randomization group is needed to show non-inferiority. Thus, the sample size for the outcome Complications greatly exceeds the needed sample size for the outcome Change in MRS.

5.2.3. Long term outcome - Ovarian cancer (superiority)

The number of new ovarian cancer cases in Sweden is 700 per year. The overall life time risk is approximately 2%. If the incidence is reduced by 50% to 1.0%, given $\beta=80\%$, $\alpha=5\%$ and a two-sided test, 2100 patients per group is needed to demonstrate superiority. The calculation is based on survival analysis (log rank test) with the assumptions of four

years accrual time, 30 years of follow-up with 30 years survival 98% and 99% and an increasing hazard rate. The estimated risk of loss to follow-up is low, since the outcome data is based on register data from The National Board of Health and Welfare. Assuming 1.5% loss to follow-up and 3% excluded due to non-eligibility detected after randomization (at surgery), 4400 patients are needed. Thus, the total sample size of 4400 patients for the long term outcome ovarian cancer exceeds the sample size for the primary outcome Complications by approximately 1600. To adequately analyze the randomized cohort regarding ovarian cancer risk, the recruitment period needs to be extended by approximately 12-18 months.

Analyses will include:

1. Only randomized patients
2. All patients registered in GynOp (and GKR if variables are interchangeable), fulfilling the inclusion criteria
3. Comparisons with women without hysterectomy and salpingectomy, through The Swedish Population Register

5.3 Inclusion criteria (for randomization)

1. Planned hysterectomy for a benign reason
2. Age < 55 years at randomization
3. Willing to be randomized
4. Vaginal route may be included if the surgeon is confident with performing vaginal salpingectomy.

5.4 Exclusion criteria (for randomization)

1. Previous bilateral oophorectomy and/or salpingectomy
2. Planned oophorectomy and/or salpingectomy (for reasons such as already diagnosed adnexal tumor, known carrier of BRCA 1/2 mutation or Lynch syndrome (hereditary nonpolyposis colorectal cancer))
3. Non-understanding of the oral or written study information

5. Treatment

The active treatment is salpingectomy.

6. Variables for analysis

Demographic variables

Already present in GynOp; symptoms causing surgery, previous treatments, time since last menstrual period, menopausal symptoms, estrogen treatment, symptoms from vagina, bladder and rectum, sexual intercourse last three months, previous pregnancies and deliveries, gynaecological diseases and previous surgery, type of professional work, present sick leave, weight, length, smoking habits, allergy, hereditary diseases, coronary and pulmonary symptoms, any other present or previous diseases, medication.

Specific study variables will be added; age at menarche, duration of breast feeding, previous use of hormonal contraceptives, previous Chlamydia infection, previous salpingitis, scale for menopausal symptoms.

Operative variables

Already present in GynOp; type of anesthesia, operative route, any pathological finding in the abdomen, procedure(s) performed, complications, use of antibiotics, operative time, blood loss, type of suturing, codes for surgery.

Complications according to Clavien-Dindo will be introduced in GynOp as permanent variables.

Post-operative variables during hospital stay

Already present in GynOp; complications, length of hospital stay, thrombosis prophylaxis, planned sick leave, diagnoses.

Complications according to Clavien-Dindo will be added as permanent variables.

Eight weeks questionnaire

Already present in GynOp; use of analgetics, bleeding, symptoms from the bladder, sick leave, time to daily activities, satisfaction after surgery, complications generally and specifically, treatment of complications.

Complications according to Clavien-Dindo will be added as permanent variables.

One-year questionnaire

Already present in GynOp; pain experience, estrogen treatment, symptoms from vagina, bladder and rectum, sexual intercourse last three months, coitus pain, result and satisfaction after surgery, complications generally and specifically, treatment of complications, hospital care, sick leave.

Specific study variables will be added; scale for menopausal symptoms.

Five-year questionnaire

Specific study variables will be added; onset of menopausal symptoms and time since onset, use of HRT, scale for menopausal symptoms.

Register data from other national registers

Use of HRT

Subsequent adnexal surgery including salpingectomy, oophorectomy, or partial resection or other intervention on the adnexa

Diagnosis of epithelial ovarian cancer; histopathology, grade, clinical stage

Diagnosis of primary tubal and peritoneal cancer; histopathology, grade, clinical stage

Diagnoses of myocardial infarction, ischemic and hemorrhagic stroke

Diagnoses of fractures

Biochemical analyses:

Anti-Müllerian hormone at baseline and after one year in a subset of patients (see 7.)

7. Substudy of anti-Müllerian hormone (AMH) levels

7.1 Background

An indirect measure of ovarian function is the serum level of AMH. There is a theoretical rationale that salpingectomy may disturb the vascular and nervous supply to the ovary, possibly causing impairment in ovarian function. Two previous studies, one RCT and one cohort study, has studied AMH levels three months after hysterectomy, comparing the change in AMH if a salpingectomy was performed at the same time or not (7,8). No difference was observed between groups. None of these studies evaluated any clinical outcome related to ovarian function, but only surrogate outcomes. In the present study, the primary outcome for ovarian function is based on clinical symptoms related to menopause. In order to strengthen the hypothesis of non-inferiority for ovarian function if salpingectomy is performed, an analysis of AMH is planned in a subset of patients.

7.2 Methods

This substudy will be conducted at the Sahlgrenska University Hospital and the associated laboratory. Consecutive patients in the study will be asked for blood samples. Specific written and oral information will be provided for this group. Blood samples are taken at baseline and after one year. Samples are handled according to laboratory instructions, frozen and stored for later analysis, when the entire cohort will be analyzed at the same time. Results will not be available until after one year of

follow-up. Change in AMH will be compared between the two groups and presented both in absolute and relative measures.

7.3 Power calculation

A decrease in AMH from baseline to one year after surgery is expected in both groups, based on a negative effect of hysterectomy on ovarian function (12) and also on increasing age. Baseline before surgery is estimated to be 0.5 mg/L and one year post-operatively 0.25 mg/L in the group with hysterectomy only (7,12). If non-inferiority is defined as 0.125 mg/L AMH, the higher limit of the two-sided 95% confidence interval for the difference in change between the two groups shall not exceed 0.125 (SD for change 0.1) with a probability of 80% ($\beta=80\%$), and an estimation of up to 0.05 larger change in the salpingectomy group, 29 patients per randomization group is needed to show non-inferiority. Estimating a 20% loss to follow-up (a second blood sample not taken), 75 patients will be recruited in this substudy.

8. Statistical methods and handling of data

8.1 Review of variables and time for registration

Variables will be registered continuously according to present routines in GynOp. The routines include assessment pre-operatively, at discharge from hospital, at eight weeks and at one year post-operatively. A five-year follow-up questionnaire to included randomized will be added for the study.

The randomization rate will be followed continuously and govern the study duration. Long term register data will be retrieved from the respective registers according to the planned follow-up (Appendix 1).

8.2 Statistical methods

For descriptive statistics mean, SD, median and interquartile range (IQR) will be used. Protocol violation is expected when unsuspected tubal or ovarian pathology is apparent at surgery. These patients will not be included in the analyses, since they do not fulfill the inclusion criteria. Both “intention to treat” (ITT) analyses, and “per protocol” analyses will be performed. Multiple imputations for missing data will be performed, when applicable. For non-inferiority design, the “per protocol” analysis will be the primary. For superiority design, the ITT analysis will be the primary.

For comparison between two groups Student’s t-test will be used for continuous variables, Mann-Whitney U-test for ordered variables and Fisher’s exact test or Chi²-test when applicable, for proportions. For dichotomous outcomes two-sided 95% CI for the difference in proportions between groups will be calculated as well as risk ratios with 95% CI. Tests for superiority will be two-sided and performed at a significance level of 0.05. Multivariable logistic regression methods will be used for adjusted analysis and stepwise logistic regressions will be used to find independent predictors of the primary outcome variables and presented as OR with 95% CI.

The long term outcomes include also time to event data. The primary analysis of time to ovarian cancer between the two groups will be the log-rank test. Unadjusted hazard ratio (HR) with 95% CI will be calculated with Cox regression models. Adjusted complementary analyses for baseline variables will be performed using multivariable Cox proportional hazard regression models with calculation of HR with 95% CI. In order to find independent predictors of development of ovarian cancer stepwise Cox proportional regression analysis will be performed.

In order to estimate, plot the hazards and calculate the absolute risk of ovarian cancer with time intervals for given values of a woman complementary analysis with Poisson regression models will also be performed.

The outcome Ovarian cancer will be analyzed in two steps; firstly by including only randomized patients, secondly by including also non-randomized patients. For comparisons within groups, Wilcoxon sign rank test will be used for continuous variables, sign test for ordered variables or dichotomous variables.

8.3 Subgroup analysis

Pre-planned subgroups for analysis are:

-pre-and post-menopausal women and surgical route.

Analyses of AMH will be performed in a subset of 75 patients with the objective to demonstrate non-inferiority between groups.

Exploratory interaction analyses will be performed between treatment and baseline variables to check if there is a homogenous treatment effect and to find subgroups with good treatment effect and subgroups with no or bad treatment effect.

8.4 Interim analysis

A data safety monitoring board (DSMB) will overlook the recruitment of patients over time, particularly to the vaginal hysterectomy arm, as well as the complications rates. The DSMD will be independent from the investigators.

After the required sample size for the short term primary outcome, Complications, is reached, randomization will continue until the sufficient sample size for the long term outcome Ovarian cancer is completed (estimated to require 12-18 months). If the results of complication data fail to demonstrate non-inferiority and on the contrary, show that salpingectomy is associated with an increased risk of complications (according to a defined limit), recruitment may be stopped in advance, if results are available before the recruitment for the long term outcome Ovarian cancer has been completed.

8.5 Handling of data

Clinical data are handled within the GynOp register. The eight-week follow-up dataset will be available to the researchers through the GynOp register research portal.

Measurements of AMH in a subset of patients will be added manually to the one-year follow-up dataset in GynOp. This dataset and all subsequent datasets will be cross-linked with other national registers. Regular security rules for register data will be applied. All final datasets will be without any identification of patients.

9. Adverse events

Adverse events will be recorded during the hospital stay in the GynOp and also reported by the patients in the post-operative questionnaires as a defined outcome.

10. Ethical considerations

Application for ethical approval will be submitted to the regional ethical committee in Göteborg. Written and oral information will be given to the patients when they are scheduled for surgery. Written information will also be provided on-line when the pre-operative questionnaire is filled out. Informed consent is signed by the patient on-line or on paper.

The planned intervention (salpingectomy) is regarded as a simple procedure. The ethical issue is whether the procedure has any negative effects that have to be balanced against a potential decrease in cancer incidence.

The sample size for the short term outcome Complications will be reached before the sample size for the long term outcome Ovarian cancer. The estimated additional recruitment period is 12-18 months. If the results of complication data fail to demonstrate non-inferiority and on the contrary, show that salpingectomy is associated with an increased risk of complications (according to a defined limit), it would be unethical to continue randomization, if the results are available before recruitment for the long term outcome Ovarian cancer has been completed.

11. Follow up-control of the study

The study will use the already established routines within GynOp for sending questionnaires and registration of data. A five year questionnaire will be added in the study. Intermediate and long term outcome data will be retrieved from national state registers (The Swedish Cancer Register, The Swedish Cause of Death Register, The Patient Register, The National Drug Register) and national quality registers (GynOp, The Swedish Quality Register for Gynaecological Cancer and if applicable also Riksstroke, Swedeheart, The Swedish Fracture Register) and The Swedish Population Register from Statistics Sweden (SCB).

11.1 Monitoring

At each clinic, the SNAKS (the Swedish Network for National Clinical Studies within ObGyn) contact person (or another representative) is responsible for the conduct of the study. The study will use established routines within GynOp for monitoring and validation of data.

11.2 Source data and CRF

Documentation of the individual patients' treatment is performed in ordinary medical records at each clinic as well as in the GynOp register.

12. Administration

12.1 Coordination group.

For the coordination of the study the principal investigator (PI) is responsible. The PI and co-workers will have repetitive contact with the SNAKS contact persons at each clinic and with representatives of the GynOp register.

12.2 Handling of data and statistics

Responsible for data in the GynOp register is Västerbottens Läns Landsting. Responsible for statistical analyses in GynOp is RCN – Registercentrum Norr. Additional statistical consultation will be provided from Statistiska konsultgruppen in Göteborg.

13. Handling of the patients after finishing the study.

The five-year questionnaire is the last study contact for randomized patients. For the long term outcome Ovarian cancer, patients will not be contacted. Instead the Swedish Cancer register, The Swedish Cause of Death Register (to check for viability and potential date of death) and The Swedish Population Register (to check for emigration) will be used.

14. Reporting policy and publication

Several publications are planned. Authorship is depending on standard rules for scientific journals.

15. Time schedule

Study preparations will start during 2016. Recruitment period for the primary outcome is estimated to be completed within 3.5 years. The long term outcome (Ovarian cancer) will require a longer recruitment period; 1.5 additional years. The follow-up through The Swedish Cancer register will be conducted up to 30 years after recruitment was completed (Appendix 1).

16. Signing of the protocol and changes in the protocol (amendments)

The study protocol will be registered in www.clinicaltrials.gov

17. Participating clinics

The aim is to include all gynaecological departments in Sweden reporting to GynOp.

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