



UMEÅ UNIVERSITET

# What impact has patient reported salpingitis on subsequent gynecologic surgery?

Research plan

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## Background

The most common cause of sexual transmitted infection (STI) is *Chlamydia trachomatis* (*C. trachomatis*). Risk factors include young age, intercourse at an early age, more than one sexual partner, history of STI etc. Genital infections with *C. trachomatis* are in 85-90% asymptomatic and can persist undetected for several months (1). Salpingitis is an upper genital tract infection caused by a polymicrobial infection where *C. trachomatis* is one of the more common pathogens involved (1, 10). Salpingitis lead to subsequent pelvic inflammatory disease (PID), approximately 15% of untreated chlamydial infections progress to PID (2, 10). Symptoms of salpingitis/PID include a variety of clinical features with a wide variation and severity of symptoms; the cardinal symptom is abrupt lower abdominal pain. Other symptoms include increased urinary frequency, dysuria and abnormal uterine bleeding or vaginal discharge. The routine treatment of salpingitis is by antibiotics and if the treatment is delayed the risk of developing complications like infertility, ectopic pregnancy and chronic pelvic pain increases (10, 11).

Seropositivity with *C. trachomatis* are associated with a two-fold increased risk of ovarian cancer (6). A large population-based study found an increased risk (HR 1.47, 95% CI 1.04–2.07) of ovarian cancer in patients with previous PID (12). These correlations suggest that infections with *C. trachomatis* and eventual subsequent salpingitis and PID have an important role in the development of ovarian cancer. Ovarian cancer is the most lethal gynecological malignancy, why plenty of research has been done on this topic.

Ovarian cancer is a heterogeneous group of tumors, where epithelial tumors are most frequent. They are classified as type I and type II; type I is associated with low-grade neoplasm that arise in a stepwise fashion from well recognized precursors and have specific mutations, for example BRAF and KRAS, while type II tumors are high-grade neoplasm with a more uncertain development (3). Type II tumors include high-grade serous carcinoma (HGSC), carcinosarcoma and undifferentiated carcinoma. Type I tumors have good prognosis whereas type II tumors are in an advanced stage in >75% of cases at diagnosis. This is because type II tumor evolve rapidly, metastasize early and are highly aggressive with subsequent poor outcome. Type II tumor account for 90% of the deaths of ovarian cancer. (3, 4).

New studies suggest that the precursor lesions to type II tumors arise in the fallopian tubes from intraepithelial carcinomas. The theory is supported by a study that found a risk reduction of 65% for ovarian cancer after unilateral salpingectomy, and a bilateral procedure an additional 50% risk reduction (9). In another study of 55 patients with pelvic serous carcinoma, 41 (75%) of them demonstrated involvement of the fallopian tubes and 93% of these involved the fimbriae (7). The main theory is that a primary tumor originated in the fallopian tube implants, by a seeding event, in the ovary and causes type II ovarian cancer (8). These connections support the evidence that the fallopian tubes have a crucial role in the development of ovarian cancer.

The hypothesis, that ovarian cancer originates from the fallopian tubes, makes it vital to investigate all aspects of disease in the fallopian tubes with their subsequent complications and gynecological disease. There is limited evidence regarding how often patient reported salpingitis is represented by macroscopically damaged tubes, and how often these changes in the fallopian tube occur without known salpingitis. Charting the presence of tubal damage and patient reported PID with subsequent gynecologic surgery and complications can increase the general knowledge about the disease and give information about how to manage and negotiate these patients in the aspect of gynecologic surgery.

## Purpose and aims

The purpose of this study is to increase the knowledge about salpingitis effects, both in a surgical perspective and long-term complications such as cancer. The primary aim of this study is to describe the association of self-reported PID with tubal damage and if there are specific trajectories of self-reported PID on type of subsequent gynecologic surgery as well as results of surgery.

### *Specific aims*

The specific aims are to answer the following questions:

- How often is patient reported salpingitis associated with macroscopic changes in the tubal tissue? How often do macroscopic changes occur with no history of salpingitis?
- What significance have known salpingitis on indication and subsequent gynecological surgery?
- Is there a difference in complications after gynecological surgery between women with or without previous salpingitis?
- Do women with previous reported salpingitis have suspected/confirmed malignancy more often than women without salpingitis?

## Materials and Methods

The study is a retrospective observational study based on data from the Swedish National Quality Register of Gynecologic Surgery (GynOp). GynOp is a nation-wide quality register that started 1997 where all major gynecological surgeries are included, and today 60 clinics throughout Sweden participates. Data in the register includes information gathered before, during and after the surgery from both patients and doctors.

Data will be analyzed on the GynOp server with no access to personal identification on the subjects.

Data from laparoscopic and abdominal surgeries will be included from when salpingitis began to be registered; hysterectomies from 1997, adnexal surgeries from 2004 and tumor surgeries from 2005. Data will be collected up to 2020. Approximately 80 000 women will be included. The material consists of a preoperative survey, medical assessment, perioperative data together with patient reported and medical follow-up eight weeks and one year postoperatively. Multiple cofounders will be used, see variable list.

The data will be analyzed with descriptive analyzes between different subpopulations; categorical variables with chi<sup>2</sup>-tests and Fishers exact tests, and continuous variables with t-tests and Mann-Whitney U. Linear and logistic multivariable regression analysis depending on outcome; compiled as binary or continuous. Potential cofounders will be discussed using Directed Acyclic Graphs (DAG's). Missing data is managed with multiple imputation if applicable.

The study is expected to be completed during the spring of 2021. It will be presented as a degree project.



## Outcome

### *Primary outcome*

Macroscopic changes, tubal pathology, in patients that undergo abdominal or laparoscopic gynecological surgery.

### *Secondary outcome*

1. Complications during operation and after eight weeks, e.g. operation time, bleeding, adherences, organ damage.
2. Operation indication and operation method – if it varies depending if the patient has reported salpingitis or not.
3. Patient reported satisfaction after one year.

## Clinical significance

Upper genital tract infection, salpingitis, is a polymicrobial infection where *C. trachomatis* is one of the most common pathogens involved. It can cause PID with complications such as infertility, ectopic pregnancy and pelvic pain (1). Recent studies have implied that type II ovarian cancer originates from the fallopian tubes (7) and that seropositivity for *C. trachomatis* is associated with a two folded increased risk for ovarian cancer (6).

This suggest that salpingitis, that causes tubal damage, has a contributing factor to the development of ovarian cancer, among other serious complications. The statement implies that it is important to know the distribution of macroscopical changes in the fallopian tubes and its complications, to give a greater understanding about how we should face and manage gynecological surgery for these patients. The result of the study will give greater knowledge about salpingitis as a risk factor for surgery and long-term complications, such as chronic pelvic pain and malignancy. It will also give input whether there is something particular we need to take into account for these patients, for example patient management and postoperative treatment. In a larger scale the outcome of the research can contribute to further studies on the subject.



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