**Prevalence and severity of endometriosis at laparoscopic treatment of tubal ectopic pregnancy**

Investigators:

Dr Jennifer Dean

Dr Stephen Lee

Dr Charlotte Reddington

Dr Michal Amir

Dr Claudia Cheng

A/Prof Martin Healey

Acute Gynaecology Unit and Gynaecology 2 Unit

Department of Gynaecology

The Royal Women’s Hospital

20 Flemington Road

Parkville VIC 3052

AUSTRALIA

**Background:**

Ectopic pregnancies occur in approximately 1-2% of spontaneous pregnancies (Farquhar, 2005). Risk factors for ectopic pregnancy are well documented but the association between endometriosis and ectopic pregnancy is less certain. It is thought that endometriosis increases the risk of ectopic pregnancy by inducing a chronic inflammatory reaction, leading to adhesion and scar formation, thereby altering tubo-ovarian anatomy (Dunselman et al., 2014; Yong et al., 2019). A recent publication based on the analysis of data derived from the Nurses’ Health Study II has shown an association between women with proven endometriosis and future ectopic pregnancy, as well as other adverse pregnancy outcomes (Farland et al., 2019). However, no studies have examined the rate and severity of endometriosis at the time of ectopic pregnancy surgery.

Given that a significant proportion of patients diagnosed with ectopic pregnancy are treated laparoscopically, we believe a study examining the prevalence, staging and anatomic features of endometriosis at the time of surgery is warranted. The diagnosis and staging of endometriosis will help the counselling of patients and future reproductive planning, especially in those with few or no other risk factors for ectopic pregnancy.

**Primary Outcome:**

* To determine the prevalence and severity of endometriosis in women at the time of laparoscopic treatment of tubal ectopic pregnancy and to demonstrate that the prevalence of endometriosis in the study sample is significantly higher than in the population.

**Secondary Outcomes:**

* To determine the prevalence and severity of endometriosis-related pain and infertility (defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse) in patients diagnosed with tubal ectopic pregnancy and proceeding to laparoscopic treatment.
* To compare the prevalence and severity of endometriosis in patients with and without risk factors for tubal ectopic pregnancy.

**Study null hypothesis:**

Women undergoing laparoscopic treatment of ectopic pregnancy are no more likely to have concurrent endometriosis than the reported overall prevalence of endometriosis in reproductive aged women of 10% (Eskenazi & Warner, 1997).

**Study design:**  Prospective cohort study

**Study Units:** Acute Gynaecology Unit which manages all gynaecological emergencies at Royal Women’s Hospital, including surgical treatment of ectopic pregnancy.

**Inclusion criteria:**

* All women presenting to the Royal Women’s Hospital (Women’s Emergency Centre, Early Pregnancy Assessment Centre, or transferred from another hospital), diagnosed with tubal ectopic pregnancy, who are clinically stable and suitable for laparoscopic surgery.

**Exclusion criteria:**

* Non-tubal ectopic pregnancy
* Unable to understand and fully comprehend consent information
* Non consent

**Patient identification, recruitment and informed consent:**

Eligible patients will be invited to participate in the study by the Acute Gynaecology Unit consultant or Receiving Gynaecology registrar or resident.

Interested participants are provided a copy of the Patient Information and Consent Form (PICF) to review and consent if they wish to proceed. Initial patient data about risk factors for ectopic pregnancy and symptoms of endometriosis is collected by the Acute Gynaecology Unit team member pre-operatively using the standardised hard-copy or electronic (Survey Monkey) questionnaire.

Patients who choose not to participate will not be disadvantaged in any way with regard to their medical care.

Consenting participants will undergo the laparoscopic treatment of ectopic pregnancy of their choice (salpingectomy or salpingotomy) as well as scoring for endometriosis using the revised American Fertility Society classification of endometriosis (r-AFS). Other laparoscopic findings will also be recorded e.g. adhesions including Fitz-Hugh-Curtis Syndrome.

The intra-operative questionnaire will be completed by the lead surgeon immediately following the procedure, in the operating theatre or in the theatre recovery area. Questions to be completed are 1-23 of the Intra-operative Questionnaire, which includes the r-AFS.

As per current practice, participants will not be consented to surgical treatment of endometriosis in the same procedure unless this is discussed pre-operatively with the patient and surgical team involved on a case-by-case basis and deemed appropriate.

**Sample size and power calculation:**

The prevalence of endometriosis in the population is estimated to be 10% (Eskenazi & Warner, 1997). A retrospective audit of patients having a laparoscopic salpingectomy for ectopic pregnancy in our institution had a 25% rate of endometriosis recorded. Using a single-sample binomial comparison approach, with a null hypothesis proportion of 10%, a true proportion of 25% , a power of 80% and a type 1 error rate set at 5%, the sample size required is 66.

**Study schedule:**

Base on the recent retrospective audit on the prevalence of endometriosis found at the time of laparoscopic treatment of ectopic pregnancy, 128 patients underwent surgery for ectopic pregnancy over a 6 month period. If we conservatively suppose that 50% of patients agree to participate in the study, recruitment is predicted to take approximately 6 months to achieve the target sample size of 66.

Once informed consent has been obtained, each participant will be allocated a trial number. All the information collected (including data collected using Survey Monkey) 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. The database will be retained for 7 years after completion of the study then deleted.

**Statistical analysis:**

Analysis of the primary hypothesis will involve using the one-sample binomial test to compare the study endometriosis rate to the population prevalence of 10%. Comparison of categorical outcomes such as presence or absence of endometriosis will be performed using Chi squared tests, while comparing continuous variables such as pain and various scales in the questionnaire measures using t-tests. If the data does not have a normal distribution, non-parametric tests such as the Mann Whitney U test will be used.P value of <0.05 will be considered significant. Logistic regression will be used to model the effects of other ectopic risk factors and their interaction with the presence of endometriosis. The study group will also be dichotomised to those with and without risk factors for ectopic pregnancy and the rates of endometriosis compared.

**Funding**

This is a low-cost study. All costs will be covered by the investigators. The investigators intend to apply for grants to aid in administrative costs.

**Conflict of interest:** None

**Study flow:**

Patient diagnosed with tubal ectopic pregnancy proceeding to laparoscopic treatment identified

No

Patient meets inclusion criteria

Yes

Patient approached to see if interested in participating in study

Patient not to be included in study

Interested patient given PICF to review

Patient responds not interested

Informed consent obtained

Patient not to be included in study

Yes

No

Pre-Op – Acute Gynaecology Unit team member and patient fills a hard copy or online (survey monkey, free version) questionnaire;

Intra-Op findings including r-ASF scoring of endometriosis;

Data analysis

**References**

Dunselman, G. A., Vermeulen, N., Becker, C., Calhaz-Jorge, C., D'Hooghe, T., De Bie, B., . . . Embryology. (2014). ESHRE guideline: management of women with endometriosis. *Hum Reprod, 29*(3), 400-412. doi:10.1093/humrep/det457

Eskenazi, B., & Warner, M. L. (1997). Epidemiology of endometriosis. *Obstet Gynecol Clin North Am, 24*(2), 235-258. doi:10.1016/s0889-8545(05)70302-8

Farland, L. V., Prescott, J., Sasamoto, N., Tobias, D. K., Gaskins, A. J., Stuart, J. J., . . . Missmer, S. A. (2019). Endometriosis and Risk of Adverse Pregnancy Outcomes. *Obstet Gynecol, 134*(3), 527-536. doi:10.1097/AOG.0000000000003410

Farquhar, C. M. (2005). Ectopic pregnancy. *Lancet, 366*(9485), 583-591. doi:10.1016/S0140-6736(05)67103-6

Yong, P. J., Matwani, S., Brace, C., Quaiattini, A., Bedaiwy, M. A., Albert, A., & Allaire, C. (2019). Endometriosis and Ectopic Pregnancy: A Meta-analysis. *J Minim Invasive Gynecol*. doi:10.1016/j.jmig.2019.09.778

World Health Organisation 2020, *Infertility definitions and terminology,* World Health Organisation, viewed 27th of March 2020, <https://www.who.int/reproductivehealth/topics/infertility/definitions/en/>