

Project plan

Title

Previous hysteroscopic surgery and its association with Abnormally Invasive Placenta (AIP)

Objective

To investigate whether hysteroscopic surgery is associated with an increased the risk for abnormally invasive placenta or placenta previa in the subsequent pregnancy and delivery.

To investigate whether hysteroscopic surgery is associated with an increased risk of severe bleeding or retained placenta in the subsequent pregnancy, suggesting the existence of undiagnosed less severe forms of AIP (1).

Hypothesis

Women with previous hysteroscopic surgery have a higher risk of AIP in the subsequent pregnancy.

Women with previous hysteroscopic surgery have a higher risk of severe bleeding in the subsequent pregnancy.

Background

Abnormally invasive placenta (AIP) is a group of disorders where the placenta attaches into the myometrium of the uterine wall and therefore fails to detach after the delivery of the fetus. It is associated with a high risk of severe postpartum hemorrhage, postpartum hysterectomy and maternal death (2). AIP is primarily associated with a history of uterine surgery, foremost caesarean section and the presence of placenta previa (3). Placenta previa is not a disorder of placental invasiveness but is strongly associated with previous uterine surgery. The incidence of AIP is increasing as women undergo more caesarean sections, are older at time of delivery, and make more use of assisted reproductive technology (1).

Prenatal detection of AIP by targeted ultrasound is of key importance to minimize postpartum hemorrhage and the need of emergency postpartum hysterectomy (4). Correctly identifying the increasing minority of women who are at risk of this disorder is a clinical challenge. In the Nordic countries only approximately 30% of AIP is detected by prenatal ultrasound (3).

There are several studies describing the connection between caesarean section, placenta previa and AIP but to our knowledge, there is only one article describing the association between invasive gynecological surgery and AIP where pre-pregnancy surgical procedures significantly increased the risk for AIP (5). The association to severe bleeding was not determined in this study.

Hysteroscopy is becoming increasingly common, particularly among women seeking care for infertility. If hysteroscopic surgery is a risk factor for AIP this should be taken into account when identifying women at risk of AIP. Hypothetically, hysteroscopic surgery may be associated foremost with focal AIP and abnormal adherence rather than invasion which may be more difficult to detect prenatally and manifest primarily as postpartum haemorrhage and may falsely be mistaken as retained placenta and/or atonic bleeding.

Method

This is a retrospective cohort study of the risk associated with previous hysteroscopic surgery on the following adverse outcomes: AIP, placenta previa, retained placenta and postpartum hemorrhage. Data will be extracted for each woman from the Swedish National Quality Register of Gynecological Surgery (GynOp registret) and linked to the Swedish Birth Register (Medicinska Födelseregistret) and the Swedish Patient register (Patientregistret). We will record background-, pregnancy- and delivery characteristics for each woman. We will adjust for the existence of potential confounding factors.

Study population:

All primiparous women who delivered a live or stillborn child over 22 weeks of gestation in Sweden during the period January 1, 1999 to December 31, 2018 (n ≈ 850000).

Exclusion criteria: Women with diagnosed uterine malformations

Exposure:

Our exposure is a history of a hysteroscopic surgery, prior to index pregnancy, according to the ICD-10 surgical intervention code registered in the Swedish National Quality Register of Gynecological Surgery:

Hysteroscopic excision (LCB25, LCB98),

Hysteroscopic resection (LCC05),

Hysteroscopic lysis of adhesions (LCG02).

Hysteroscopic endometrial resection (LCB28)

Hysteroscopic endometrial destruction (LCB 32)

Other diagnosis registered to account for confounding factors are:

Laparoscopic hysterotomy (LCB01),

Laparoscopic extirpation of myoma (LCB 11),

Laparoscopic excision or destruction of intrauterine anomaly (LCB 97),
Intrauterine surgery and uterine biopsy (LCA*),
Excision and destruction av intrauterine anomaly via hysterotomy (LCB*),
Resection of the uterus via laparotomy (LCC00),
Suture of the uterus via laparotomy (LCG 10),
Reconstruction of the uterus via laparotomy (LCG40),
Curettage and suction (LCH*, MBA*).

The non-exposed (comparison) group will be women without hysteroscopic intervention prior to pregnancy.

Outcomes:

Our outcomes are the occurrence, according to ICD-10 diagnostic codes recorded in the Birth Register, of:

1. placenta accreta (O43*)
2. placenta previa (O44*)
3. retained placenta (O73*)
4. Postpartum hemorrhage >1000ml and 2000ml (O72*).

Maternal background variables:

Age, country of birth, Body Mass Index (BMI), Assisted Reproductive Technology (IVF), smoking, diabetes, hypertensive disorder, previous uterine surgery via laparoscopy or laparotomy.

Pregnancy variables:

Pregnancy induced hypertension, preeclampsia, gestational diabetes, stillbirth, fetal growth restriction, multiple births.

Delivery variables

Gestational age, onset of labour (spontaneous, induction, no labour), oxytocin use, labor dystocia, type of delivery (spontaneous, VE/forceps, caesarean section), fetal gender, fetal

weight, small for gestational age birth (SGA), large for gestational age birth (LGA) Apgar score.

Statistics:

Risk associations will be calculated in a stratified logistic regression model and an unconditional multivariate logistic regression model and presented as odds ratios (OR) with 95% confidence intervals (CI).

Research Team and competence

These two studies are part of a larger planned PhD project investigating clinical pathways to improve outcomes for women with AIP including improving prenatal targeted screening and intrapartum management.

Margit Endler, M.D has a PhD on the epidemiology and pathophysiology of retained placenta, a leading cause of postpartum hemorrhage and a strong competence in register-based research.

Associate professor Pelle Lindqvist is a senior consultant at Södersjukhuset and is part of the collaborative Nordic Obstetric Surveillance Study Group (NOSS) on placenta accreta spectrum disorders, which recently published results on placenta accreta among over 600 000 births in the period 2009-2012.

Gita Strindfors, M.D, is a senior consultant in obstetrics and part of the International Society of Abnormally Invasive Placenta and will perform these studies as part of her PhD program.

Study I will be a collaboration between the research group at Södersjukhuset and The Department of Women´s and Children´s Health (KBH) at Karolinska Institutet.

Timeline

Study I

Apr-May 2019	Application for access to registry data
Oct-Dec 2019	Data extraction, linking, assessment, finalization of study variables and statistical methodology
Jan-May 2020	Data analysis / interpretation
Sep 2020	Results in article form

Significance

AIP is a disorder that put the mother at high risk of severe bleeding, hysterectomy and even death. Its incidence is increasing and finding ways to increase prenatal detection and improve intrapartum management is crucial to reduce morbidity and mortality.

The study aims to improve the prenatal detection of AIP by investigating a new potential risk factor for this disorder. AIP is uncommon which makes large-data research difficult. The Swedish National Quality Register of Gynecological Surgery now contains 20-year detailed data on hysteroscopic surgery which, together with the pregnancy and delivery data on all births in Sweden in the Birth Registry, provides a unique possibility to study this association with statistical reliability.

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2. Khong TY. The pathology of placenta accreta, a worldwide epidemic. *Journal of clinical pathology*. 2008 Dec;61(12):1243-6. PubMed PMID: 18641410. Epub 2008/07/22. eng.
3. Thurn L, Lindqvist PG, Jakobsson M, Colmorn LB, Klungsoyr K, Bjarnadottir RI, et al. Abnormally invasive placenta-prevalence, risk factors and antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries. *BJOG : an international journal of obstetrics and gynaecology*. 2016 Jul;123(8):1348-55. PubMed PMID: 26227006. Epub 2015/08/01. eng.
4. Melcer Y, Jauniaux E, Maymon S, Tsviban A, Pekar-Zlotin M, Betser M, et al. Impact of targeted scanning protocols on perinatal outcomes in pregnancies at risk of placenta accreta spectrum or vasa previa. *American journal of obstetrics and gynecology*. 2018 Apr;218(4):443 e1- e8. PubMed PMID: 29353034. Epub 2018/01/22. eng.
5. Baldwin HJ, Patterson JA, Nippita TA, Torvaldsen S, Ibiebele I, Simpson JM, et al. Antecedents of Abnormally Invasive Placenta in Primiparous Women: Risk Associated With Gynecologic Procedures. *Obstetrics and gynecology*. 2018 Feb;131(2):227-33. PubMed PMID: 29324602. Epub 2018/01/13. eng.