Endometriosis, especially mild disease: a risk factor for miscarriages

Alexandra Sabrina Kohl Schwartz, M.D.,[a,b] Monika Martina Wölfler, M.D.,[c,d] Vera Mitter, M.Sc.,[b] Martina Rauchfuss, M.D.,[e] Felix Haeberlin, M.D.,[f] Markus Eberhard, M.D.,[g] Stephanie von Orelli, M.D.,[h] Bruno Imthurn, M.D.,[a] Patrick Imesch, M.D.,[i] Daniel Fink, M.D.,[i] and Brigitte Leeners, M.D.[a]

[a] Department of Reproductive Endocrinology, University Hospital Zurich, Zurich, Switzerland; [b] Division of Gynecological Endocrinology and Reproductive Medicine, Bern University Hospital, University of Bern, Bern, Switzerland; [c] Division of Gynecological Endocrinology and Reproductive Medicine, Medical University of Graz, Graz, Austria; [d] Department of Obstetrics and Gynecology, RWTH Aachen University Hospital, Aachen, Germany; [e] Department of Psychosomatics, Charité University Hospital Berlin, Berlin, Germany; [f] Women's Hospital, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [g] Women's Hospital, Cantonal Hospital Schaffhausen, Schaffhausen, Switzerland; [h] Maternité, Stadtspital Triemli, Zurich, Switzerland; and [i] Department of Gynecology, University Hospital Zurich, Zurich, Switzerland

Objective: To investigate the prevalence of miscarriage in women with endometriosis (WwE) compared with disease-free control women (CW).
Design: Cross-sectional analysis nested in a retrospective observational study (n = 940).
Setting: Hospitals and associated private practices.
Patient(s): Previously pregnant women (n = 268) within reproductive age in matched pairs.
Intervention(s): Retrospective analysis of surgical reports and self-administered questionnaires.
Main Outcome Measure(s): Rate of miscarriage, subanalysis for fertility status (≤12 vs. >12 months' time to conception), endometriosis stages (revised American Society of Reproductive Medicine classification [rASRM] I/II vs. III/IV) and phenotypic localizations (superficial peritoneal, ovarian, and deep infiltrating endometriosis).
Result(s): The miscarriage rate was higher in WwE (35.8% [95% confidence interval 29.6%–42.0%]) compared with CW (22.0% [16.7%–27.0%]); adjusted incidence risk ratio of 1.97 (95% CI 1.41–2.75). This remained significant in subfertile WwE (50.0% [40.7%–59.4%]) vs. CW (25.8% [8.5%–41.2%]) but not in fertile WwE (24.5% [16.3%–31.6%]) vs. CW (21.5% [15.9%–26.8%]). The miscarriage rate was higher in women with milder forms (rASRM I/II 42.1% [32.6%–51.4%] vs. rASRM III/IV 30.8% [22.6%–38.7%], compared with 22.0% [16.7%–27.0%] in CW), and in women with superficial peritoneal endometriosis (42.0% [32.0%–53.9%]) compared with ovarian endometriosis (28.6% [17.7%–38.7%]) and deep infiltrating endometriosis (33.9% [21.2%–46.0%]) compared with CW (22.0% [16.7%–27.0%]).
Conclusion(s): Mild endometriosis, as in superficial lesions, is related to a great extent of inflammatory disorder, possibly leading to defective folliculogenesis, fertilization, and/or implantation, presenting as increased risk of miscarriage.
Clinical Trial Registration Number: NCT02511626. (Fertil Steril® 2017;108:806–14. ©2017 by American Society for Reproductive Medicine.)
Key Words: Endometriosis, infertility, miscarriage, pregnancy outcome, superficial peritoneal endometriosis

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/19403-24600

Endometriosis is a chronic and often progressive disease, which is defined by endometriotic tissue outside the uterine cavity that is sensitive to cyclic steroid hormone regulation (1–3). With a prevalence of 6%–10% of the female population, it is one of the most important benign gynecologic diseases in women of reproductive age (4). Endometriosis is associated with dysmenorrhea, dyspareunia, or chronic pelvic pain. Endometriosis is known to reduce female fertility (4–6) and has an impact on the obstetric outcome of affected women (7–10).

In women with endometriosis (WwE) multifactorial reasons result in a reduction in fertility: reduced tubal motility and passage (11, 12), inhibiting inflammatory factors

Received June 29, 2017; revised August 7, 2017; accepted August 14, 2017.
S.v.O. reports personal fees from Pfizer. A.S.K.S. has nothing to disclose. M.M.W. has nothing to disclose. V.M. has nothing to disclose. M.R. has nothing to disclose. F.H. has nothing to disclose. M.E. has nothing to disclose. B.I. has nothing to disclose. P.I. has nothing to disclose. D.F. has nothing to disclose. B.L. has nothing to disclose.
Reprint requests: Alexandra Sabrina Kohl Schwartz, M.D., University Hospital Zurich, Department of Reproductive Endocrinology, 8091 Zurich, Switzerland (E-mail: alexandra.kohlschwartz@usz.ch).

Fertility and Sterility® Vol. 108, No. 5, November 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.08.025

deriving from the peritoneal fluid (13), and a diminished quality of the oocytes affect the chances of a successful implantation after natural conception as well as after assisted reproductive technology (ART) (14–17). However, not all the underlying mechanisms are yet fully understood. Over the last few years improvements in pharmacologic, surgical, and ART treatment have led to an increasing number of pregnancies in WwE (18). The success of pregnancy depends on the placentation and the endometrial function later in pregnancy (19, 20). Abnormal local estrogen production and an altered endometrial response to P (P resistance) result in a changed microenvironment. This coats the embryo in early pregnancy (21, 22) possibly affecting the "quality of implantation." Miscarriage is the most common complication during the first trimester, with an incidence rate of 30%–50% in the general population, depending primarily on the age of the women (23, 24). There is no conclusive answer to the question of whether miscarriage rates are increased in WwE: earlier clinical studies investigated primarily the effect of surgical treatment (ablation of endometriotic lesions) on the prevalence of pregnancy complications; these studies were not adjusted for age (25–27). Some newer studies considering age as a risk factor showed an association of endometriosis with previous pregnancy losses (8, 9, 28, 29), but others did not (7, 30–32). A large Canadian cohort study over 12 years with registry data from 784 WwE and 30,284 control women (CW) reported a significantly higher rate of miscarriages in WwE (odds ratio 1.89, 95% confidence interval [CI] 1.23–2.93); however, the diagnostic quality of endometriosis was limited (8). The most recent study on previously pregnant women with and without endometriosis was conducted at a specialized referral center. It found a higher miscarriage rate in endometriosis-affected women, 29.1% (95% CI 23.9%–34.3%), compared with CW 19.4% (95% CI 16.1%–22.7%) ($P=.001$) (7). Because of the high number of women with progressive disease (several surgeries before inclusion in the study) and severe endometriosis lesions, women with mild or asymptomatic disease were rather underrepresented in this collective.

The primary aim of this study was to evaluate and compare miscarriage rates in a population of women with surgically confirmed endometriosis and a broad variety of clinical manifestations, to reflect the average female population affected by endometriosis. To improve our understanding of the association between endometriosis and miscarriage, we included in the analysis the phenotypical disease localization and the fertility status.

MATERIALS AND METHODS

This was a cross-sectional analysis about the prevalence of miscarriages nested in a retrospective observational study (n = 940) on the quality of life in WwE.

Questionnaire

We designed a questionnaire focusing on the women's health and obstetric history. We collected sociodemographic data and asked the women whether they had difficulties conceiving and for how long they tried to become pregnant.

Recruitment

Women from the ages of 18 to 45 years were recruited from women treated between December 2010 and December 2015 at participating hospitals or associated private practices: university hospitals in Switzerland, Germany, and Austria (University Hospital Zurich, Charité–Medical University Berlin, University Hospital of Graz, and RWTH Aachen University), cantonal hospitals in Switzerland (Schaffhausen, Winterthur, St. Gallen, Solothurn), the Stadtspital Triemli Zurich, and in several associated private medical practices. Indication for surgery was made by the treating physician on the basis of pelvic pain symptoms (dysmenorrhea and/or dyspareunia and/or chronic pelvic pain for at least 6 months) and/or endometriosis-suspicious lesions detected by rectovaginal palpation and/or ultrasound examination. Inclusion criteria were defined as not being pregnant and being able to complete the questionnaire (without linguistic, mental, or psychological impairment). Patients having undergone surgery for the diagnosis of endometriosis and fulfilling inclusion criteria were invited to participate and were asked for informed consent. Control women without clinical suspicion of endometriosis (no severe dysmenorrhea, no heavy cyclic abdominopelvic pain) fulfilling the inclusion criteria were recruited during annual check-ups. In total 647 women affected by endometriosis and 666 CW were invited to participate. Of those invited, written consent was received from 505 WwE (78.0%) and 435 CW (65.3%).

Surgical Reports

Surgical reports for each surgical intervention were obtained from the patients' clinics.

From 468 of 505 WwE (92.7%), we obtained surgical reports with sufficient details to do a correct staging and grading of the lesions. In 438 of 468 WwE (93.6%) the diagnosis was confirmed histologically after surgical resection; 30 of 468 WwE (6.4%) were diagnosed surgically, primarily after laser evaporation of light lesions. To avoid bias, all surgical and histologic records were reviewed by two blinded investigators.

The documents reviewed contained the total number of endometriosis-associated surgeries, the histologic confirmation of endometriosis, a description of the localization and size of endometriosis lesions, and the dimensions of adhesions. The revised classification of the American Society for Reproductive Medicine (rASRM) (33) was used to categorize the endometriosis into the four stages. This staging was applied as it was initially developed to define chances for pregnancy (34). Additionally, the lesions were classified into three phenotypes: superficial peritoneal endometriosis (SUP), ovarian endometriosis (OMA), and deep infiltrating endometriosis (DIE), as previously described by other investigators (35, 36). Deep infiltrating endometriosis lesions were classified as