

Impact of Endometriosis on Pregnancy and Delivery – a Retrospective Cohort Study

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Research Article

Keywords: Pregnancy and Delivery, Endometriosis, Cohort Study, disease

Posted Date: March 16th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-297650/v1>

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Abstract

Purpose:

The aim of the study was to assess the impact of endometriosis on subsequent pregnancy and delivery.

Methods:

retrospective analysis by questionnaire / interview of cases (endometriosis laparoscopically removed / child wish) vs. controls (endometriosis laparoscopically excluded / child wish) from the University Hospital Muenster, Germany, treated between 2009 and 2016; analysis of pregnancy rate, mode of delivery and complications using Clavien-Dindo-classification, role of deep infiltrating endometriosis using ENZIAN classification; data analysis using t-test with $p < 0.050\%$ being considered significant.

Results:

Identification of 973 consecutive cases vs 789 consecutive controls; inclusion of 501 cases: (pregnancy rate 57.5%) and 219 controls (pregnancy rate 60.7%). Primary cesarean section: trend to more in controls ($p=0.202$). Secondary cesarean section: trend to more in cases ($p=0.111$). Miscarriage: more in controls ($p=0.038$). DIE with risks equal to other types of endometriosis. Adenomyosis and bladder endometriosis: increased risk of secondary cesarean section. Pregnancy: more bleeding ($p=0.005$), early uterine contractions ($p=0.012$), cervical insufficiency ($p=0.042$), slightly more pre-eclampsia ($p=0.080$), amniorrhaxis ($p=0.220$). Delivery: more bleeding ($p=0.007$), vaginal tear ($p=0.009$), symphysis diastasis ($p=0.022$), less episiotomy ($p=0.002$), prolonged labour ($p=0.011$). Puerperium: more bleeding ($p=0.022$), infectious complications $p=0.007$). Complications more in cases (Clavien Dindo I ($p=0.005$) or II ($p=0.010$); controls slightly more III ($p=0.055$)). Cases vs published control groups from general population: more placenta praevia ($p=0.042$), placental abruption, miscarriage ($p<0.001$; relative risk 2.23 (1.84-2.70)), delivery by cesarean section ($p<0.001$).

Conclusion:

Complications during pregnancy, delivery and puerperium occur more frequently in cases. The risk of miscarriage and delivery by cesarean section is increased. Endometriosis patients should receive counselling with regard to pregnancy and delivery. They should have access to specialized centers of care. Recommendations regarding mode of delivery should not exclude vaginal delivery also in cases of deep infiltrating endometriosis

Introduction

Endometriosis is defined as a disease in which endometrium-like tissue consisting of glands and stroma is present outside of the uterine cavity. Approximately 10 % of women of reproductive age are affected by this disease [1]. Prevalence is estimated to be at 0.8 to 2 % [2]. Typical symptoms include different types

of pain symptoms and infertility. 30 to 50 % of patients presenting with infertility are estimated to be affected by endometriosis [3–5].

Endometriosis is an estrogen dependent condition, which mainly is treated by surgery or medical therapy consisting mainly of hormonal treatment by progestogens. This might explain why symptoms often improve during pregnancy due to a changing hormonal environment with increasing influence of human chorionic gonadotrophin, a placental progestogen. On the other hand, there is also a detrimental effect of endometriosis on pregnancy and delivery, as the risk of adverse pregnancy outcome has recently been reported to be higher for women with endometriosis [6–9]. Many patients with endometriosis suffer from subfertility and therefore undergo infertility treatment, including assisted reproductive techniques such as in vitro fertilization and intracytoplasmic sperm injection, which may by itself constitute a risk factor for complications during pregnancy [10]. The aim of this study was to analyse reproductive outcome of women with endometriosis. In a second step, data from endometriosis patients was compared to reproductive outcome of women with subfertility for other reasons than endometriosis. Within both groups some women underwent infertility treatment while others conceived naturally. Therefore, this study compared the reproductive outcome of women with endometriosis to that of women without endometriosis, depending on whether they underwent infertility treatment or not. Also, outcome data was analysed using the Clavien-Dindo classification concerning complications [11–13] and the ENZIAN classification concerning the role of deep infiltrating endometriosis [14–16].

Material And Methods

All endometriosis cases undergoing surgery because of the disease in the Department of Gynecology and Obstetrics at the University Hospital of Muenster, Germany, since it had become a certified tertiary endometriosis referral centre according to Endometriosis Research Foundation (Stiftung Endometrioseforschung)-criteria between 2009 and 2016 were identified from patient records. As a control group patients from the same period undergoing laparoscopy because of infertility during which endometriosis was excluded were equally identified from patient records. Both groups received similar questionnaires by mail.

In these questionnaires patients were asked to report any treatment regarding endometriosis as well as any kind of infertility treatment received after treatment for endometriosis in the Department of Gynecology and Obstetrics at the University Hospital Muenster, Germany. Furthermore, patients were asked to report on occurring pregnancies, their course and outcome, including possible complications as well as on mode of delivery and possible complications in their course, as well as during puerperium.

Miscarriage was defined as the spontaneous termination of a pregnancy. Any intervention or medication to end a pregnancy in contrast was considered to be an abortion.

Those patients not responding to the questionnaires received an additional phone call and were asked to participate in the study and were interviewed directly.

To evaluate the possible influence of specific endometriosis locations on pregnancy and its outcome, data was analysed using the ENZIAN classification of deep infiltrating endometriosis. The ENZIAN classification was introduced in order to be able to describe the exact extent of deep infiltrating endometriosis as this is not the case in the older revised American Society of Reproductive Medicine classification of endometriosis [14]. In the ENZIAN classification localisation of endometriotic lesions is described with regard to three defined compartments, as well as to their size. If there was more than one lesion in a compartment, the largest one was used for classification. Furthermore, lesions outside of the three compartments were classified using the letter “F” plus the structure involved [16]. As concluded by Haas et. al. the morphological precision with which lesions can be described, is the main advantage of this classification [15, 16].

The Clavien-Dindo-Classification was used to assess the complications occurring during pregnancy, delivery and puerperium according to their severity from grade 1 to 5 [11–13]. C-sections were not considered a complication or surgical intervention in the sense of the classification, but as a mode of delivery. There was no analysis of fetal or neonatal outcome performed in the study.

Statistical analysis

IBM SPSS Statistics version 25 (IBM Corporation, New York, NY, USA) was used and differences were calculated using the t-test. The reproductive outcome was calculated as relative risk for women with and without endometriosis. For the relative risk 95% confidence interval (CI) was calculated. A value of $p < 0.050$ % was considered significant for every statistical analysis.

Ethical approval

The study was approved by the local ethics committee “Ethikkommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität” (Ethical approval number 2016-076-f-S, dated 13 September 2016). Informed consent was obtained from all participants and / or their legal guardians. The study was performed in accordance with the Declaration of Helsinki.

Results

Between 2009 and 2016, 2764 patients were operated because of endometriosis. 973 out of those 2764 patients stated the desire to become pregnant in the future or already having given birth since the start of the surveyed period in 2009 and after having been diagnosed with and operated for endometriosis.

323 out of these 973 women (33.2%) replied to the survey directly. Another 178 patients out of the missing 646 who had not replied to the survey initially were additionally contacted by telephone, resulting in an overall return rate of 501 out of 973 patients or 51.5%. 51 women refused participation in this study (5.2%). Another 36 women did not desire to become pregnant. These 87 patients were excluded from further analysis. 472 patients ultimately were lost to follow-up (48.5%) [figure 1]. Of the 414 women that returned the questionnaire, 238 experienced 374 pregnancies.

789 women who had endometriosis excluded by laparoscopy but had undergone infertility treatment at the University Hospital of Muenster for other reasons were also addressed by the survey. 198 women replied to the survey (25%). Another 54 could be reached by phone in the following weeks (6.8%). Out of those 33 women declined to participate. 547 patients were lost to follow up. The overall return rate for the survey was 31.9% [figure 2]. There were 200 reported pregnancies in 131 women.

Patient characteristics, pregnancy rate and pregnancy outcome are reported in table 1. Patients treated for endometriosis were not significantly younger than controls (34.4 vs. 34.8 years; $p=0.562$). There was no significant difference in total pregnancies between the two groups with 1.57 pregnancies per patient in the endometriosis group and 1.50 pregnancies per patient in the control group ($p=0.34$). Birth by secondary cesarean section seemed to be more frequent in the endometriosis group whereas birth by primary cesarean section seemed to be more frequent in patients from the control group but these differences were not statistically noticeable ($p=0.111$ / $p=0.202$). Natural birth was equally frequent in about half of patients of each group ($p=0.34$). Miscarriage rate was higher in patients from the control group ($p=0.038$).

Pregnancy outcome dependend on mode of conception and presence of endometriosis is reported in table 2. Miscarriage rate was highest in patients without endometriosis and natural conception ($p=0.011$). Primary cesarean sections seemed to be more frequent in patients with conception by assisted reproduction techniques (ART) but this difference was not statistically noticeable ($p=0.092$). Secondary cesarean sections were least frequent in patients from the control group achieving pregnancy by ART ($p=0.04$).

Complications according to Clavien-Dindo classification are reported in tables 3 and 4.

Influence of different types of endometriosis

First the outcome for women with ENZIAN A, B and C endometriosis were compared to all other groups in the ENZIAN classification. 335 pregnancies were included. In 213 of these cases, the women suffered from A, B or C endometriosis. While miscarriage was not significantly higher for patients with A, B or C endometriosis (29.1 % vs. 24.4%, $p = 0.173$), obstetric complications were much higher in the group of women not suffering from A, B or C endometriosis. Pregnancy duration was very similar in both groups (38.8 weeks vs. 38.7 weeks; $p=0.84$), however women without A, B or C endometriosis were noticeably more likely to need a secondary cesarean section (36.9% vs. 23.7%, $p = 0.020$).

Comparing patients with ENZIAN-B, but without ENZIAN A/C to patients with ENZIAN A/C but without ENZIAN B a secondary cesarean section was needed in 20.6% of the cases vs. 23.7% ($p = 0.357$).

The pregnancy outcomes of women with FA endometriosis (adenomyosis) were compared to women with endometriosis at any other location. It was shown that, while the age of women at birth (34.2 vs 34.4 years; $p=0.54$) and percentage of miscarriage (28.8% vs. 27.2%, $p = 0.398$) did not differ in both groups, there were differences concerning complications during pregnancy and labour. 37.8% of women with FA

endometriosis were in need of a secondary cesarean section. Women with deep infiltrating endometriosis in other locations had a secondary C-section in only 25.4% of cases, so that the relative risk is at 1.43 (0.91-2.23, 95% CI). Women with FA endometriosis were able to give vaginal spontaneous birth in only 35.2% of cases, which is significantly lower than in the average German population (35.2% vs 62.2%, $p < 0.001$). Pregnancy duration with FA endometriosis was on average more than half a week shorter but that difference was not statistically significant (38.4 vs. 39.0 weeks, $p=0.212$).

Women with endometriosis in the rectovaginal septum and the vagina ($n=71$) were not reported to suffer from lacerations under delivery more often than other women with endometriosis ($n=156$). Nor were they more likely to suffer from perineal laceration (12.7% vs 12.8%; $p = 0.488$) nor labial tear (9.9% vs 10.3; $p =0.463$). One woman with C1 endometriosis of the rectum reported that she suffered an inflammation of the colon.

15 women who answered the survey suffered from ENZIAN FI endometriosis. While the average pregnancy duration was 37.3 weeks and therefore shorter than for all other groups, with only seven pregnancies in this group no definitive conclusions can be drawn concerning the impact of FI endometriosis on pregnancy risks.

58 women covered by this survey were diagnosed with endometriosis of the bladder. Only 33.3% of all children were born naturally. This is the lowest number for any group analysed. While the average pregnancy duration is 38.8 weeks, 38.9% of the children were born by secondary cesarean section. Reported reasons were mainly cardiotocography abnormalities and obstructed labour. Numbers for miscarriage were similar to the average woman with endometriosis (27.6% vs 28.0%; $p=0.468$).

Complications

While for some complications during and after pregnancy the number of women affected is too small to draw conclusions, trends in the numbers are still noticeable. During pregnancy women with endometriosis suffered from bleeding significantly more often (15.2% vs 7.0%, $p = 0.005$). Early uterine contractions (9.5% vs 3.9%, $p = 0.012$) and cervical insufficiency (5.7% vs 2.3%, $p = 0,042$) were significantly more likely in the endometriosis-group. Also, there was a trend towards more pre-eclampsia (3.8% vs 1.6%; $p=0.08$), and less amniorrhaxis (3% vs 4.7%; $p=0.22$), while the prevalence of unspecific symptoms like high blood pressure, diabetes or nausea did not differ significantly in the two groups compared. The disease seems to have an impact mainly on the function of the uterus itself and not the whole body.

During labour the risk of vaginal tear (7.2% vs 2.3%, $p = 0.009$) was significantly higher for women with endometriosis, while there was no significant difference concerning the risk of perineal rupture (10.2% vs 10.5%, $p = 0.055$). Similar to complications during pregnancy, the risk of bleeding during labour was much lower in the control group (2.3% vs 0%, $p = 0.007$). The risk of a pathological cardiotocography was not significantly higher in one of the two groups (9.5% vs. 7.0%, $p = 0.190$). Even though women with

endometriosis suffered less often from prolonged labour (1.9% vs. 7.0%, $p = 0.011$), the risk of symphysis pubis diastasis (1.5% vs 0%, $p = 0.022$) was higher for this group of patients.

Bleeding was also an issue during puerperium (1.5% vs 0%; $p=0.022$). However more surprisingly the risk of infection seemed to be higher for women with endometriosis. Scar infections (2.3% vs 0%; $p =0.007$), as well as fever (0.8% vs 0%; $p=0.078$) was not present in the control group, but in some of the endometriosis-patients. In general, patients with endometriosis seem to suffer from complications during puerperium more often.

Discussion

The present study demonstrates that delivery by primary cesarean section showed a trend towards being more frequent in controls and being associated with conception by ART, while delivery by secondary cesarean section showed a trend towards being more frequent in endometriosis patients. Miscarriages occurred more frequently in controls. Deep infiltrating endometriosis was not associated with an increased risk of miscarriage, delivery by secondary cesarean section or obstetric complications when compared to other types of endometriosis. Adenomyosis and bladder endometriosis was associated with an increased risk of secondary cesarean section compared to other types of endometriosis. During pregnancy endometriosis was associated with increased risk of bleeding, early uterine contractions and cervical insufficiency and there was a trend towards more pre-eclampsia and amniorrhesis. During delivery endometriosis was associated with increased risk of bleeding, vaginal tear and symphysis pubis diastasis. During puerperium endometriosis was associated with increased risk of bleeding, infectious complications and complications in general. Complications were mainly Clavien Dindo I or II categories in case of endometriosis, while controls showed a trend towards higher risk of Clavien Dindo III complications. Clavien Dindo IV and V complications did not occur. When compared to control groups from the literature, which other than in this study's controls represent the general population, patients from the study's endometriosis group showed an increased risk of placenta praevia and placental abruption, as well as miscarriage and delivery by cesarean section.

Return rate for the questionnaire was good in the endometriosis group (51.5 %) and acceptable in the control group (31.9 %). Due to the chronicity of endometriosis many of the patients affected were treated at the University Hospital of Muenster for a long time, which may explain the higher return rate for women with endometriosis when compared to the control group as a result of higher compliance. Only cases of women with endometriosis diagnosed and classified by a specialist were included in the survey, which may be a strong point of this study. The answers given by the patients however could not always be verified by analysing original medical documents. Especially symptoms like pain, nausea and even light bleeding might be underreported as these were considered to be common symptoms in pregnancies and therefore not noteworthy.

As in Sharma et al [17] pregnancy rate was similar in patients with endometriosis and controls. While Sharma et al found this similarity only in younger patients with endometriosis under 35 years, in the

present study pregnancy rate in older endometriosis patients also was comparable to in vitro fertilization controls [17].

Similar to Lin et al [18], whose study showed an increased risk of placenta praevia in pregnant women with endometriosis, the group of women with endometriosis in this study suffered from placenta praevia noticeably more often than in the control group (0.8% vs 3%, $p = 0.042$). While placental abruption was not proven to be associated with endometriosis in the Chinese study, in this survey 2 women with endometriosis stated to have suffered from this condition, while none of the control group did. However, the numbers are too small for statistical analysis.

While, statistically, women with endometriosis were more likely to suffer from minor complications like Clavien-Dindo I (43.3% vs 32.5%, $p = 0.005$) and Clavien-Dindo II (29.7% vs 21%, $p = 0.01$), more severe complications which needed surgical, endoscopic or radiological intervention (Clavien-Dindo III) tended to be more likely to occur in the control group (14.2% vs 19.5%, $p = 0.055$). This may be because complications like early uterine contractions or cervical insufficiency, which proved to be more frequent in women with endometriosis, are treated conservatively. However, an episiotomy, which was needed more often in the control group (0.4% vs 7%, $p = 0.002$), counts as a surgical intervention and may therefore distort the picture.

Miscarriage rate is noticeably lower for women with endometriosis compared to the reference group (27.6% vs 34.9%, $p = 0.038$) [table 2]. However, comparing these results to the equivalent age group of pregnant women in Denmark between 1978-1992 (30-35 years vs. 34.4 years) the risk of miscarriage is noticeably higher for women suffering from endometriosis (12.4% vs 27.6%, $p < 0.001$) [19]. Relative risk for miscarriage in women with endometriosis compared to the average population is 2.23 (1.84-2.70). A Japanese cohort study suggests a much lower relative risk of 1.24 (1.20-1.29, 95% CI) [16]. However usually only women with severe cases of endometriosis and known history of pregnancy complications are referred to a specialized endometriosis centre like the University of Muenster, which may explain higher numbers in miscarriage for the control group.

Surprisingly, miscarriage rate was highest in the group of women without endometriosis who did not undergo infertility treatment but were only seeking consultation at the Center of Reproductive Medicine because of infertility (42.7%). The rate is noticeably higher than in the group of women with endometriosis who did not undergo infertility treatment (42.7% vs. 28.8%, $p = 0.011$). This may be because some of these women did not have problems to conceive but actually suffered from habitual abortion, having undergone miscarriage 5 to 6 times and thus increasing the overall miscarriage rate.

The rate of secondary cesarean sections in the group of women without endometriosis who had undergone infertility treatment showed a trend towards being lower than in the endometriosis group overall (20.8% vs 29.7%, $p = 0.057$). This is probably not due to fewer complications, but rather the consequence of the trend towards a higher rate of primary cesarean sections (23.6% vs 16.8%, $p = 0.11$) due to increased expectancy of complications, as meta analyses show an increased risk for obstetric and perinatal complications in this group [20]. Generally speaking, the risk for a secondary cesarean section

seems to be noticeably higher in patients with endometriosis than in the average population in Germany (29.7% vs 15.9% $p < 0,001$) [21], while there is no significant difference in the number of planned cesarean sections (16.8% vs 15.4%, $p = 0.283$). This contradicts a Swedish survey stating that the adjusted odds ratio (OR) of pre-labour cesarean sections is 1.64 (1.54-1.75, 95% CI), whereas the OR for emergency cesarean sections was only 1.18 (1.10-1.27, CI 95%) [22]. However, the rate of emergency cesarean sections in Sweden is only 8.6 % and therefore the lowest out of the 31 European countries analysed in the study by Macfarlane et al, while the rate is at 15.9% in Germany [21]. This suggests that a cesarean section is indicated much faster in Germany than in Sweden, the patient characteristics differ between the countries or guidelines lead to a different kind of management. The higher rate of emergency cesarean sections may indicate that there were more unforeseen complications in this group. This may support recent data according to which adverse pregnancy outcomes and obstetrical complications are more common in women suffering from endometriosis [23, 24]. However, one must take into account that endometriosis can occur in various locations and with different severity and may therefore have very different effects on pregnancy. Therefore, ENZIAN score was used to further break down the results.

First, the outcome for women with ENZIAN A, B and C endometriosis were compared to all other ENZIAN categories. Miscarriage rate was similar between the groups. Obstetrical complications occurred noticeably more often in patients without ENZIAN A, B and C. Also, there were noticeably more secondary cesarean sections in this group. This finding is inconsistent with the results of a study conducted by Allerstorfer et al., which shows a higher rate of cesarean sections for women with A or C endometriosis [25]. However, Allerstorfer et al. compared these two groups mainly to patients with ENZIAN B endometriosis, which in contrast are included in our study group. To be able to compare the findings, the patients with ENZIAN-B, but without ENZIAN A/C were selected. In this group a secondary cesarean section was needed in 20.6% of the cases. There is no noticeable difference to patients with ENZIAN A/C, but without ENZIAN B, which were only slightly more likely to need a secondary cesarean section (23.7%, $p = 0.357$). The lower rate of cesarean sections for patients with ENZIAN A, B or C may have many reasons. One of them might be that in 3.6 % of the pregnancies in women without A, B or C endometriosis breech presentation occurred, while this was not reported to be the case in the 213 pregnancies with endometriosis in ENZIAN A, B and C locations. For women without breech position the risk of needing a secondary cesarean section decreased from 36.9% to 35.4%. Also, obstructed labour made an unplanned cesarean section necessary in 4.7% of cases in this group, while again this was not reported for women with A, B or C endometriosis. Even though numbers for pregnancy duration and type of delivery may be accurate, information given by patients about complications are expected to be lower than in reality, as some participants answered the survey in much less detail than others, often stating that they were in need of a secondary cesarean section, however leaving out the reason why this was necessary. For example other studies suggest that the incidence of obstructed labour in the general population is even higher than stated by the women without ENZIAN A, B or C (8.9% vs 4.7%) [26]. However, this might mostly be due to the design of the study, being dependent on information given by the patients themselves.

Miscarriage rate for patients with adenomyosis was similar to that of patients with deep infiltrating endometriosis. Secondary cesarean section was necessary more frequently in patients with adenomyosis. Women with adenomyosis had a significantly decreased probability of vaginal spontaneous delivery as opposed to the average German population (35.2% vs 62.2%, p-value < 0.001). As Leyendecker et al [27] suggest that adenomyosis presents itself with a dysfunction of the endometrial-subendometrial unit. As this disease can affect all myometrial uterine muscle layers this may increase the risk for obstructed labour. While prolonged labour occurs in 4.4% (n=2) of the cases of adenomyosis and only 1.5% (n=3) of the cases with endometriosis in other locations the numbers are too small to draw definitive conclusions.

As endometriosis of the uterus seems to increase the risk of complications during labour it may seem obvious that endometriosis of the rectovaginal space / vagina and the rectum may increase the risk of perineal laceration and bowel complications. However, women with endometriosis in these locations were not reported to suffer from lacerations more often than other women with endometriosis, suggesting that endometriosis does not generally weaken the tissue in this cohort. One woman with C1 endometriosis of the rectum reported that she suffered an inflammation of the colon.

Patients with bladder involvement had the lowest rate of spontaneous delivery compared to other groups with deep infiltrating endometriosis. Reported reasons were mainly cardiotocography abnormalities and obstructed labour. Numbers for miscarriage were similar to the average woman with endometriosis. While bladder endometriosis did not seem to have a negative impact on early pregnancies, this changed as the uterus grew and came closer to the bladder – and therefore to the location of endometrial lesions - during the pregnancy. Other studies show that pregnancy outcome is favourable after removal of bladder-endometriosis [28].

Limitations of this study mainly are due to limited sample size, retrospective design of the study, response rate, the control group suffering from infertility and possibly differing surgical techniques between the surgeons involved.

Conclusions

This study shows that women with endometriosis have a higher risk of miscarriage. Moreover, the risk for cesarean sections is increased. This however varies depending on the location of endometriotic lesions. Especially women with adenomyosis, who also suffer from prolonged labour, are often in need of a cesarean section. While the risk for placenta praevia and abruption of the placenta are higher than in the average population with too small of a sample size no clear recommendation can be made. The data suggests that the risk for bleeding during pregnancy, but also during and after labour is much higher for women suffering from endometriosis. Also early uterine contractions and cervical insufficiency occurred noticeably more often. According to the Clavien-Dindo classification severe complications (III) did not occur more often during the pregnancy of women with endometriosis, however complications that normally do not need any treatment, or only a pharmacological treatment, are more likely to happen.

Endometriosis of the rectovaginal space, the vagina and the rectum does not seem to increase the risk of severe lacerations during vaginal delivery. Counselling of endometriosis patients with regard to pregnancy and delivery is recommended. Patients should have access to specialized centers of care also with regard to pregnancy and delivery as increased risks are reported. Recommendations regarding mode of delivery should not exclude vaginal delivery in cases of deep infiltrating endometriosis.

Declarations

Authors' contributions

SDS: Protocol/project development, Data collection and management, Data analysis, Manuscript writing/editing

MB: Data collection, Data analysis, Manuscript writing/editing

MG: Data analysis, Manuscript writing/editing

RS: Data analysis, Manuscript writing/editing

LK: Data analysis, Manuscript writing/editing

Competing interest statement

SDS, MB, MG and RS declar no competing interest.

LK reports personal fees from Ferring Pharmaceuticals A/S, personal fees from MITHRA Pharmaceuticals SA, personal fees from Novartis Pharma GmbH, personal fees from palleos healthcare, personal fees from abbvie, personal fees from Actavis Group, personal fees from AstraZeneca, personal fees from Gedeon Richter, personal fees from Dr. Kade/Besins, personal fees from Pantarhei, personal fees from Roche Pharma AG, personal fees from Shionogi, personal fees from Exeltis, outside the submitted work.

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Tables

Table 1
Patient characteristics, pregnancy rate and pregnancy outcome.

Parameter	with endometriosis (n = 414)	without endometriosis (n = 219)	P-value
patients with pregnancy, n	238 (57,5%)	133 (60,7%)	0.214
total pregnancies, n	374	200	0.34
median age when giving birth (years)	34,4	34.8	0.562
primary cesarean section (n)	39 (16.8%)	25 (20.5%)	0.202
secondary cesarean section (n)	69 (29.7%)	29 (23.8%)	0.111
natural birth (n)	124 (53.5%)	68 (55.7%)	0.34
abortion (n)	11 (2.9%)	3 (1.5%)	0.112
miscarriage (n)	100 (27.6%)	69 (34.9%)	0.038

Table 2

Pregnancy outcome depending on infertility treatment (calculation of p-values: miscarriage: endometriosis / natural conception vs. no endometriosis / natural conception; natural birth: endometriosis / natural conception vs. endometriosis / ART; primary Cesarean section: both endometriosis groups vs. both no endometriosis groups; secondary Cesarean section: endometriosis / ART vs. no endometriosis ART; abortion: *both ART groups vs both no ART groups, #both endometriosis groups vs. both no endometriosis groups).

Parameter	Endometriosis / natural conception (n = 182)	Endometriosis / ART (n = 192)	No Endometriosis / natural conception (n = 98)	No endometriosis / ART (n = 102)	<i>P</i> value
miscarriage, n	51 (28.8%)	49 (26.3%)	41 (42.7%)	28 (27.7%)	0.011
natural birth, n	67 (62%)	57 (46.7%)	27(55.1%)	40 (55.6%)	0.009
primary cesarean section, n	12 (11.1%)	26 (21.3%)	8 (16.3%)	17 (23.6%)	0.092
secondary cesarean section, n	29 (26.9%)	39 (32%)	14 (28.6%)	15 (20.8%)	0.040
abortion, n	5 (2.8%)	6 (3.1%)	2 (2.0%)	1 (1.0%)	*0.46 #0.12

Table 3

Number of complications per group.

Clavien-Dindo-Grade	Endometriosis (n = 374)	No endometriosis (n = 200)	<i>P</i> -value
I	162 (43.3%)	65 (32.5%)	0.005
II	111 (29.7%)	42 (21%)	0.010
III	53 (14.2%)	39 (19.5%)	0.055
IV	0	0	n.a.
V	0	0	n.a.

Table 4
Details on complications per group.

Time	Endometriosis	No endometriosis
During pregnancy	Vaginal bleeding (n = 40, 15.2%; p = 0.005)	Vaginal bleeding (n = 9, 7%)
	Early uterine contractions (n = 25, 9.5%; p = 0.012)	Early uterine contractions (n = 5, 3.9%)
	Cervical insufficiency (n = 15, 5.7%; p = 0.042)	Cervical insufficiency (n = 3, 2.3%)
	Diabetes mellitus (n = 12, 4.6%)	Diabetes mellitus (n = 7, 5.4%)
	Pre-Eclampsia (n = 10, 3.8%; p = 0.08)	Pre-Eclampsia (n = 2, 1.6%)
	Rupture of the amniotic sac (n = 8, 3%; p = 0.22)	Rupture of the amniotic sac (n = 6, 4.7%)
	Placenta praevia (n = 8, 3%)	Placenta praevia (n = 1, 0.8%)
	Hypertension (n = 6, 2.3%)	Hypertension (n = 3, 2.3%)
	Placental insufficiency (n = 4, 1.5%)	Placental insufficiency (n = 1, 0.8%)
	HELLP Syndrome (n = 3, 1.1%)	HELLP-Syndrome (n = 2, 1.6%)
	Small for gestational age (n = 2, 0.8%)	Small for gestational age (n = 2, 1.6%)
	Anaemia (n = 1, 0.4%)	Anaemia (n = 1, 0.8%)
	Velamentous cord insertion (n = 1, 0.4%)	Velamentous cord insertion (n = 2, 1.6%)
	Pneumonia (n = 1, 0.4%)	Pneumonia (n = 1, 0.8%)
	Nausea (n = 1, 0.4%)	Nausea (n = 1, 0.8%)
	B-Streptococcus infection (n = 3, 1.1%)	Borreliosis (n = 2, 1.6%)
	Kidney congestion (n = 3, 1.1%)	Upper respiratory infection (n = 1, 0.8%)
	Haematoma (n = 3, 1.1%)	Cholestasis (n = 1, 0.8%)
	Hyperemesis (n = 3, 1.1%)	B-Streptococcus infection (n = 1, 0.8%)
	Pregnancy dermatosis (n = 2, 0.8%)	Ovarian cyst (n = 1, 0.8%)
	Cystitis (n = 2, 0.8%)	Necrosis of the femoral head (n = 1, 0.8%)
	Premature placental abruption (n = 2, 0.8%)	Ovarian torsion (n = 1, 0.8%)
	Miscarriage of 1 out of 2 embryos (n = 1, 0.4%)	Liver calcification (n = 1, 0.8%)
	Appendicitis (n = 1, 0.4%)	Carpal-tunnel-syndrome (n = 1, 0.8%)
	Thrombosis (n = 1, 0.4%)	
	Listeria infection (n = 1, 0.4%)	

Time	Endometriosis	No endometriosis
	Bacterial vaginal infection (n = 1, 0.4%)	
	Vaginal mycosis (n = 1, 0.4%)	
	Oligohydramnios (n = 1, 0.4%)	
	Sinus thrombosis (n = 1, 0.4%)	
	Herpes Zoster (n = 1, 0.4%)	
	Colitis (n = 1, 0.4%)	
	Ovarian hyperstimulation syndrome (n = 1, 0.4%)	
	Rectal prolapse (n = 1, 0.4%)	
	Hypothyroidism (n = 1, 0.4%)	

Time	Endometriosis	No endometriosis
During labour	Pathological cardiotocography (n = 25, 9.5%; p = 0.190)	Pathological cardiotocography (n = 9, 7%)
	Green amniotic fluid (n = 14, 5.3%)	Green amniotic fluid (n = 5, 3.9%)
	Perineal rupture of unknown degree (n = 14, 5.3%)	Perineal rupture of unknown degree (n = 8, 6.2%)
	Perineal rupture 1. Degree (n = 1, 0.4%)	Perineal rupture 1. degree (n = 1, 0.8%)
	Perineal rupture 2. Degree (n = 8, 3%)	Perineal rupture 2. Degree (n = 10, 7.8%)
	Perineal rupture 3. Degree (n = 4, 1.5%)	Perineal rupture 3. degree (n = 2, 1.6%)
	Vaginal tear (n = 19, 7.2%; p = 0.009)	Vaginal tear (n = 3, 2.3%)
	Breech presentation (n = 4, 1.5%)	Breech presentation (n = 4, 3.1%)
	Episiotomy (n = 1, 0.4%; p = 0.002)	Episiotomy (n = 9, 7%)
	Prolonged labour (n = 5, 1.9%; p = 0.011)	Prolonged labour (n = 9, 7%)
	Occipito-posterior-presentation (n = 1, 0.4%)	Occipito-posterior-presentation (n = 5, 3.9%)
	High longitudinal position (n = 1, 0.4%)	High longitudinal position (n = 1, 0.4%)
	Bleeding (n = 6, 2.3%; p = 0.007)	High longitudinal position (n = 1, 0.4%)
	Symphysis pubis diastasis (n = 4, 1.5%; p = 0.022)	Prolapse of the umbilical cord (n = 3, 2.3%)
	Oblique presentation (n = 1, 0.4%)	Myoma tear (n = 1, 0.8%)
	Bronchospasm (n = 1, 0.4%)	Cephalic presentation (n = 1, 0.8%)
		Perinatal asphyxia (n = 1, 0.8%)
		Uterine atony (n = 1, 0.8%)

Time	Endometriosis	No endometriosis
After labour	Curettage (n = 4, 1.5%)	Curettage (n = 5, 3.9%)
	Scar-infection (n = 6, 2.3%, p = 0.007)	Painful scar (n = 1, 0.8%)
	Depression (n = 2, 0.8%)	Depression (n = 3, 2.3%)
	Mastitis puerperalis (n = 4, 1.5%)	Mastitis puerperalis (n = 2, 1.6%)
	Iron deficiency anaemia (n = 1, 0.4%)	Iron deficiency anaemia (n = 2, 1.6%)
	Cystitis (n = 1, 0.4%)	Cystitis (n = 2, 1.6%)
	Hypotony (n = 1, 0.4%)	Hypotony (n = 1, 0.8%)
	Bleeding (n = 4, 1.5%; p = 0.022)	Mammary abscess (n = 1, 0.8%)
	Headache (n = 3, 1.1%)	
	Oedema (n = 3, 1.1%)	
	Intraabdominal adhesions (n = 2, 0.8%)	
	Hypertonia (n = 2, 0.8%)	
	Joint stiffness (n = 2, 0.8%)	
	Fever (n = 2, 0.8%; p = 0.078)	
	Dislocation of the pelvis (n = 1, 0.4%)	
	Vaginal discharge (n = 1, 0.4%)	
	Hematoma (n = 1, 0.4%)	
	No urge to urinate (n = 1, 0.4%)	
	Uterine cyst (n = 1, 0.4%)	
	Hysterectomy (n = 1, 0.4%)	
	Post-Partum pains (n = 1, 0.4%)	
	Allergical reaction (n = 1, 0.4%)	
	Hearing loss (n = 1, 0.4%)	
	Haemorrhoids (n = 1, 0.4%)	
	Herpes simplex infection (n = 1, 0.4%)	

Figures

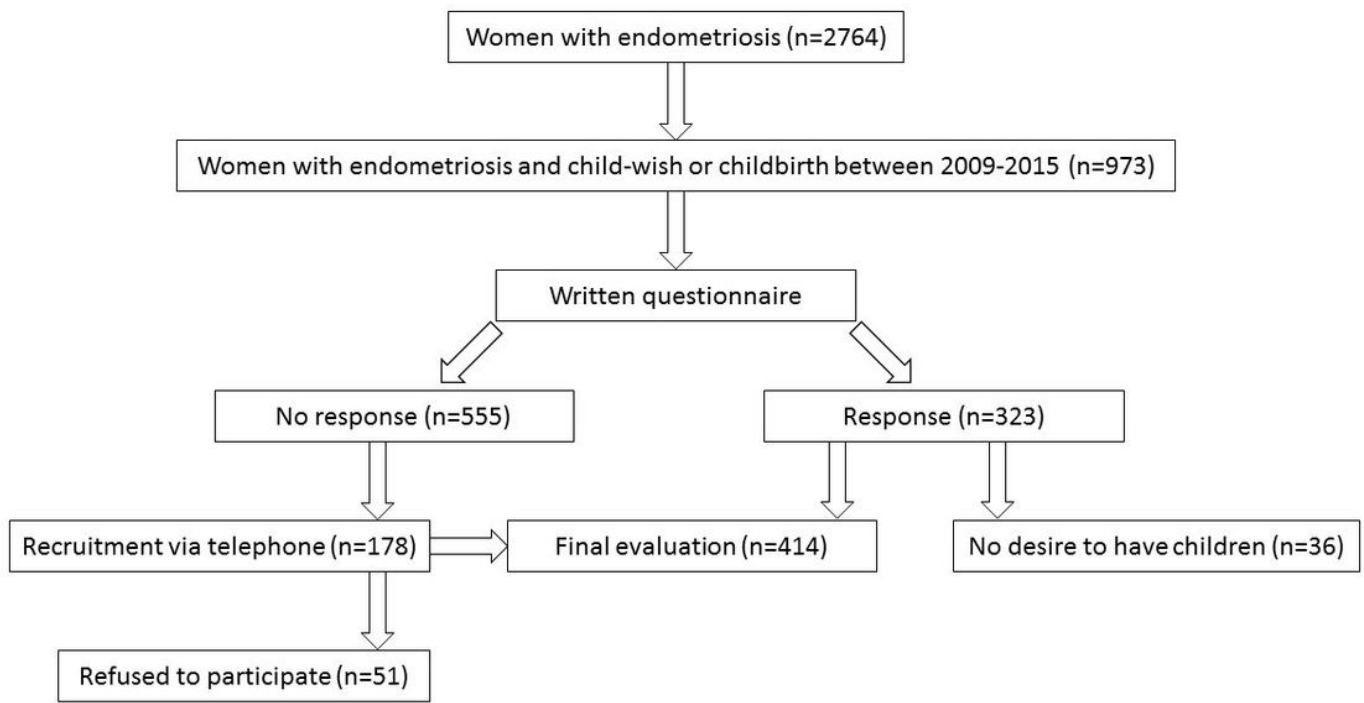


Figure 1

Description of endometriosis cases.

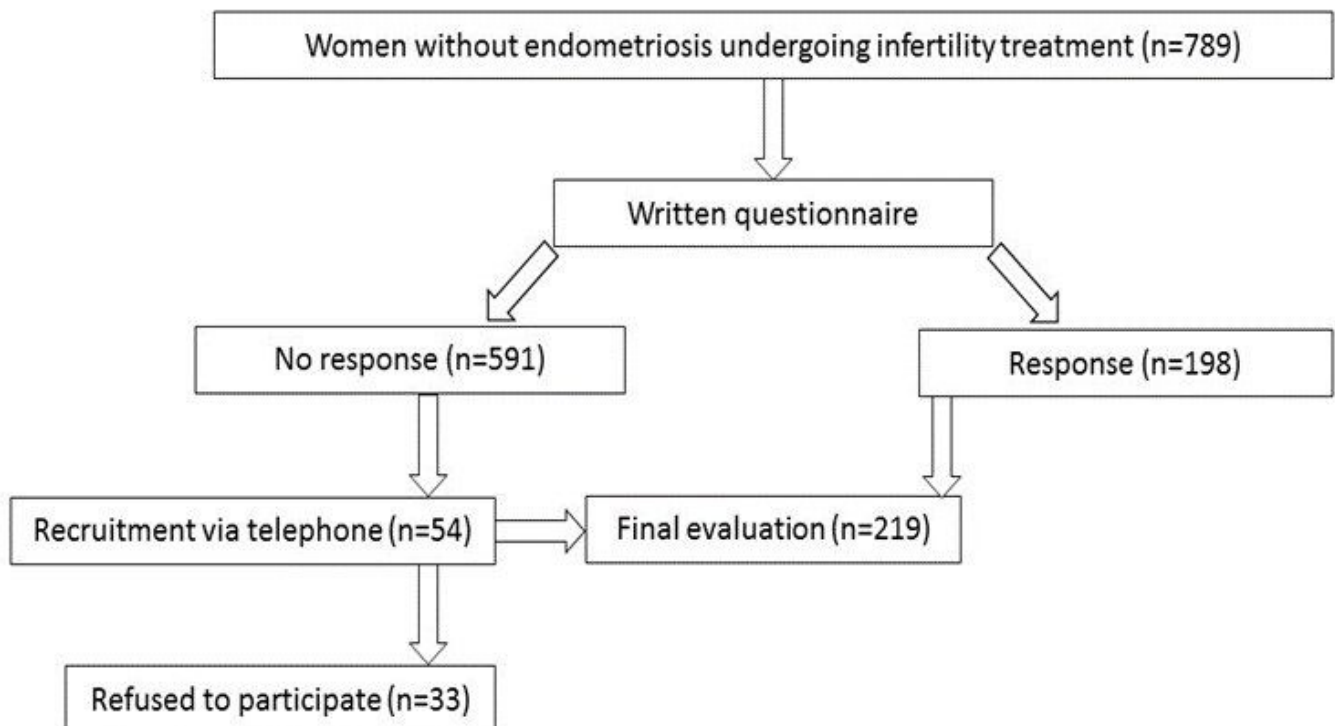


Figure 2

Description of controls.