

# The impact of endometriosis and adenomyosis on the female reproductive system

Citation for published version (APA):

Nirgianakis, K. (2022). *The impact of endometriosis and adenomyosis on the female reproductive system: risks and management approaches*. [Doctoral Thesis, Maastricht University]. ProefschriftMaken. <https://doi.org/10.26481/dis.20220224kn>

## Document status and date:

Published: 01/01/2022

## DOI:

[10.26481/dis.20220224kn](https://doi.org/10.26481/dis.20220224kn)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

## General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

[www.umlib.nl/taverne-license](http://www.umlib.nl/taverne-license)

## Take down policy

If you believe that this document breaches copyright please contact us at:

[repository@maastrichtuniversity.nl](mailto:repository@maastrichtuniversity.nl)

providing details and we will investigate your claim.

## Impact

Endometriosis is a very prevalent disorder in women of premenopausal age. Due to the associated chronic pain and infertility it often leads to a significant reduction in quality of life (1). Moreover, the economic impact is substantial, as chronic and debilitating pain from endometriosis may hinder work productivity, while infertility can cause major psychosocial, emotional and financial strain to affected women and their partners (2). As a result, national action plans have been declared with the aim to improve the quality of life for individuals living with endometriosis, including a reduction in the impact and burden of disease at individual and population levels (3).

Adenomyosis is another similar gynecological disease associated with abnormal uterine bleeding, pelvic pain and infertility. It is characterized by the presence of endometrial-like tissue in the myometrium. Like endometriosis, it can lead to a significant reduction in quality of life. Moreover, it is often coexistent with endometriosis, which makes the treatment approach even more challenging.

We believe that, concerning endometriosis and adenomyosis, our current work may have a significant impact on patients, physicians and research society, which could be divided in the three following categories.

Firstly, we confirmed the high risk of endometriosis recurrence after surgery and showed that this is independent of the endometriosis lesion subtype (superficial lesions, ovarian lesions, deep-infiltrating lesions). The median time to recurrence was 30 months after surgery. Moreover, a significant proportion of the patients presented more severe lesions at recurrence (deep infiltrating lesions), which suggests endometriosis progression over time might occur. The recurrence risk was higher in young patients and if residual endometriosis tissue was identified on the margins of resected bowel. These findings support long-term adjuvant hormonal treatments, which have the potential to reduce the recurrence risk (4-6). Therefore, we believe our work will further encourage physicians and patients to accept such long-term treatments. The benefits of a broad implementation and acceptance of this approach will be less recurrent surgeries with all the advantages related to that (lower risk of complications, lower health care costs). Our work encourages researchers to further investigate the mechanisms related to endometriosis recurrence as well as effectiveness and tolerance to specific treatments. This would aim to identify prognostic and predictive tools to allow for a personalized disease management.

Secondly, endometriosis is an estrogen-dependent disorder with a significant inflammatory nature. The inflammatory nature is one of the reasons for pelvic pain and infertility. GnRHa is a group of drugs acting in endometriosis by inducing a hypo-estrogenic state, which resembles menopause. We showed that GnRHa also mediate a significant regression of the inflammatory microenvironment of endometriotic lesions. By significantly reducing inflammatory cytokines and growth factors in the peritoneal cavity, GnRHa may contribute to pain relief in more ways than just the induction of a hypo-estrogenic state. Directly targeting some of these factors with non-hormonal treatments may achieve the same anti-inflammatory effect while avoiding the significant side effects associated with hormonal treatment (hot flashes, sleep disorders, decreased libido, mood disorders).

The development of novel drugs for endometriosis with improved effectiveness and tolerability is urgent and the above findings may be a first step to this direction.

Finally, it has been recently shown that endometriosis and adenomyosis are associated with several pregnancy complications. We showed that the higher risk of placental disorders is independent of the mode of conception in endometriosis and that a previous excision of endometriosis neither reduces nor increases the risk of pregnancy complications. More importantly, women with previous surgery for deep-infiltrating endometriosis had a similar possibility of successful vaginal birth, if attempted, to women without endometriosis. Concerns that the surgery for deep-infiltrating endometriosis with or without bowel or vaginal involvement may predispose to failed vaginal delivery are refuted by our study. This is valuable information to both physicians and patients to decide on the delivery method. Another important finding of our studies is that adenomyosis is associated with a significantly lower clinical pregnancy rate and higher miscarriage rate after ART, especially when a short GnRH agonist or antagonist protocol is administered for ovarian stimulation. On the contrary, an ultra-long GnRHa protocol might be capable of ameliorating these risks. If this is confirmed in prospective studies, it will be a very important tool to treat the adenomyosis-associated infertility. Finally, adenomyosis is associated with a higher risk of preterm delivery, preeclampsia, caesarean section, fetal malpresentation, SGA, low birth weight, and PPH. The association could be confirmed after adjustment of these outcomes for age and mode of conception. Gynecologists should be aware of these risks to indicate proper controls enabling an early diagnosis and treatment of possible complications.

**References:**

1. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: a multivariate analysis of over 1000 patients. *Human reproduction* 2007;22:266-71.
2. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Human reproduction* 2012;27:1292-9.
3. Australia Co. National Action Plan for Endometriosis. In: Health Do, ed., 2018.
4. Vercellini P, Somigliana E, Daguati R, Vigano P, Meroni F, Crosignani PG. Postoperative oral contraceptive exposure and risk of endometrioma recurrence. *American journal of obstetrics and gynecology* 2008;198:504.e1-5.
5. Lee SR, Yi KW, Song JY, Seo SK, Lee DY, Cho S et al. Efficacy and Safety of Long-Term Use of Dienogest in Women With Ovarian Endometrioma. *Reproductive sciences* 2018;25:341-6.
6. Somigliana E, Vercellini P, Vigano P, Benaglia L, Busnelli A, Fedele L. Postoperative medical therapy after surgical treatment of endometriosis: from adjuvant therapy to tertiary prevention. *Journal of minimally invasive gynecology* 2014;21:328-34.