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Aspects related to fertility treatment outcomes

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LUND UNIVERSITY

DOCTORAL DISSERTATION

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Results: The ovarian reserve markers were associated with LBR but had a modest predictive ability in relation to live birth. The prevalence of endometriosis was 260/1191 (21.8%) women, out of which three quarters had no previous knowledge about the presence of the disease. In total 111/1160 (9.6%) women had direct ultrasonographic features of adenomyosis, whereas 272/1160 (23.4%) women had indirect signs of the disease. The presence of endometriosis reduced the chance of live birth with 37%. Women with adenomyosis had similar chances of live birth as women without, after adjusting for potentially confounding factors. However, women with indirect signs of adenomyosis had a reduced chance of live birth. MUSA features of adenomyosis were poor predictors of live birth.

Conclusions: Endometriosis was present in one in five women referred for IVF treatment and lowered the chance of live birth. The disease was previously undiagnosed in most women.They may be deprived of correct fertility counseling and individualized treatment. Ovarian reserve markers were associated with LBR. Even if the predictive ability of ovarian reserve markers in relation to live birth was poor, their performance was superior to that of MUSA features of adenomyosis.

Key words: Ultrasound, endometriosis, adenomyosis, infertility, subfertility, assisted reproductive treatment, IVF, ICSI, MUSA, IDEA, antimüllerian hormone, ovarian reserve

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Till Jonas och barnen. För att ni finns.

Sometimes the place you are used to is not the place you belong.
Robert Katende

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Abstract

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Conclusions: Endometriosis is common in women undergoing assisted reproductive treatment. Most women are undiagnosed, and the disease may explain their cause of subfertility. Endometriosis affects the ovarian reserve and lowers the chance of live birth. Direct MUSA features of adenomyosis did not correlate to live birth rates, whereas indirect features were associated with reduced live birth rates. MUSA features of adenomyosis were poor predictors of live birth. Subfertile women with undiagnosed endometriosis or adenomyosis may be deprived of correct fertility counseling and individualized management. Women with symptoms suggestive of the diseases should undergo systematic ultrasound examinations.

Populärvetenskaplig sammanfattning

Bakgrund

Endometrios och adenomyos är hormonberoende sjukdomar som drabbar uppskattningsvis 10-15% av alla kvinnor i barnafödande ålder. Sjukdomarna, som ofta samexisterar, innebär att livmoderslemhinna återfinns på organ eller bukhinna i bukhålan (endometrios), eller i livmoderns muskelvägg (adenomyos). Sjukdomarna orsakar ofta smärta, antingen konstant i nedre delen av magen eller i samband med menstruation, tarmtömning eller samlag. Sjukdomarna associeras ofta med en nedsatt förmåga att bli gravid. Det är inte helt fastställt om sjukdomarna påverkar den så kallade äggreserven, det vill säga det kvarvarande antal ägg i äggstockarna som en kvinna har vid en viss ålder. Äggreserven kan mätas indirekt på olika sätt, antingen genom ett blodprov (antimüllerskt hormon, s-AMH) eller genom att räkna antalet äggblåsor i äggstocklarna vid ultraljudsundersökning. Båda dessa markörer speglar antalet kvarvarande ägg i äggstockarna väl. Deras korrelation med antal födda barn efter konstgjord befruktning är dock inte helt fastställd.

I genomsnitt tar det ca 5-10 år för en kvinna med endometrios att få sin diagnos, trots uttalade symptom. Eftersom endometrios och adenomyos ofta är underdiagnosticerade, lider många kvinnor i det tysta. Många av dessa kvinnor har dessutom en ofrivillig barnlöshet och måste genomgå konstgjord befruktning, så kallad IVF-behandling. Man tror att upp till 30-50% av alla kvinnor som har svårt att bli gravida är drabbade av endometrios eller adenomyos. Eftersom det är okänt hur många ofrivilligt barnlösa kvinnor som verkligen är drabbade av endometrios respektive adenomyos, är det inte helt fastställt i vilken utsträckning sjukdomarna verkligen påverkar förmågan att bli gravid eller hur utfallet blir efter konstgjord befruktning.

Tidigare diagnosticerades endometrios i första hand med hjälp av titthålsoperation och adenomyos genom vävnadsundersökning efter att livmodern opererats bort. Med hjälp av modern teknologi, har möjligheterna att diagnosticera sjukdomarna med hjälp av ultraljudsundersökning ökat. Detta innebär att det är lättare att ställa diagnos även på yngre kvinnor.

Idag saknas dock en enhetlig terminologi och tydliga kriterier för att diagnosticera endometrios respektive adenomyos med hjälp av ultraljud. Detta har försvårat jämförelser av studier som undersökt sjukdomarnas förekomst och deras samband med resultatet efter konstgjord befruktning. För några år sedan föreslog internationella grupper av ultraljudsexperter olika ultraljudsmässiga kriterier och definitioner som ska användas för att ställa diagnoserna endometrios (IDEA) och adenomyos (MUSA) vid ultraljudsundersökning. Användningen av dessa kriterier behöver utvärderas i större studier.

Syfte

Det är oklart hur många av alla kvinnor som genomgår konstgjord befruktning som lider av endometrios respektive adenomyos enligt dagens fastställda ultraljudskriterier. Det är dessutom oklart om kvinnor som diagnosticerats med sjukdomarna enligt dessa kriterier, har en sämre chans att få barn med hjälp av konstgjord befruktning jämfört med kvinnor som inte har sjukdomarna. Vidare är det oklart i vilken utsträckning endometrios respektive adenomyos påverkar den så kallade äggreserven. Många barnlösa par som ska genomgå konstgjord befruktning efterfrågar om man kan förutspå utfallet av behandlingen. Hur stor är chansen att behandlingen kommer att lyckas och leda till ett levande fött barn?

I våra studier ville vi ta reda på om olika markörer för äggreserven är associerade med antalet födda barn efter konstgjord befruktning. Vidare ville vi undersöka hur många av de kvinnor som genomgår konstgjord befruktning som faktiskt lider av endometrios respektive adenomyos. Vi ville undersöka om förekomsten av sjukdomarna påverkar äggreserven eller är kopplat till utfallet efter konstgjord befruktning. Dessutom ville vi undersöka om man med hjälp av artificiell intelligens (AI) kan skapa en användbar modell, för att se om olika kliniska variabler såsom s-AMH eller ultraljudstecken till endometrios respektive adenomyos kan användas för att förutspå utfallet efter konstgjord befruktning.

Metoder

I delstudie I jämfördes olika markörer för äggreserven, för att se om dessa kunde användas för att förutsäga resultatet efter konstgjord befruktning. Värdet av s-AMH mättes hos 454 kvinnor, vilket sedan korrelerades med antalet födda barn. I delstudie II-V inkluderades totalt 1191 kvinnor som skulle genomgå konstgjord befruktning. Samtliga kvinnor undersöktes med systematisk ultraljudsundersökning, för att se hur många som hade sjukdomarna endometrios eller adenomyos enligt fastställda ultraljudskriterier. Av de kvinnor som sedan genomgick konstgjord befruktning jämförde vi om det var någon skillnad i antalet födda barn eller i äggreserven hos kvinnor med, respektive utan sjukdomarna. Vi använde också en AI modell för att undersöka om de olika variablerna kunde användas för att förutspå om kvinnan skulle få ett barn efter konstgjord befruktning.

Resultat

I delstudie I fann vi ett samband mellan AMH-värdet i blodet och antalet födda barn efter konstgjord befruktning. Trots det fann vi att man för den enskilda kvinnan inte kunde förutspå om hon skulle få ett barn enbart genom att analysera AMH-värdet.

Delstudie II visade att drygt en femtedel av alla kvinnor som genomgick konstgjord befruktning hade tecken till endometrios. Trots att många av dessa kvinnor hade uttalade symptom som är typiska för endometrios och adenomyos, var det bara en

fjärdedel av kvinnor med ultraljudsmässiga tecken till endometrios som faktiskt kände till att de hade sjukdomen.

I delstudie III fann vi att var tionde kvinna hade typiska, så kallade direkta, tecken till adenomyos, medan ca en fjärdedel hade något enskilt tecken som eventuellt kan tyda på adenomyos, så kallade indirekta tecken. Tecken till adenomyos ökade med åldern och var också vanligare hos kvinnor som hade endometrios.

I delstudie IV-V fann vi att kvinnor som led av endometrios, hade ca 37% lägre chans att få barn efter konstgjord befruktning jämfört med kvinnor som inte hade sjukdomen. Kvinnor med direkta tecken till adenomyos hade däremot samma chans att få barn efter konstgjord befruktning som kvinnor utan adenomyos, efter att resultaten korrigerats för att ta hänsyn till olika faktorer som kan påverka utfallet av konstgjord befruktning, till exempel ålder, äggstockarnas äggreserv och förekomsten av endometrios. Kvinnor med indirekta tecken till adenomyos hade dock en lägre chans att få barn efter konstgjord befruktning jämfört med friska kvinnor även efter att resultaten korrigerats. En möjlig orsak är att många kvinnor med indirekta tecken samtidigt hade endometrios, vilket därmed skulle kunna påverka resultatet.

Slutsatser

Även om ett samband mellan en kvinnas äggreserv och antalet födda barn efter konstgjord befruktning kunde påvisas, är det många andra faktorer som samverkar och påverkar resultatet. Man kan därför inte använda ett enskilt blodprov eller ultraljudsfynd för att förutspå utfallet efter IVF behandling för den enskilda kvinnan. Dock kan markörer för äggreserven användas i rådgivande syfte och för att planera behandlingar med konstgjord befruktning.

En stor andel barnlösa kvinnor som söker hjälp för att bli gravida lider av endometrios eller adenomyos. Trots att de ofta har uttalade symptom som påverkar livskvaliteten, har majoriteten aldrig blivit diagnosticerade. Förekomsten av endometrios kan påverka chansen att bli gravid efter konstgjord befruktning. Medvetenheten om endometrios och adenomyos behöver öka, både hos allmänheten och bland läkare. Fler kvinnor skulle behöva remitteras för systematisk ultraljudsundersökning. Inte bara för att få en diagnos, utan framför allt för att få adekvat hjälp med korrekt behandling och rådgivning. Större studier behövs för att undersöka om visa typer av behandlingar skulle kunna öka chanserna för kvinnor med endometrios att få barn med hjälp av konstgjord befruktning.

Thesis at a glance

Paper	Aim	Results and Conclusion
I	To evalute the association between s-antimüllerian hormone (s-AMH) and cumulative live birth rates after In vitro fertilization (IVF) treatment. To compare the predictive ability of s-AMH to antral follicle count and ovarian sensitivity index in relation to live birth.	The cumulative live birth rate was associated with s-antimüllerian hormone levels. The predicitive ability of s- antimüllerian hormone in relation to live birth was poor and equal to that of antral follicle count and ovarian sensitivity index.
II	To determine the prevalence of endometriosis at systematic transvaginal ultrasonography in subfertile women scheduled for their first In vitro fertilization (IVF) treatment, using the International Deep Endometriosis Analysis (IDEA) group definitions.	Out of 1191 women, in total 260 (21.8%) women had endometriosis on ultrasound examination. Of these, three quarters of women were previously unaware of having the disease. For many women, the presence of endometriosis explained their cause for subfertility. More women with typical symptoms suggestive of endometriosis should be referred for systematic ultrasound examination.
III	To determine the prevalence of direct and indirect features of adenomyosis at 2D and 3D ultrasonography, in subfertile women scheduled for their first IVF treatment, using the Morphological Uterus Sonographic Assessment (MUSA) group definitions.	Out of 1160 women, in total 111 (9.6%) women had direct features of adenomyosis and 272 (23.4%) women had indirect features. Increasing age, presence of endometriosis or previous pregnancy increased the odds for having any features of adenomyosis. The use of 3D ultrasound was an important complement to conventional 2D ultrasound for the diagnostics.
IV	To evaluate the cumulative live birth rate after the first IVF treatment in women with or without endometriosis diagnosed by ultrasonography.	The cumulative live birth rate was lower in women with endometriosis (78/234; 33.3%) compared to women without the disease, [348/806 (43.2%)], p=0.007. Women with endometriosis had a lower chance of live birth compared to women without the disease, adjusted relative risk 0.63 (95% CI; 0.48-0.82).
V	To evaluate the cumulative live birth rate after the first IVF treatment in women with or without adenomyosis, and to evaluate the predictive value of clinical variables and MUSA features of adenomyosis in relation to live birth, using a machine learning model.	Cumulative live birth rates were lower in women with direct features of adenomyosis [25/102 (24.5%; 95% CI, 17.5-31.5)] compared to women without [399/935 (42.7%; 95% CI, 39.5-45.8)], p<0.001. However, after adjustments were made for potentially confounding factors such as age, presence of endometriosis or ovarian reserve parameters, the chance of live birth was similar between the two groups, adjusted relative risk 0.83; 95% CI, 0.56-1.22. Women with indirect features had a lower chance of live birth compared to women without, adjusted relative risk 0.64, (95% CI, 0.47-0.87)], p=0.005. The prognostic ability of clinical variables and MUSA features in relation to live birth was poor, which was confirmed by the machine learning model.

List of original papers

I. **Alson S**., Bungum L., Giwercman A., Henic E. Anti-müllerian hormone levels are associated with live birth rates in ART, but the predictive ability of anti-mullerian hormone is modest. Eur J Obstet Gynecol Reprod Biol 2018;225: 199-204

II. **Alson S**., Jokubkiene L., Henic E., Sladkevicius P. Prevalence of endometrioma and deep infiltrating endometriosis at transvaginal ultrasound examination of subfertile women undergoing assisted reproductive treatment. Fertil Steril 2022;118: 915-923

III. **Alson S**., Jokubkiene L., Henic E., Sladkevicius P. Prevalence of adenomyosis features in women scheduled for assisted reproductive treatment, using the Morphological Uterus Sonographic Assessment (MUSA) group definitions. Acta Obstet Gynecol Scand. 2024 Feb 27. doi:10.1111/aogs.14812.

IV. **Alson S**., Henic E., Jokubkiene L., Sladkevicius P. Endometriosis diagnosed by ultrasound is associated with lower live birth rates in women undergoing their first in vitro fertilization/intracytoplasmic sperm injection treatment. Fertil Steril 2024: Jan 19:S0015-0282(24)00026-8. doi: 10. 1016/j.fertnstert.2024.01.023.

V. **Alson S**., Hansson S.R., Björnsson O., Henic E., Sladkevicius P. Adenomyosis does not correlate to live birth rates after the first IVF/ICSI treatment, when using the revised Morphological Uterus Sonographic Assessment group definitions. *Submitted*

Abbreviations

2D	Two dimensional
3D	Three dimensional
AFC	Antral follicle count
AI	Artificial intelligence
AMH	Antimüllerian hormone
ART	Assisted reproductive treatment
AUC	Area under the curve
BMI	Body mass index
B-mode	Brightness mode
CI	Confidence interval
CLB	Cumulative live birth
CLBR	Cumulative live birth rate
COS	Controlled ovarian stimulation
COX-2	Cyclooxygenase-2
DE	Deep endometriosis
DNA	Deoxyribonucleic acid
ECLI	ElectroChemiLuminiscence Immunoassay
ESHRE	European Society for Human Reproduction and Endocrinology
ET	Embryo transfer
ERβ	Estrogen receptor β
FET	Frozen embryo transfer
FSH	Follicle stimulating hormone
GnRH	Gonadotropin releasing hormone
GQE	Good quality embryo
ICSI	Intracytoplasmic sperm injection
IDEA	International Deep Endometriosis Analysis
IUI	Intrauterine insemination
IVF	*In vitro* fertilization

JZ	Junctional zone
kHz	Kilohertz
LB	Live birth
LBR	Live birth rate
ML	Machine learning
MHz	Megahertz
MRI	Magnetic resonance imaging
MUSA	Morphological Uterus Sonographic Assessment
OPU	Ovum pick up
OR	Odds ratio
OSI	Ovarian sensitivity index
p-value	Probability value
PG	Prostaglandin
PGE_2	Prostaglandin E_2
POD	Pouch of Douglas
PR	Pregnancy rate
rASRM	the revised American Society for Reproductive Medicine
RMC	Reproductive medicine centre
ROC	Receiver operating characteristics
ROS	Reactive oxygen species
RR	Relative risk
RVS	Recto vaginal septum
SHAP	Shapley Additive exPlanations
SPSS	Statistical package for social sciences
TIAR	Tissue injury and repair
TVUS	Transvaginal ultrasonography
USL	Uterosacral ligaments
VAS	Visual analogue scale
XGBoost	Extreme gradient boosting

Preface

As an obstetrician and gynaecologist, I meet many women that have failed to conceive. Often, their lives have been put on hold while they wait for their dream of having a child to come true. In addition, many of these women suffer from excruciating pain, which at times is debilitating. Some may faint at work or must stay in bed for several days every month. Others describe how every footstep or intimate situation feels like having a knife stabbed into their abdomen. Common for these women are the questions they ask me. What is the cause of my pain? Why hasn´t anyone told me what is wrong when I have been suffering for so long? Will I ever have a child? Listening to their stories has come to affect me. This thesis is for all the brave women I have met over the years.

Introduction

Background

Endometriosis and adenomyosis are hormone-dependent, often coexisting diseases, affecting around 10 - 15% of all women of reproductive age (1, 2). Typical, and often debilitating symptoms are dysmenorrhea, dyspareunia, pelvic pain and dyschezia. Endometriosis and adenomyosis are often associated with subfertility and may be present in up to 20–50% of women undergoing assisted reproductive treatment (ART) (3, 4). However, the precise mechanisms and the causal links between endometriosis, adenomyosis and subfertility remain unknown.

Various studies report significant differences in the prevalence of endometriosis and adenomyosis (5, 6). Consequently, results regarding the impact of the diseases on the ovarian reserve or ART outcomes are conflicting. Partly, differences in reported prevalence and ART results may be explained by a lack of uniform diagnostic criteria and methods used to detect and classify adenomyosis and endometriosis.

The gold standard for diagnosing endometriosis and adenomyosis has been surgery with histopathological confirmation, often with considerable diagnostic delay. However, operating on all subfertile women is not feasible and hysterectomy is not an alternative for women who wish to preserve their fertility. Transvaginal ultrasonography (TVUS) with improved resolution has emerged as a non-invasive, sensitive, and specific method to diagnose both endometriosis and adenomyosis (7, 8). Clearly defined ultrasound criteria to describe endometriosis and adenomyosis at TVUS are prerequisites for a correct diagnosis and for studying the potential impact of the diseases on fertility treatment outcomes.

This thesis attempts to investigate the above-mentioned aspects of endometriosis and adenomyosis concerning prevalence in subfertile women, and association with ovarian reserve parameters and fertility treatment outcomes, when using clearly defined ultrasonographic definitions.

Ultrasound

Basic principles

Ultrasound refers to sound waves, with a frequency typically higher than 20 kHz. In gynaecology, ultrasound is used as a non-invasive imaging technique for visualizing internal structures of the pelvis.

The ultrasound transducer contains piezoelectric crystals, that generate high frequency sound waves when an electric voltage is applied. The ultrasonic waves can then be transmitted through the body. When the ultrasound waves encounter a boundary between tissues with different densities, some of the waves are reflected as echoes to the same piezoelectric crystals that emitted the sound waves. The returning echoes are then converted into electric signals, that reflect the composition and density of the encountered tissues. The ultrasound system will process these signals. By calculating the distance, intensity and time delay of the echoes, grayscale images that represent the different densities of the internal structures will be generated.

2D ultrasound

In two-dimensional (2D) ultrasound, or brightness-mode (B-mode), an image that represents a cross-section of the scanned tissue will be generated, as shown in figure 1. The brightness, or grayscale level of each pixel in the image corresponds to the intensity of the reflected echoes. The intensity depends on the difference between two densities. For example, the difference in density between soft tissue and bone or between soft tissue and air is large. Therefore, the reflected signals will generate a strong current, which results in a bright boundary between the tissues in the ultrasound image. If the difference in density is small, a weak current is generated, which results in a dark boundary between the two different tissues. If the media have the same densities, no signals are reflected, and no current is generated. The resultant image looks black. Measurements of different structures are made in B-mode.

3D Ultrasound

Three-dimensional (3D) ultrasound images are generated through the acquisition of multiple consecutive images (tomograms) through the mechanical movement of the ultrasound beam within the transvaginal probe. A volume set is stored on the computer memory (9). The volume dataset can then be examined using section reconstruction, surface rendering or volume rendering. It is possible to rotate and reconstruct any chosen section within the volume dataset, which is the major advantage over 2D imaging. For example, it is possible to obtain a coronal view of the uterus, allowing for evaluation of the fundal and lateral aspects of the junctional zone (JZ), which is not possible with conventional 2D ultrasound (10), (Figure 2).

As this may improve the diagnostic accuracy for adenomyosis (11), the use of 3D TVUS is usually recommended for the diagnostics (8, 12).

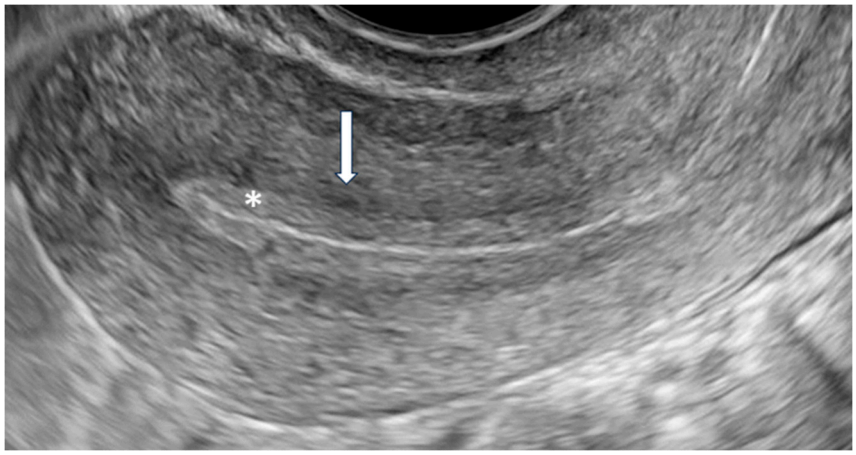

Figure 1. A 2D (B-mode) image of the uterus in the sagittal view.
2D= two-dimensional; B-mode= brightness mode. The arrow indicates a hypoechoic, regular junctional zone, whereas the asterisk marks the hyperechoic endometrium of the uterus.

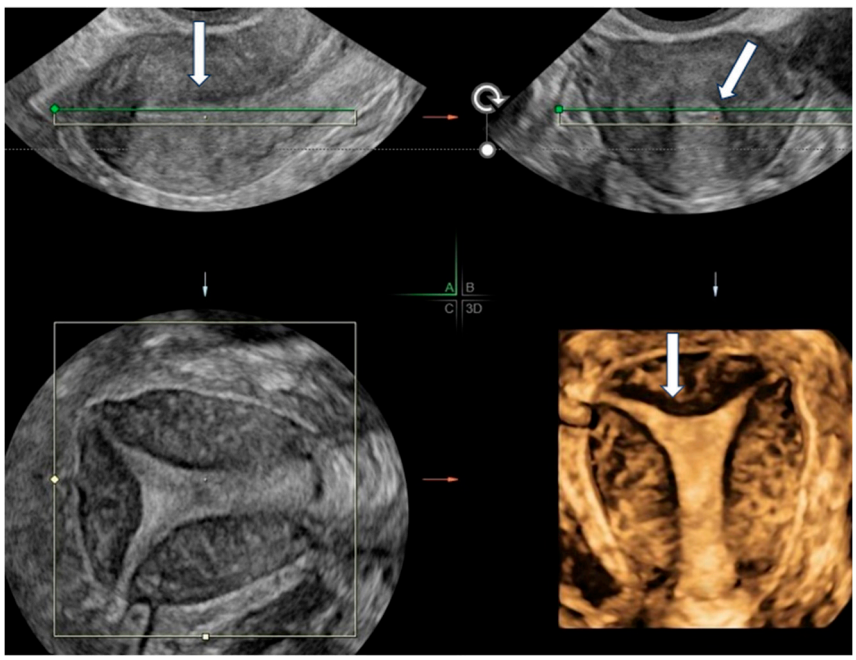

Figure 2. A 3D ultrasound image of the uterus in the multiplanar view.
3D= three-dimensional. The coronal plane of the uterus is shown in the bottom row. The arrow indicates a regular and uninterrupted junctional zone, which is better visualized in the coronal plane.

Subfertility and markers of the ovarian reserve

Subfertility

Subfertility (often used interchangeably with the term infertility) is a failure to achieve pregnancy after one year of unprotected, regular sexual intercourse (13). Approximately 10% of all couples are believed to be affected (14).

The main reason for subfertility is male in 20 - 30%, female in 20 -30% and combined male and female in 25 - 50%. For the remaining couples, the reason for subfertility is unexplained. Environmental and lifestyle factors such as smoking, or obesity can affect fertility. Among female factors are ovulatory dysfunction, tubal occlusion, uterine factors, endometriosis, and a diminished ovarian reserve (15).

The ovarian reserve

The ovarian reserve is the quantity of remaining oocytes in the ovaries at a given time (16). A female is born with approximately 500 000 to 1 million oocytes. Over time, this number is depleted as part of normal ovarian ageing (17). The quality of the oocyte also declines as a result of mitochondrial dysfunction and oxidative stress (18). When no oocytes remain, the woman enters menopause (19). The speed with which this happens is individual and related to several factors such as genetics and lifestyle.

The ovarian reserve can only be measured indirectly through markers such as serum antimüllerian hormone (s-AMH) or antral follicle count (AFC). These markers have been found to correlate well with the functional ovarian reserve, which is the number of growing follicles 2 – 5 mm, out of which one will be selected to be the dominant follicle and subsequently ovulate.

The AMH and AFC are thought to be equivalent markers for assessment of the ovarian reserve prior to ART (20). They are used to plan fertility treatments and to monitor ovarian response to Follicle stimulating hormone (FSH) -stimulation (21).

Antimüllerian hormone (AMH)

Antimüllerian hormone is a glycoprotein exclusively secreted by the granulosa cells surrounding the primordial, pre-antral and small antral follicles in the ovary (22). The AMH has an inhibitory effect on the pool of primordial follicles and acts by limiting the number of follicles available for recruitment, as well as by influencing the FSH-dependent growth of ovarian follicles (23). The expression of AMH is lost in follicles > 8 mm after FSH- dependent selection. Despite a certain intra-and intercycle variability, the s-AMH level is used as a proxy of the functional ovarian reserve (24), (Figure 3). However, even if s-AMH has been shown to correlate well with the ovarian response in ART and with time to menopause (25, 26), it is not

predictive of spontaneous pregnancy (27). Moreover, contrary to what was initially indicated (28), its use as a predictive marker of live birth (LB) after ART has later been questioned (29, 30, 31, 32).

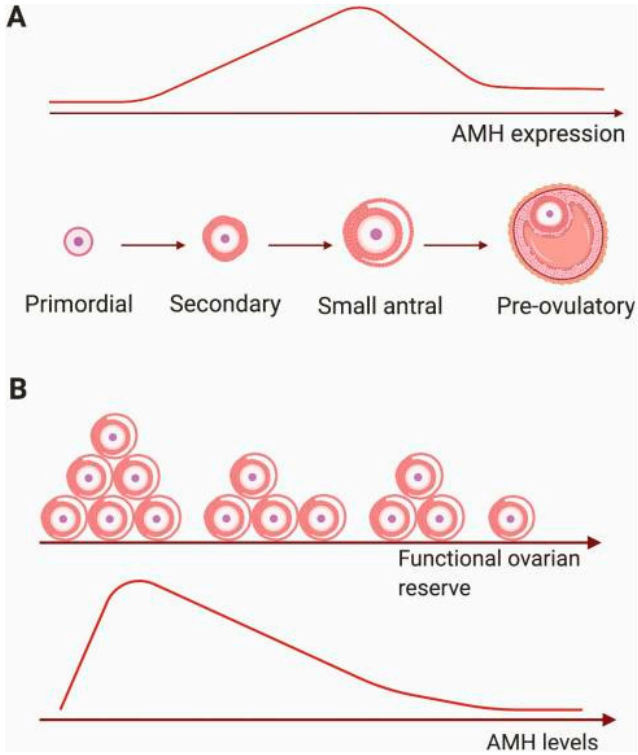

Figure 3. Antimüllerian hormone expression and concentration in relation to folliculogenesis and ovarian reserve.
AMH=Antimüllerian hormone. (A) AMH expression increases from the secondary stage until the small antral follicle stage. In preovulatory follicles, AMH is only expressed in cumulus granulosa cells surrounding the oocyte (dark pink layer). (B) With increasing age, the functional ovarian reserve decreases, with a reduction of the number of small antral follicles and a decrease in serum AMH levels.
Reprinted with permission from Anti-Mullerian Hormone and Ovarian Reserve: Update on Assessing Ovarian Function. L. M. E. Moolhuijsen and J. A. Visser. J Clin Endocrinol Metab 2020 Vol. 105 Issue 11, CC by 4.0.

Antral Follicle Count (AFC)

The AFC is the number of antral follicles 2 – 10 mm visible on TVUS in early follicular phase. The AFC strongly correlates with s-AMH levels (20). Between experienced examiners, the interobserver reliability is high and intercycle variability is low (33). However, in ovaries containing large cysts that stretch the ovarian cortex, the visualization of small antral follicles at TVUS may be reduced and the AFC therefore underestimated (34). For this reason, AFC may be of limited use for estimating the ovarian reserve in the presence of endometriomas.

Endometriosis

Definition

Endometriosis is an oestrogen-dependent inflammatory disease defined by ectopic endometrium-like tissue lesions primarily affecting the pelvic organs (1). Endometriosis exists in three clinically distinct forms; I) Superficial endometriosis describes endometriotic lesions on the peritoneal surface, II) endometriomas are ovarian cysts lined by endometrial mucosa and III) Deep endometriosis (DE), previously termed deep infiltrating endometriosis (DIE), considered to be the most aggressive form, is defined as endometriosis infiltrating deeper than 5 mm under the peritoneum (35). Common for all three forms are ectopic endometrial epithelial or stromal cells, chronic bleeding, and inflammation.

Aetiology

The exact cause of endometriosis is not fully understood. The pathophysiology is likely multifactorial, involving genetic (36, 37), hormonal, immune, and environmental factors. Several theories exist that attempt to explain the development and progression of the disease.

The most accepted theory on the pathogenesis of endometriosis suggests that retrograde menstruation flows through the fallopian tubes into the peritoneal cavity, where endometrial debris gets attached to the peritoneum, invades the tissue, and establishes a blood supply (38). Due to a suboptimal immune response, the implants are not properly cleared from the peritoneum, enabling endometriosis to develop. Why disease would develop only in some women, even if most women have retrograde menstruation to some extent, is not known (1).

Alternative theories propose that remaining cells from embryologic Müllerian duct migration may develop into endometriotic lesions under the influence of oestrogen (39), or that endometriosis originates from stem cells that circulate in the blood (40). Others have suggested that endometriosis is the result of metaplasia of the cells lining the peritoneum into endometrium-like tissue (41), or that hematogenous or lymphatic dissemination of endometrial cells may result in their distant implantation (39).

Prevalence

Approximately 5 – 10% of women of reproductive age are believed to be affected by endometriosis (1). However, the time between the first symptoms and visible endometriosis lesions confirming the disease is usually considerable (42), and the number of unreported cases may be substantial. The disease is likely to be much more prevalent among subfertile women than in the general female population. Estimations of the prevalence of endometriosis among subfertile women vary largely and range from 6 to 50% (4). This variation is probably due to a

heterogeneity in study design, as well as a lack of uniform diagnostic criteria and methods used to detect and describe the endometriotic lesions. Traditionally, the diagnosis was made after surgery in combination with histopathology. However, only a selection of symptomatic women undergo surgery, and not all women with endometriosis have typical symptoms. It would be optimal if more women were diagnosed at an earlier stage of endometriosis development. There is a knowledge gap regarding the prevalence of endometriosis diagnosed at TVUS in subfertile women.

Adenomyosis

Definition

Adenomyosis is a hormone-dependent disease, often coexisting with endometriosis (43). The disease is characterized by proliferation of ectopic endometrial glands and stroma within the myometrial wall, leading to hyperplasia and hypertrophy of the surrounding myometrium (2). Adenomyosis may be focal or diffuse (Figure 4).

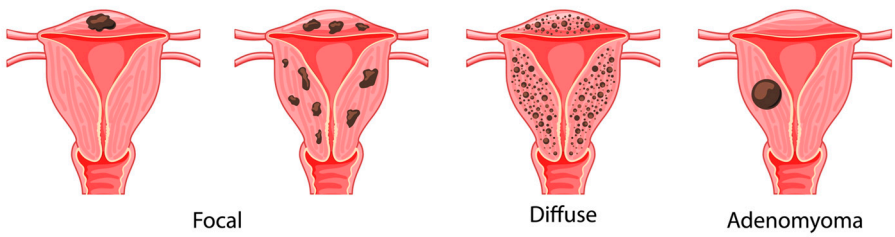

Figure 4. Different phenotypes of adenomyosis. Images showing the uterus in the coronal plane, with adenomyosis lesions (brown) in the myometrial wall. Image used under license from Shutterstock.

The JZ, or endo-myometrial interface, is the hormone-dependent inner 1/3 of the myometrium, believed to be of vital importance in the embryo implantation process (44). The JZ probably plays an important role in the development of adenomyosis. Minor changes of the JZ have been suggested to be early signs of the disease (45) and may also be related to endometriosis (46) and subfertility.

Aetiology

The definitive cause of adenomyosis is unknown. The disease is more common in women with endometriosis (47). Adenomyosis is often associated with oestrogen dominance, with an imbalance between oestrogen and progesterone (48). Oestrogen stimulates the growth and proliferation of endometrial tissue. Increased exposure to oestrogen, particularly in the absence of sufficient progesterone, may contribute to

the development of adenomyosis (48). Known risk factors are an early menarche, short menstrual cycles, obesity and increasing age (49). Parity and surgical trauma to the uterus are other risk factors (50, 51), suggesting that disruption of the endomyometrial border is important in the development of the disease (52). There is evidence to suggest a genetic predisposition to adenomyosis (48). Individuals with a family history of adenomyosis may be at higher risk, indicating a potential genetic component.

Different theories have been proposed to explain the pathogenesis and development of adenomyosis. However, the pathophysiology is likely multifactorial, and proposed mechanisms may interact in different ways among individuals.

The theory of tissue injury and repair (TIAR), suggests that adenomyosis is the result of repeated microtrauma to the JZ, induced by hyperperistalsis of the uterus or by trauma such as pregnancy or curettage (53). Subsequent repair processes, mediated by oestrogen, may in turn induce more inflammation and increase the peristalsis in a vicious circle. This could lead to additional disruption of the JZ with resultant invagination of basal endometrium into the myometrium. In addition, hyperperistalsis may also cause desquamation of fragments of basal endometrium into the tubes and subsequently into the peritoneal cavity, resulting in endometriosis in the pelvis. This way, adenomyosis and endometriosis may share the same pathophysiology. However, this theory has been disputed by others (54). Instead adenomyosis has been suggested to be caused by aberrant endometrial stem cells that move towards the myometrium instead of the functional layer of the endometrium (55), alternatively originates from metaplasia of remnants of the Müllerian ducts (54).

Prevalence

The reported prevalence of adenomyosis ranges from 5-70% depending on different populations examined and different diagnostic modalities and definitions used to establish the diagnosis (5). In a highly selected population consisting of women undergoing hysterectomy, the reported prevalence of adenomyosis varies between 20-70% (56). Women of reproductive age with a wish to conceive are underrepresented in such studies. Over the last years, Magnetic Resonance Imaging (MRI) and TVUS have emerged as sensitive and specific methods for diagnosing adenomyosis. This has enabled non-invasive studies on the prevalence of adenomyosis. In women attending a general gynaecology clinic at a university hospital, ultrasonographic signs of adenomyosis were found in 22% of all women (57). However, there is a knowledge gap regarding the prevalence of adenomyosis in women with subfertility, adhering to strict ultrasonographic criteria.

Subfertility in endometriosis and adenomyosis

Endometriosis and adenomyosis are associated with subfertility (3). Whereas healthy women have fecundity rates of 15-20% per month, this rate is 2%-10% in women with untreated endometriosis (58, 59). Women with mild endometriosis have lower probability of pregnancy over 3 years (36%) compared to women with unexplained infertility (55%) (60). Clinical and epidemiological data regarding fertility in women with adenomyosis are scarce, as the diagnosis previously was made only after hysterectomy (61). Studies on baboons have shown that adenomyosis is strongly associated with lifelong infertility (62). Further, several studies have indicated that endometriosis and adenomyosis are associated with a worse pregnancy outcome compared to healthy women. An increased risk of preeclampsia, preterm delivery, small for gestational age rates and placenta previa has been implicated in women with the diseases (63, 64, 65). Closer monitoring of their pregnancies has been suggested (66).

Endometriosis and adenomyosis may be the cause of infertility in up to 20–50% of women undergoing ART (4). However, whether endometriosis and adenomyosis affect ART results remains controversial, as results are contradictive. Some studies have indicated significantly lower pregnancy rates (PR) (24%) in women with adenomyosis compared to healthy women (45%) after IVF treatment (67, 68). Reduced LBR and increased miscarriage rates in women with the disease have also been reported (63). In other studies, women with endometriosis undergoing IVF treatment had lower PR and LBR compared to women without (69, 70). A retrospective study found that women with endometriosis diagnosed at laparoscopy had a 24% less likelihood of a LB compared to those with unexplained infertility (71). However, several meta-analyses have disputed such associations, and instead suggested that IVF/ICSI outcomes in women with endometriosis or adenomyosis are similar to those without the diseases (72, 73, 74, 75, 76). It is likely that different results may be explained by heterogeneities regarding study design, diagnostic methods and criteria used to diagnose endometriosis and adenomyosis.

The lack of reliable data regarding the prevalence of endometriosis and adenomyosis in subfertile women hampers the interpretation of studies regarding a possible association between the diseases, subfertility, and ART outcomes. There is a knowledge gap regarding IVF/ICSI outcomes in women with endometriosis or adenomyosis diagnosed by TVUS, using uniform sonographic definitions (77).

The precise mechanisms and the causal links between endometriosis and adenomyosis with subfertility in affected women remain unclear. Moreover, it has not been established whether different phenotypes of the diseases have similar effects, or whether there exists a biologic gradient, with inferior outcomes in more extensive disease (78). Further, it is unknown whether endometriosis and adenomyosis act additively or independently (65).

Proposed mechanisms underlying subfertility

Prerequisites for a successful IVF/ICSI treatment outcome are embryos of top quality and a receptive endometrium for implantation. *In vivo,* zygote transport within the fallopian tubes is also important. The main determinant of embryo quality is the quality of the oocyte, whereas endometrial receptivity is dependent on an appropriate hormonal environment (79). Endometriosis and adenomyosis may interfere with these factors in different ways (Figure 5). Proposed mechanisms are local hyperestrogenism and progesterone resistance, inflammation, oxidative stress, aberrant angiogenesis, increased uterine contractility, and genetic changes (80, 81), some of which are described below. However, the reasons for subfertility in endometriosis and adenomyosis are likely to be multifactorial.

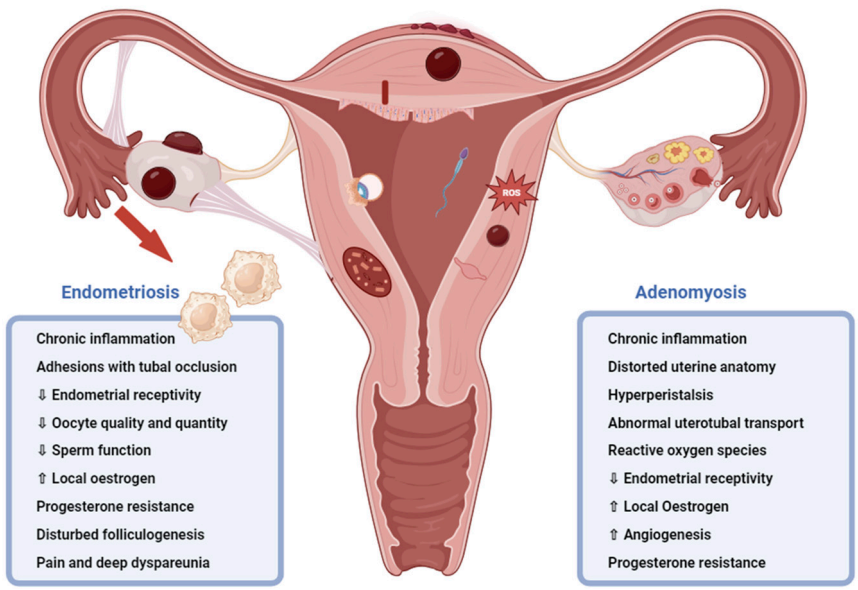

Figure 5. Proposed mechanisms for subfertility in women with endometriosis and adenomyosis. ROS= Reactive oxygen species. The image was created with BioRender.com

Inflammation

The presence of ectopic endometrium is associated with elevated levels of inflammatory mediators such as prostaglandins (PG), cytokines, chemokines and angiogenic factors (4, 39). Whether the inflammation is a result of, or predisposes to endometriosis, is not known (59). Dysfunctional macrophages, that express elevated levels of cyclo-oxygenase-2 (COX-2), are present in increased numbers. These produce more amounts of PG compared to those of women without endometriosis. PGE_2 increase uterine contractility and is believed to be of importance for pain and infertility (1). In women with adenomyosis, there is an

abnormal inflammatory response within the myometrium, with abnormally high levels of free radicals (reactive oxygen species, (ROS)) (82).

Inflammatory mediators and oxidative stress may negatively impact gamete function and quality, thereby compromising fertility. Suggested consequences are affected oocytes, sperm deoxyribonucleic acid (DNA) fragmentation and reduced sperm motility (83).

Local hyperestrogenism and progesterone resistance

Inflammation in endometriosis and adenomyosis is strongly linked to local hyperestrogenism and progesterone resistance. Oestrogen promotes the growth and proliferation of endometrial tissue. Oestrogen receptor B (ERβ), which mediates oestrogen action, is present at much higher levels in ectopic than in eutopic endometrium (84). Menstrual blood from women with adenomyosis contains increased levels of oestradiol (85).

In a positive feedback mechanism, oestrogen stimulates COX-2 through ERβ, with a subsequent increase in PGE_2. This, in turn, stimulates aromatase, which is involved in the biosynthesis of oestrogen (1) and present at increased levels in adenomyosis and endometriosis (86), Figure 6.

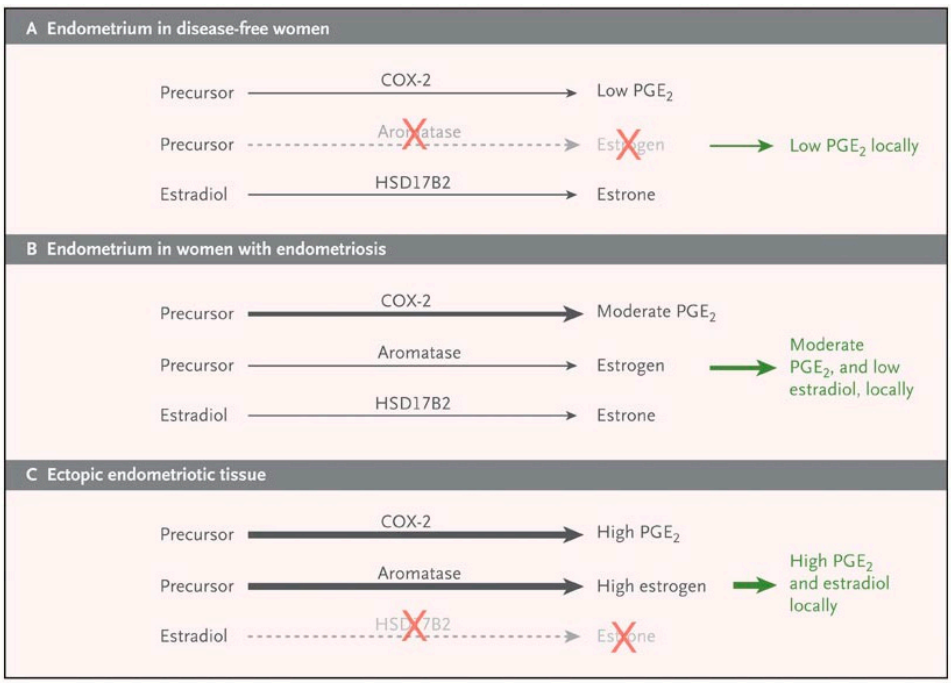

Figure 6. Normal endometrium and endometriosis.
COX-2=cyclooxygenase-2; PGE2 =Prostaglandin E2 ; HSD17B2= 17β-hydroxysteroid dehydrogenase 2.
Reproduced with permission from Bulun SE. N Engl J Med 2009;360:268-279, Copyright Massachusetts Medical Society.

Progesterone induces the differentiation of endometrial epithelial and stromal cells during the menstrual cycle, and thus inhibits the oestrogen-dependent proliferation of epithelial cells. In ectopic endometrium however, levels of progesterone-receptors are downregulated. This causes progesterone resistance, impaired decidualization and high levels of oestradiol, which possibly increases oestradiol-driven inflammation in a positive feedback cycle (87, 88).

Distorted Pelvic Anatomy

In advanced endometriosis, inflammation may result in anatomical distortion of the pelvic organs due to adhesions and fibrosis. This may affect ovaries and fallopian tubes and inhibit ovulation and/or ovum capture through the fimbriae. Transport of the fertilized oocyte through the fallopian tubes may also be impaired (59).

Adenomyosis may cause anatomical distortion of the uterine cavity, with subsequent obstruction of the tubal ostia that may perturb sperm transport and embryo migration (82). Moreover, alterations of normal myometrium, with hyperplastic tissue and destruction of the JZ, may cause dysfunctional uterine peristalsis and an increased intrauterine pressure. This may affect sperm transport (89) as well as embryo migration and implantation, and lead to a defective spiral artery remodelling at decidualization (90).

Endometrial receptivity

A functionally altered endometrium in endometriosis and adenomyosis may compromise embryo implantation. An impaired implantation in women may be caused by a reduced expression of Homeobox A10 (HOXA10) genes (91, 92), adhesions molecules and implantation markers necessary for the interaction between endometrium and embryo (92) (82). However, this issue remains controversial, as similar expression of genes that predict receptivity was found in samples of eutopic endometrium from infertile women with or without endometriosis (83).

Impaired Ovarian Reserve

Increased oxidative stress, inflammation, and compromised follicular development and ovulation due to a dysfunctional hypothalamo–pituitary–ovarian axis, have been associated with a quantitative as well as qualitative reduction of the ovarian reserve in endometriosis (93). Evidence suggests that women with endometriomas have lower s-AMH levels and a faster decline of their ovarian reserve compared to healthy women (94, 95, 96). A limited pool of available oocytes may affect the chances of successful fertilization and conception.

Moreover, embryo quality reflects the oocyte quality (97). Some studies have found that embryos from women with endometriosis develop more slowly than from women without the disease (98). Others have found reduced implantation rates and

embryo quality when using donor oocytes from women with endometriosis and conversely, when women with endometriosis received oocytes from healthy women, implantation rates were normal (99). This implies that there may be alterations of the oocytes in women with endometriosis.

Other factors

An aberrant immune response may impair embryo implantation and increase the risk of pregnancy complications (100). Increased angiogenesis in endometriosis and adenomyosis may also be associated with subfertility (101). Many women experience pain and dyspareunia, which may raise concern on the chances of conceiving (102).

Diagnostics of endometriosis and adenomyosis

Typical symptoms associated with endometriosis and adenomyosis are chronic pelvic pain, dysmenorrhea, dyschezia, deep dyspareunia, dysuria, and subfertility. Women with adenomyosis often experience abnormal uterine bleeding. However, these symptoms are common in several gynaecological conditions and not specific for endometriosis or adenomyosis. Moreover, many women are asymptomatic. Although symptoms associated with endometriosis and adenomyosis may have a profoundly negative impact on affected women´s quality of life (103), it takes an average 5 - 10 years from the first symptom until a diagnosis is made (42). Effective treatment and adequate advice regarding reproductive health depend on an early diagnosis. Therefore, a shortened time to diagnosis is essential.

Surgery and histopathology

The gold standard for diagnosing endometriosis and adenomyosis is histopathology following surgery; endometriosis after laparoscopy and adenomyosis after hysterectomy. However, invasive methods have several limitations. Women that undergo surgery are a selected population, and hysterectomy is not an alternative for women with adenomyosis wishing to preserve their fertility. Moreover, no uniformly accepted histologic diagnostic criteria exist (104, 105). To some extent, the detection of endometriosis at surgery depends on the surgeon´s skill and is subject to interobserver variability (106, 107, 108). Interestingly, it is believed that almost all women would have subtle endometriotic lesions (109), that may have disappeared on subsequent laparoscopy (110). Further, different classification systems for endometriosis focus on different aspects of the disease (111). The most commonly used system to correlate surgical findings of endometriosis with infertility is the revised American Society for Reproductive Medicine (rASRM) (59). However, the rASRM does not consider DE in retroperitoneal structures. Other

staging systems are the Endometriosis Fertility Index, which aims to predict spontaneous PR in women with surgically documented endometriosis (112). The #ENZIAN can be applied to classify endometriosis at TVUS, MRI as well as surgery (113). The need for surgery in most classification system constitutes a limitation, as most women are managed conservatively.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an accurate method for diagnosing endometriosis and adenomyosis. The reported sensitivity for detecting adenomyosis is 88-93% and specificity 67-91% (114). In a meta-analysis, the pooled sensitivity and specificity for detecting DE were 66-85%, and 93-97% respectively (115). For diagnosing endometrioma, the specificity has been reported to be as high as 98%, as blood is easily detected on MRI (116). Diagnostic criteria for adenomyosis include a thickened and irregular JZ (12), as well as direct and indirect signs of endometrial glands present within the myometrial wall (117). Limitations with MRI are the cost, low availability, and an inability to interact with the patient during examination, why tenderness and sliding of the organs cannot be evaluated.

Ultrasound

Diagnosis of Endometriosis

With improved technology and resolution over the last decade, ultrasound has become the primary diagnostic tool for the detection of endometrioma and DE. Compared to MRI and laparoscopy, TVUS is cheap, accessible, dynamic, non-invasive and without side-effects. The diagnostic accuracy for DE on TVUS compared to MRI was evaluated in a systematic review and meta-analysis (115). The overall diagnostic performance was equal for both techniques. The pooled sensitivity for TVUS ranged from 59-85%, and the specificity from 86-96%, depending on which structures that were evaluated. The highest sensitivity was for DE in the rectosigmoid, and the highest specificity for DE in the rectovaginal septum (RVS). Other systematic reviews that have evaluated the diagnostic performance of TVUS regarding DE and endometrioma have found similar sensitivities and specificities, with highest performance for endometrioma and DE in the bowel (118, 119).

Superficial peritoneal endometriotic lesions are undetectable at TVUS. Instead, so called" soft markers", namely site-specific tenderness or reduced organ sliding during TVUS, can be used as a proxy for peritoneal endometriosis or adhesions (120). The diagnostic accuracy for predicting obliteration of the pouch of Douglas (POD) using the" sliding sign" technique has been shown to be high for gynaecologic ultrasound specialists, with sensitivities and specificities ranging from

92,9-100% and 90,9-100% respectively (121). Recently, a new technique called sonoPODography, that enables detection of superficial endometriosis in the POD, has also been described (122).

At TVUS, a typical endometrioma appears as a unilocular cyst (up to four locules) with ground glass echogenicity and without any papillary projections (123), (Figure 7a). Deep endometriosis appears as hypoechoic or heterogenous nodules with smooth or irregular contours, Figure 7b (124).

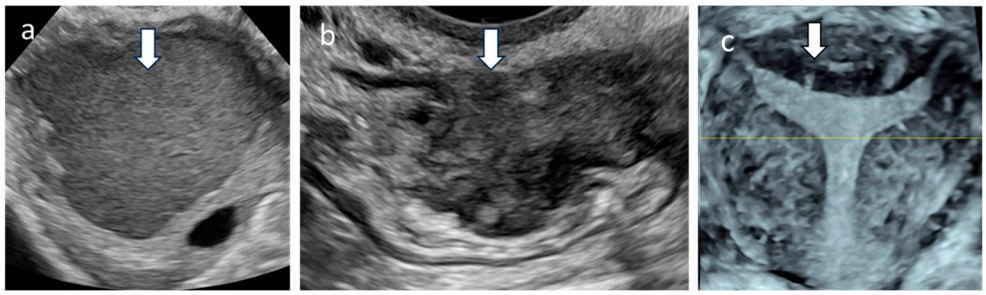

Figure 7. Ultrasound images.

A) Endometrioma, b) hypoechoic nodule with irregular contours in the bowel wall, c) three-dimensional image of the uterus in the coronal plane, visualizing small changes in the junctional zone, as indicated by the arrow.

International Deep Endometriosis Analysis (IDEA) group consensus

To facilitate comparison between studies, the International Deep Endometriosis Analysis (IDEA) group has described a systematic approach to examining the pelvis in women with suspected endometriosis. Terms and measurements to describe the appearance, location, and extent of endometriosis at TVUS have been defined (124), (Figure 8). The IDEA method has shown good agreement with surgery (125, 126). Implementation of the systematic IDEA approach will facilitate comparison between studies regarding prevalence of endometriosis and the correlation between ultrasonographic appearance with symptoms such as subfertility. In this thesis, we have used the IDEA terms and definitions to describe endometriosis lesions.

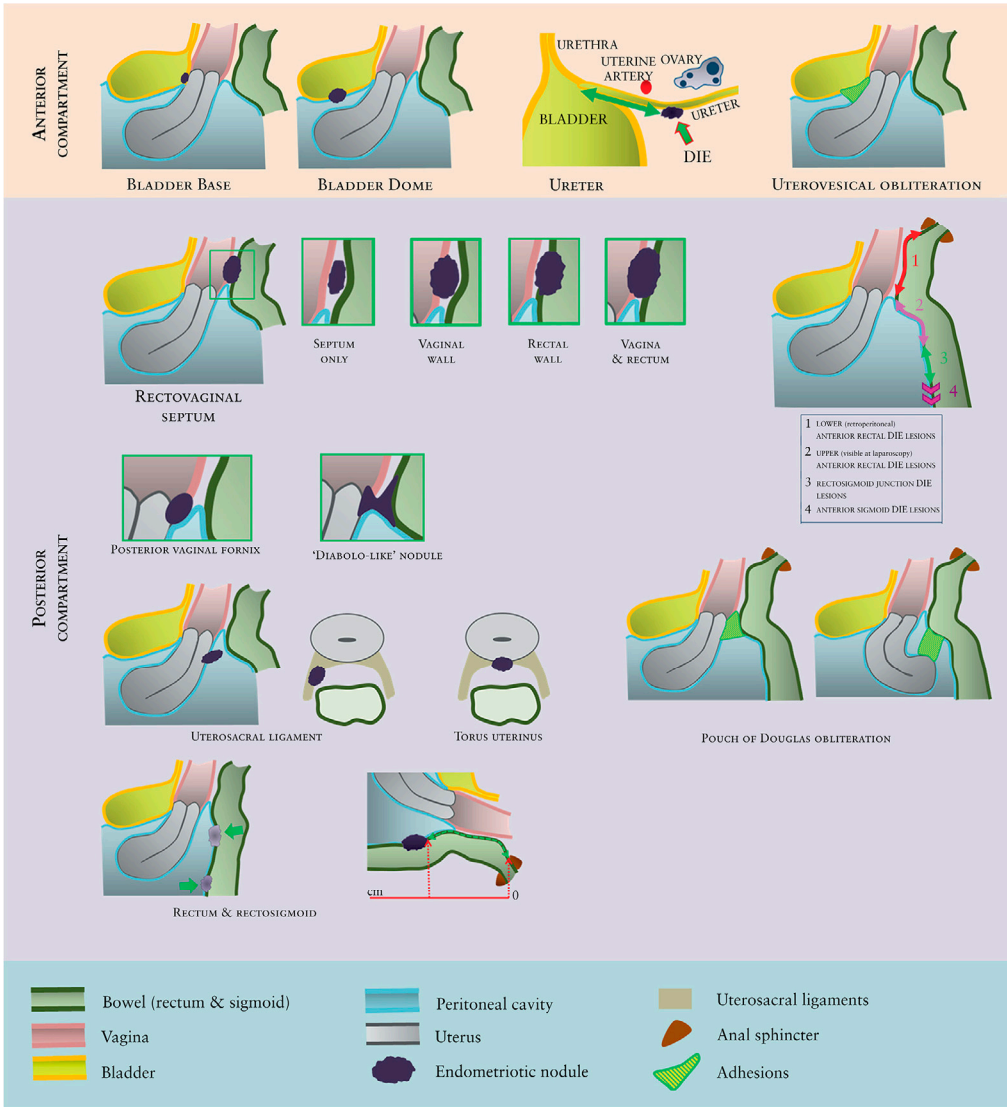

Figure 8. Schematic drawings of anterior and posterior compartmental locations of deep infiltrating endometriosis, as proposed by the International Deep Endometriosis Analysis (IDEA) group.

With permission from Guerriero et al (2016), Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol, 48: 318-332. https://doi.org/10.1002/uog.15955.

Diagnosis of adenomyosis

TVUS has emerged as the first-line non-invasive tool for diagnosing adenomyosis (127). Different features of adenomyosis at TVUS reflect histological findings well (128). Recent meta-analyses have found high diagnostic accuracy of TVUS for adenomyosis, comparable with MRI. Sensitivity and specificity were 81% (95% CI 77-84) and 87% (95% CI 81-91) respectively, with an area under the receiver-operating-characteristics (ROC) curve of 0.88 (95% CI 0.85–0.91) (129).

The development of 3D ultrasound has enabled assessment of small changes of the JZ in the fundus and lateral parts of the uterus, which is not possible to delineate with 2D ultrasound, Figure 7c (10). Therefore, the use of 3D TVUS is believed to be important in the diagnostics of adenomyosis (130).

On 3D TVUS, an irregular and thickened JZ represents hyperplasia of smooth muscle cells, whereas an interrupted JZ reflects invading endometrial glands. However, changes seen in the JZ on 3D TVUS can be physiological and must not always be correlated with adenomyosis (12). Whether minor changes in the JZ only visible on 3D TVUS are of importance for fertility and ART outcomes is not known.

Morphological Uterus Sonographic Assessment (MUSA) group consensus

Clearly defined ultrasonographic features of adenomyosis are prerequisites for a correct diagnosis and management of women with the disease. So far, different definitions and diagnostic criteria for adenomyosis have been used in different studies. A uniform terminology is essential to compare studies that evaluate the correlation between adenomyosis, subfertility and reproductive treatment outcomes.

The international Morphological Uterus Sonographic Assessment (MUSA) group has suggested a uniform classification system to describe adenomyosis at TVUS (128, 131). In a revised version, the MUSA group suggest distinguishing between direct and indirect ultrasonographic features of adenomyosis (8). Direct features represent ectopic myometrium and are pathognomonic of adenomyosis, whereas indirect features are secondary to ectopic endometrium and merely suggestive of the disease (Figure 9). Many studies that evaluate the correlation between adenomyosis and subfertility use JZ thickness >7 mm or >12 mm as a sign of adenomyosis. However, the MUSA group has omitted JZ thickness as a sonographic criterion for adenomyosis, due to lack of scientific evidence of its clinical usefulness and due to difficulties in establishing a clinically relevant cutoff level for JZ thickness (8).

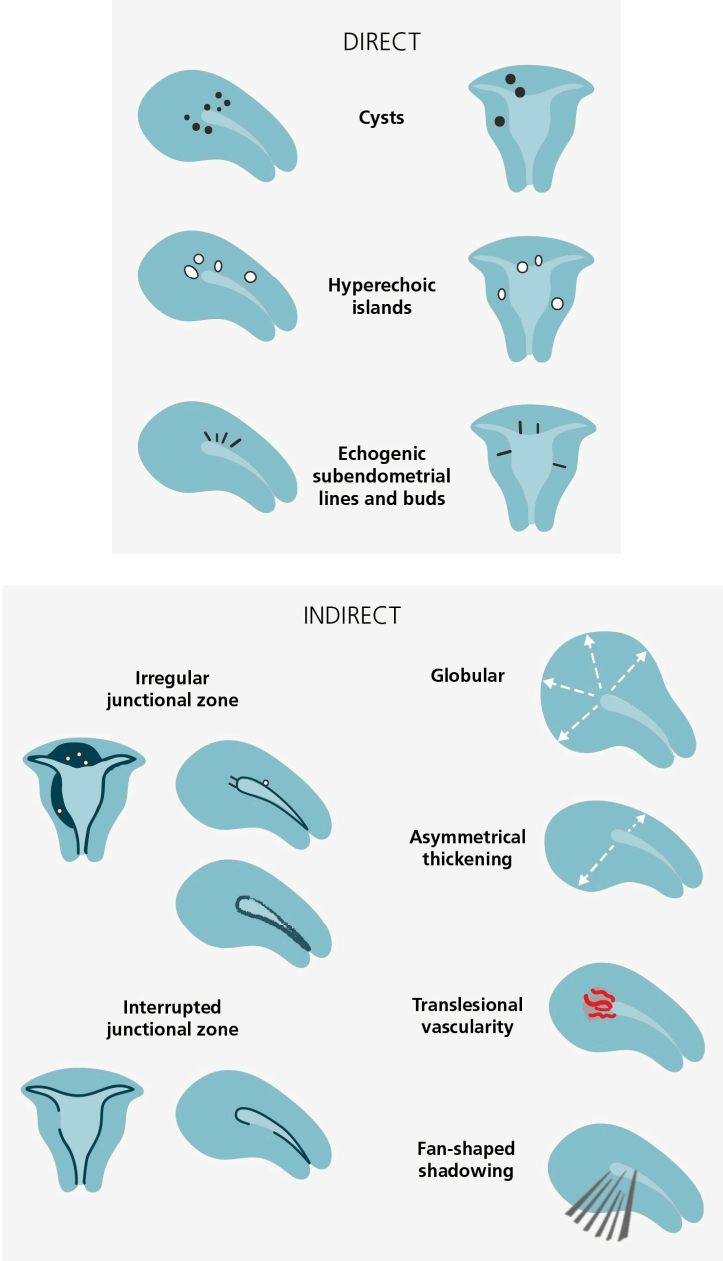

Figure 9. Schematic representation of direct and indirect features of adenomyosis

Direct and indirect features of adenomyosis as seen on two-dimensional and corresponding three-dimensional images.

Adapted with permission from Harmsen MJ, Van den Bosch T er al. Consensus on revised definitions of Morphological Uterus Sonographic Assessment (MUSA) features of adenomyosis: results of modified Delphi procedure. Ultrasound Obstet Gynecol. 2022. doi: 10.1002/uog.24786.

When the diagnostic performance of each individual MUSA criterion was assessed in a recent meta-analysis, the best individual criterion was lines and buds with an area under the ROC curve of 0.83 (129). Results from another meta-analysis concluded that the pooled area under the ROC curve for diagnosing adenomyosis based on finding an irregular JZ on 3D TVS was 0.81 (11). However, the clinical relevance and diagnostic importance of each feature regarding subfertility and the outcome after ART needs to be validated in large prospective studies (8). There is a knowledge gap regarding whether an assessment of the JZ could aid in patient management when there is uncertainty about a diagnosis of adenomyosis (8). Moreover, the additional value of the use of coronal planes at 3D TVUS for the assessment of location, extent, and size of adenomyotic lesions needs to be investigated further (128). In this thesis, we have used the MUSA definitions to evaluate the prevalence and ultrasonographic characteristics of different features of adenomyosis in subfertile women at 2D and 3D TVUS.

Assisted reproductive treatment

In Sweden, assisted reproductive treatment (ART) is provided within the tax-funded health care system for women that fulfil specific criteria.

In ART, the ovaries are stimulated with supraphysiologic doses of gonadotropins, (FSH), to achieve growth of multiple ovarian follicles and subsequently several oocytes. After being collected through the vagina, the oocytes are fertilized in the laboratory. Fertilized embryos are thereafter cultured for 2-5 days, whereafter an embryo of good quality is transferred to the womb. In case of surplus embryos of good quality, these can be frozen and thawed for transfer on a later occasion.

ART include *In vitro* Fertilization (IVF) treatment, which means that spermatozoa and oocytes are mixed whereafter one sperm fertilizes the oocyte after natural selection. In Intracytoplasmic Sperm Injection (ICSI), one sperm is instead injected into the oocyte. For women with endometriosis, usually IVF/ICSI is recommended as the first line treatment. In case of subfertility of unknown cause, intrauterine inseminations (IUI) can sometimes be offered instead.

There are different treatment protocols commonly used to prevent premature ovulation during FSH-stimulation. The antagonist (short) protocol, that blocks the pituitary with gonadotropin releasing hormone (GnRH) antagonists, is usually chosen for the first treatment for most women. In the agonist (long) protocol, the pituitary is downregulated with GnRH agonists starting on day 21 of the menstrual cycle preceding the stimulation cycle. It has been suggested that the use of an ultralong GnRH agonist protocol for 3-6 months prior to ART start, would increase live birth rates (LBR) in women with endometriosis or adenomyosis (132). The theory is that these suppress inflammatory parameters and improve endometrial

receptivity in women with endometriosis or adenomyosis. However, others have disputed the value of this strategy, why it is presently not routinely recommended (133).

Women with endometriomas or DE are not routinely offered surgery prior to ART, due to concerns of damaging the ovarian reserve (133). However, surgery may be offered to those with large or rapidly growing endometriomas, which may hamper the access to follicles at ovum pick-up (OPU).

As women with endometriosis may have an increased risk of intraabdominal infections after OPU, they are routinely offered antibiotic prophylaxis in conjunction with OPU.

Artificial intelligence

Machine learning, XGBoost

Machine learning (ML) is a subfield of artificial intelligence (AI), that focuses on designing algorithms and models that enable computers to automatically learn from patterns and relationships in data, and make predictions based on those without being explicitly programmed for each task (134). Models can be based on various mathematical and statistical approaches, such as linear regression and decision trees. Some models may be inspired by biological systems. The ML algorithms can be categorized into two main learning paradigms; I) Supervised learning involves training models to make predictions using labelled data, whereas II) unsupervised learning involves finding unexpected patterns and structures in unlabelled data. Prediction models based on supervised ML have been suggested to have superior predictive performance compared to conventional statistical methods (134, 135). Different ML models have been tested in reproductive medicine and endometriosis care to make clinically useful predictions (136, 137).

The eXtreme Gradient Boosting (XGBoost) is a powerful and widely used ML algorithm, known for its efficiency and effectiveness in predictive modelling tasks (138). It belongs to the family of gradient boosting algorithms that use decision trees to build a solution (Figure 10). The XGBoost can analyse large datasets with numerous predictors and handle non-linear relationships between variables, such as clinical variables or MUSA features and their association with ART outcomes. This way, important features that contribute to the predictive performance of the model can be identified. XGBoost is particularly popular in structured data analysis, such as regression and classification problems.

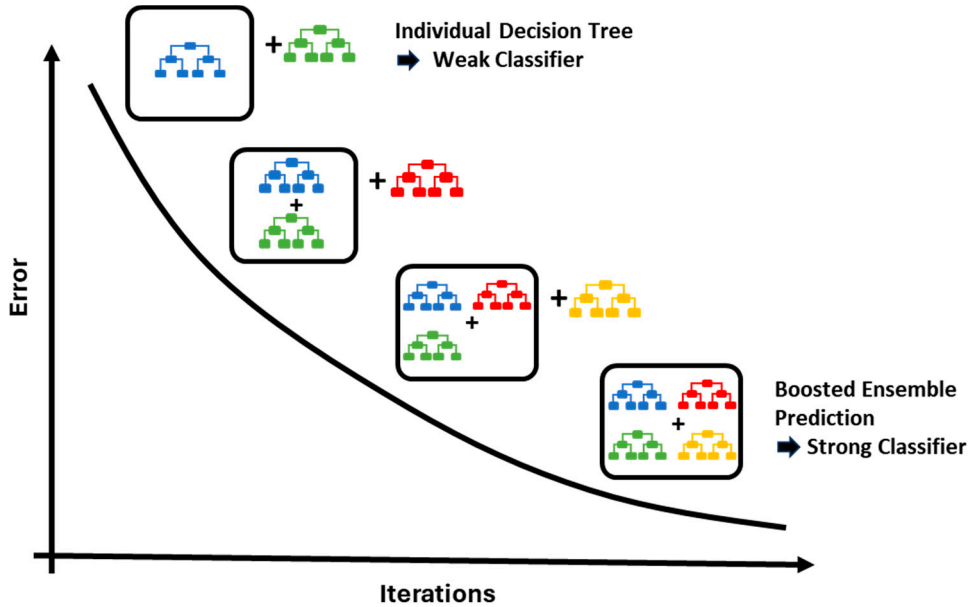

Figure 10. Decision tree in eXtreme Gradient Boosting

The SHAP (SHapley Additive exPlanations) is a method used for explaining individual predictions made by machine learning models (139). It provides a way to understand the contribution of each feature to the final prediction. The core idea behind SHAP is to assign each feature's contribution to the prediction based on its importance and interaction with other features, analogous to the Shapley value concept from cooperative game theory. Overall, SHAP provides a powerful framework for interpreting and understanding the behaviour of complex machine learning models, enhancing their transparency and trustworthiness.

Rationale

When the present research was developed, the knowledge regarding the value of s-AMH as predictor of live birth rate (LBR) was limited. Evidence regarding a strong correlation between s-AMH and cumulative LBR (CLBR) was conflicting. Most studies evaluated LBR after fresh embryo transfer (ET). However, s-AMH correlates with oocyte yield after controlled ovarian stimulation (COS) (140, 141). With improvements in vitrification techniques over the last years, an increasing number of embryos are frozen and transferred on a later occasion (142). Therefore, studies on the correlation between s-AMH and LBR should analyse CLBR after fresh as well as frozen ET (142).

Further, there were no studies that described the prevalence of endometriosis and adenomyosis in subfertile women using ultrasonography with the IDEA or MUSA terminology respectively (122). No study had assessed the CLBR after the first IVF/ICSI treatment in women with or without endometriosis diagnosed by ultrasonography, using the IDEA definitions (122). Likewise, no study had assessed the CLBR after the first IVF/ICSI treatment in women with or without adenomyosis diagnosed by ultrasonography using the revised MUSA definitions. The only study that investigated the IVF/ICSI outcomes in women with different features of adenomyosis diagnosed with ultrasonography did not use the revised MUSA definitions (67). No study had examined any differences in ovarian reserve parameters in these women. The predictive value of the revised MUSA features in relation to LB was not known. It had also yet to be established whether 3D ultrasound performed any better than conventional 2D ultrasound at finding early signs of adenomyosis that may be clinically relevant in reproductive medicine.

Aims

The overall aim of this thesis is to improve our knowledge of the disease panorama of endometriosis and adenomyosis, and to increase our understanding on how the diseases affect the ovarian reserve and fertility treatment outcomes.

Specific aims:

I. To evaluate the association between s-AMH levels and CLBR in patients undergoing their first IVF/ICSI treatment, and to compare s-AMH levels with AFC and Ovarian Sensitivity Index (OSI) as predictors of live birth.

II. To determine the prevalence of endometriosis at TVUS in subfertile women planned for their first ART, using the IDEA terminology.

III. To determine the prevalence of direct and indirect ultrasonographic features of adenomyosis at 2D and 3D TVUS in subfertile women planned for their first ART, using the revised MUSA definitions.

IV. To examine if endometriosis, diagnosed at TVUS using the IDEA definitions, impacts CLBR or ovarian reserve parameters in women undergoing their first IVF/ICSI treatment.

V. To examine if adenomyosis, diagnosed at TVUS using the MUSA definitions, impacts CLBR in women undergoing their first IVF/ICSI treatment.

VI. To establish whether clinical variables or ultrasound features of endometriosis and/or adenomyosis can be used to predict live birth after IVF/ICSI treatment, when using a ML algorithm.

Material and methods

Study design

An overview of the study design is presented in Table 1.

Table 1. Design of the different studies included in this thesis

Paper	Design	Subjects	Exposure	Outcome measure
I	Prospective cohort study	454 subfertile women	IVF/ICSI	CLBR in relation to s-AMH. Predictive value of s-AMH, AFC and OSI on LB.
II	Prospective cross-sectional study	1191 women scheduled for ART	TVUS, IDEA	Prevalence of DE and/or endometrioma using the IDEA definitions.
III	Prospective cross-sectional study	1160 women scheduled for ART	TVUS, MUSA	Prevalence of direct and indirect features of adenomyosis using the revised MUSA definitions.
IV	Prospective cohort study	1040 subfertile women	IVF/ICSI	CLBR in women with or without endometriosis on TVUS.
V	Prospective cohort study	1037 subfertile women	IVF/ICSI	CLBR in women with or without direct or indirect features of adenomyosis on TVUS. Predictive value of clinical variables and MUSA features in relation to live birth, using a ML model.

IVF= In vitro fertilization; ICSI= intracytoplasmic sperm injection; s-AMH= serum-antimüllerian hormone; AFC= antral follicle count; OSI= ovarian sensitivity index; LB= live birth, DE= deep endometriosis; ART= assisted reproductive treatment; IDEA= International Deep Endometriosis Analysis; MUSA= Morphological Uterus Sonographic Assessment; TVUS= transvaginal ultrasonography, CLBR= cumulative live birth rate; ML= Machine learning

This thesis consists of five papers based on prospective, observational studies that were all carried out at the Reproductive Medicine Centre (RMC), at Skåne university hospital, Malmö, Sweden.

We included two separate cohorts of women:

Cohort A, used in paper I, consists of women undergoing their first *In vitro* fertilization (IVF) or Intracytoplasmic sperm injection (ICSI) treatment between September 2010 and June 2015. In total 499 women were enrolled, and finally 454 women were included. In paper I, we evaluated the CLBR in relation to the s-AMH level and compared the s-AMH level with the AFC and OSI as predictors of LB.

Cohort B was used in papers II-V. This cohort consists of consecutively included women that were referred to RMC for their first ART between December 2018 – May 2022. Out of 1224 eligible women, in total 1191 women met the inclusion criteria and were enrolled (Figure 11). All women underwent a systematic TVUS examination prior to starting their first IVF/ICSI treatment, which took place between January 2019 and October 2022. Using the IDEA and MUSA definitions respectively, the prevalence of DE and/or endometrioma (described as endometriosis throughout the thesis) and direct or indirect features of adenomyosis were determined. We evaluated the CLBR, s-AMH and AFC in women with ultrasonographic features of endometriosis or adenomyosis, compared to women without any of those features. In addition, we used a ML algorithm to develop a model for the prediction of LB after IVF/ICSI treatment.

Study subjects

Eligibility criteria

Eligible for publicly subsidized ART were all non-smoking women aged ≥25 - ≤39 years, with more than one year´s subfertility and without any children with the present partner. A BMI ≤ 30 kg/m^2, or a more than 10% weight loss in case of a BMI > 30 - ≤ 35 kg/m^2, was also required.

Exlusion criteria

Exclusion criteria for the different papers are presented in Table 2.

Women that had previously undergone surgical removal of superficial endometriosis, with no remaining visible lesions were excluded from *cohort B*. The reason for this is that even if visible endometriosis lesions are eradicated surgically, the disease *per se* may remain. Therefore, it would have been wrong to classify these women as “not having endometriosis”.

Current hormonal treatment may alter the ultrasonographic appearance of the myometrium. Therefore, women using hormonal treatment were excluded from all papers that examined features of adenomyosis.

Table 2. Exclusion criteria for the different papers.

Exclusion criteria	Paper I	Paper II	Paper III	Paper IV	Paper V
Irregular menstrual cycle < 20 days or >35 days	*				
Only one ovary	*				
Previous endometriosis surgery		*	*	*	*
Unretrievable ultrasound images		*	*	*	*
Hormonal treatment	*		*		*
IUI instead of IVF/ICSI				*	*

IUI= Intrauterine insemination, IVF= In vitro fertilization, ICSI= Intracytoplasmic sperm injection. The asterisk * indicates the papers in which the different variables were excluded.

Questionnaire

Previous births, miscarriages, termination of pregnancies, extrauterine pregnancies and previous surgeries were documented for all women. Women in *cohort B* filled in a questionnaire regarding current or previous hormonal treatment and the presence of symptoms such as dysmenorrhea, pelvic pain, dyspareunia, dysuria or dyschezia (Appendix 1). The intensity of symptoms was reported subjectively, using a 100-mm visual analogue scale (VAS), with the left extreme indicating no pain, and the right extreme the worst possible imaginable pain.

A flowchart demonstrating the inclusion of women in *cohort B* is presented in Figure 11.

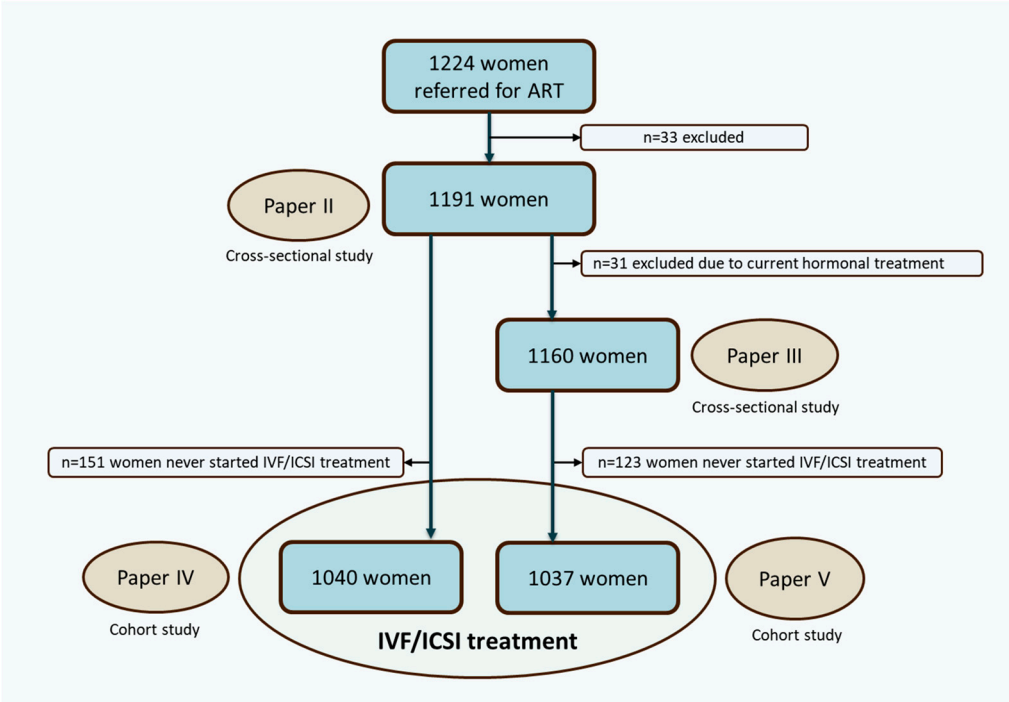

Figure 11. Flowchart demonstrating the inclusion of women in cohort B.
ART= Assisted reproductive treatment; IVF= In vitro fertilization treatment; ICSI= Intracytoplasmic sperm injection. Women included in paper IV and V come from the same cohort and are overlapping. The left side of the flowchart describes studies on endometriosis, whereas the right side describes studies on adenomyosis.

Antimüllerian hormone - AMH

For *cohort A*, s-AMH was analyzed solely for study purposes and the results were not known during treatment. A blood sample was taken before treatment, whereafter serum was isolated and stored at -80º before analyzed in batches. For *cohort B*, analysis of s-AMH had been introduced as clinical routine. Therefore, s-AMH was analyzed for all women regardless of study participation and the results were known during treatment. Analyses of s-AMH for all studies were performed at the Department of Clinical Chemistry, Skåne university hospital, using the ElectroChemiLuminiscence Immunoassay (ECLI) provided by Roche Elecsys AMH. The coefficients of variation were 2% at 6.86 pmol/l and the lowest detectable level was 0.07 pmol/l.

Ovarian sensitivity index - OSI

The ovarian sensitivity index (OSI) is calculated as a measure of the ovarian responsiveness, to be used when different stimulation regimens have been used for different women (143, 144). It is defined as the number of retrieved oocytes times 1000, divided by the total dose of FSH given during ovarian stimulation.

Ultrasound examination

All women in *cohort A* were examined by one of six investigators, using a BK Medical scanner 8806 with a 4-9 MHz transvaginal transducer, and the AFC was documented.

2D and 3D transvaginal ultrasound examination

All women in *cohort B* underwent a pelvic examination and a systematic TVUS examination in the lithotomy position by the author. For all ultrasound examinations, we used a Voluson 10 Expert (GE Medical systems, Zipf, Austria) high resolution ultrasound machine, with a 5-9 MHz transvaginal transducer (RIC5-9D). For subsequent retrieval and offline analysis, all images, video clips and 3D volumes were stored on the information and imaging management systems Syngo® Dynamics (Siemens Medical Solutions Health Services, Malvern, PA, USA) and ViewPoint with the integrated software 4D view (GE Healthcare, München, Germany).

The systematic TVUS examination included a dynamic 2D and 3D assessment of the uterus, endometrium, and adnexa in three orthogonal planes.

The AFC, defined as the sum of all follicles 2-10 mm in the volumes of both ovaries, was assessed.

The myometrial walls were measured in the midsagittal plane at the thickest point from the external uterine serosa to the basal line of the endometrial-myometrial interface. Asymmetrical myometrial thickening was defined as a more than five mm difference in the thickness of the anterior and posterior myometrial walls, or a ratio between the thickness of the walls well above one.

The 3D volumes of the uterus were acquired using a sweep angle of 120º, as described by others (130). The multiplanar view allows visualization of the rendered coronal plane of the uterus. The myometrium and JZ were assessed by tilting and scrolling through the rendered 3D volume of the uterus. To distinguish between a vascular component and a myometrial cyst, and to evaluate the presence of intra- or translesional vascularity, we used Power Doppler (fixed preinstalled settings:

frequency, 5–9 MHz (‘normal’); pulse repetition frequency, 0.3 – 0.6 kHz; gain, −4.0; wall motion filter, ‘low 1’ (40 Hz)).

The whole pelvis was examined with particular attention for endometriotic lesions and/or features of adenomyosis. All lesions were measured in three orthogonal planes and described using the IDEA terminology (124), or the revised MUSA terms and definitions (8, 128, 131) respectively.

Endometriosis

Endometriosis was diagnosed if DE or endometriomas were detected at TVUS. Endometriomas were unilocular cysts with ground glass echogenicity (123), whereas DE was defined as heterogenous or hypoechoic nodules with irregular or smooth contours (124), (Figure 12). The anterior and posterior compartments of the pelvis were evaluated. The anterior compartment consists of the urinary bladder, the uterovesical region and the distal ureters. Structures located in the posterior compartment are the uterosacral ligaments (USL), the vagina (vaginal wall and fornices), rectovaginal septum (RVS) and bowel (lower and upper anterior rectum, the rectosigmoid junction and sigmoid), (Figure 12). “Diabolo”-like nodules were hourglass-shaped DE nodules in the posterior vaginal wall that extended into the anterior rectal wall, (Figure 13).

The pelvis was evaluated for adhesions using the real-time sliding sign technique (121) to assess the mobility of the uterus. A negative sliding sign indicated adhesions in the pelvis and obliteration of the POD (Figure 13), whereas a positive sliding sign indicated the absence of extensive adhesions. When adhesions were visible between the bowel and an ovary or between an ovary and the uterus, but the uterus was gliding freely against the bowel, this was reported as “moderate adhesions” (145). Ovaries lying in close proximity in the pelvis due to adhesions, “kissing ovaries”, were documented, as this finding is associated with endometriosis (146), (Figure 14). Images that describe the ultrasonographic findings are presented in Figures 12- 14.

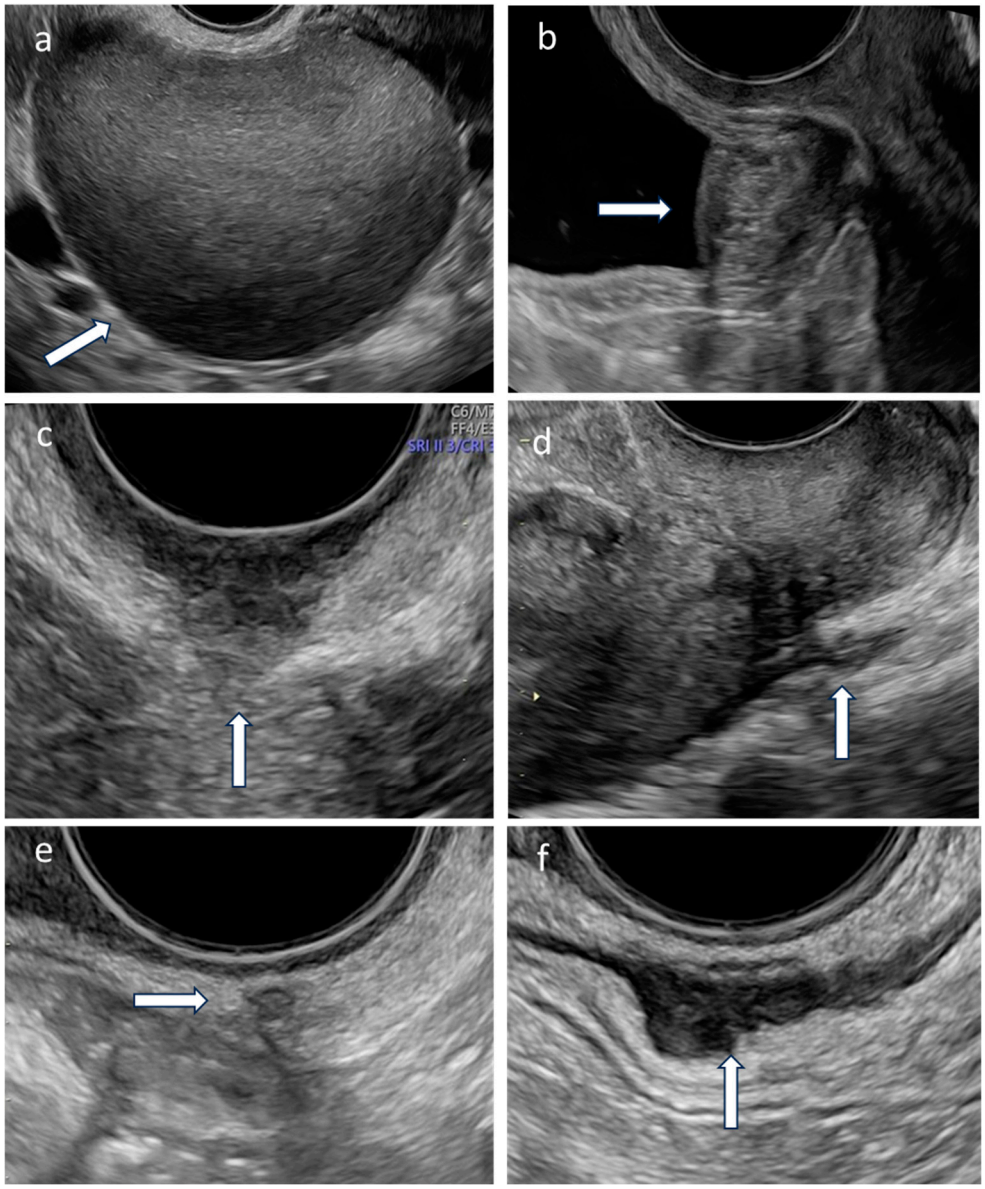

Figure 12. Ultrasonographic findings of endometriosis in different locations
Endometriosis lesions in the particular anatomic location are indicated by the arrow. a) Endometrioma, b) urinary bladder, c) vaginal wall, d) uterosacral ligament, e) rectovaginal septum, f) bowel wall

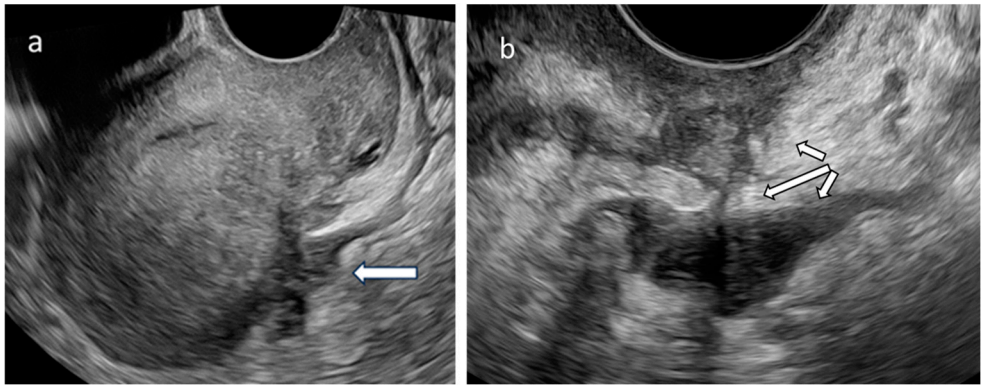

Figure 13. Endometriosis in different locations,

The specific endometriosis lesion is indicated by the arrow. a) Obliteration of the Pouch of Douglas, due to endometriosis in the bowel wall and in the uterosacral ligament, with the bowel adherent to the posterior uterine wall. Ear sign. b) “Diabolo-like” nodule, with a nodule in the vaginal wall extending into the anterior rectal wall.

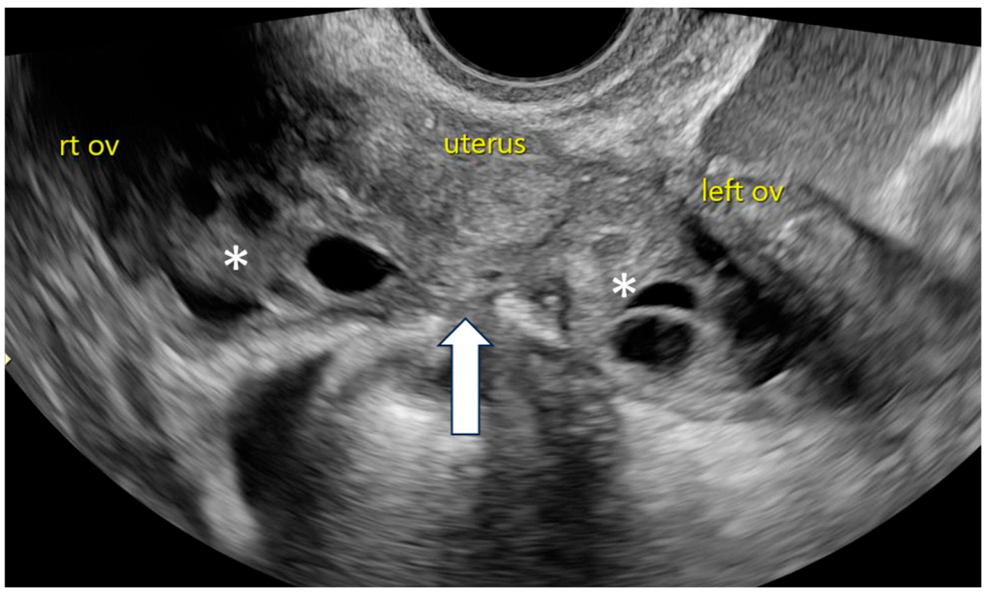

Figure 14. Kissing ovaries.

The uterus and ovaries in a transverse section on transvaginal ultrasonography. Rt ov= right ovary; left ov= left ovary. The ovaries are marked by asterisks.The arrow marks the point were the ovaries are adherent to each other and to the uterine posterior wall in the pouch of Douglas.

Adenomyosis

Ultrasonographic features of adenomyosis, were described using the original and revised MUSA definitions (8, 128, 131). All features were classified as either direct or indirect (Table 3). Direct features are pathognomonic for adenomyosis whereas indirect features are only indicative of the disease.

Table 3. Direct and indirect features of adenomyosis

Indirect features	Direct features
Globular uterus	Myometrial cysts
Fan-shaped shadowing	Hyperechogenic islands
Asymmetrical myometrial thickening	Subendometrial lines and buds
Irregular junctional zone	
Interrupted junctional zone	
Translesional vascularity	

Direct and indirect features of adenomyosis as suggested by the Morphological Uterus Sonographic Assessment (MUSA) group.

As myometrial cysts or lines and buds in the JZ constitute an irregularity, these were reported as indirect as well as direct features if present. Irregularities of the JZ were evaluated subjectively, as a general impression including focal thickness. If no portion of the JZ was visible, due to poor image quality or due to myomas, the JZ was describes as unassessable. Examples of the direct features of adenomyosis are shown in Figure 15, indirect features on 2D images in Figure 16, and indirect features on 3D images in Figure 17.

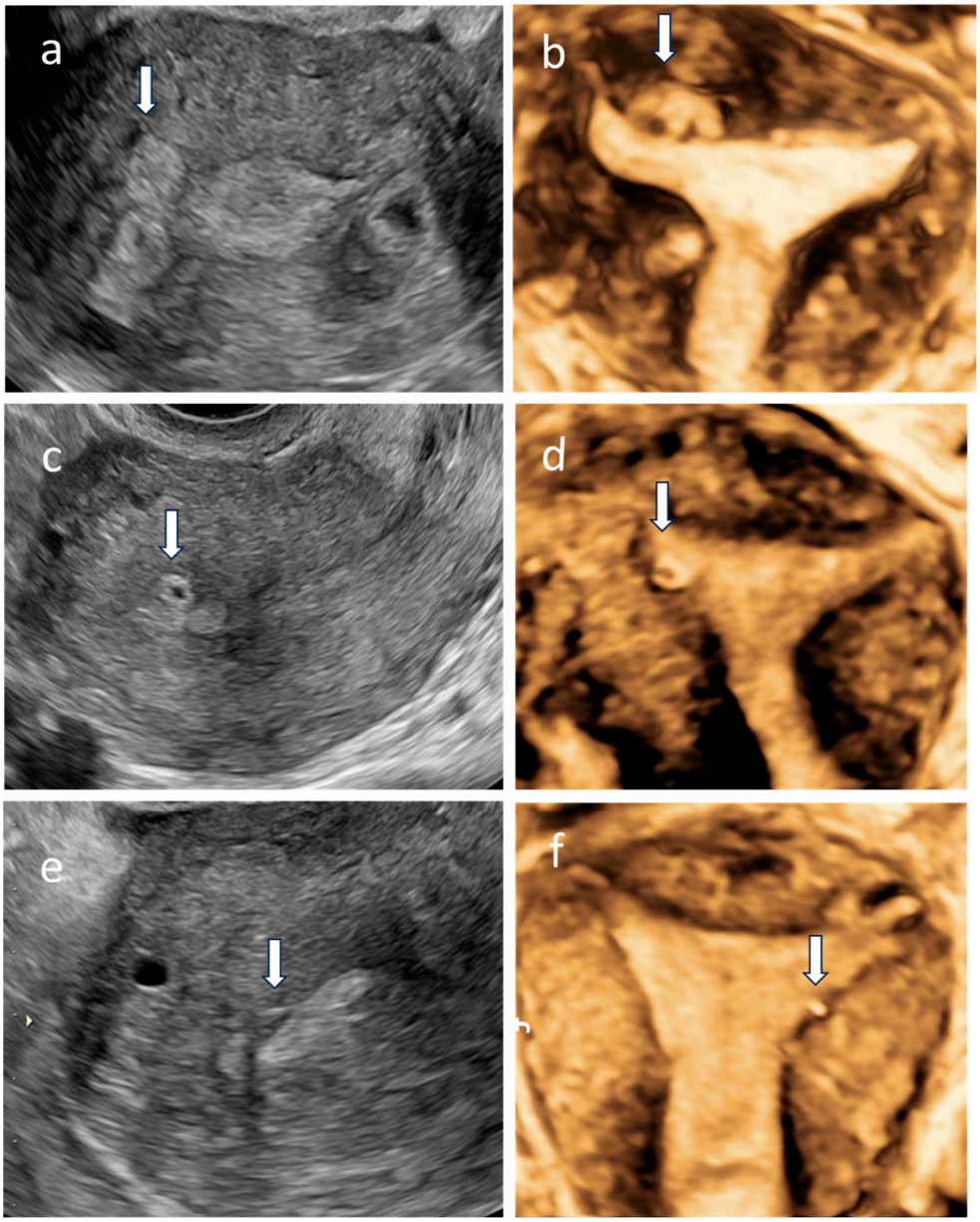

Figure 15. Direct features of adenomyosis.
Direct features of adenomyosis on two-dimensional images in the left row and on corresponding three-dimensional images of the coronal plane of the uterus in the right row. Some images may have several features. The arrow marks the feature. a and b) hyperechogenic islands; c and d) myometrial cysts; e and f) subendometrial lines and buds. Modified, with permission from Alson et al (147).

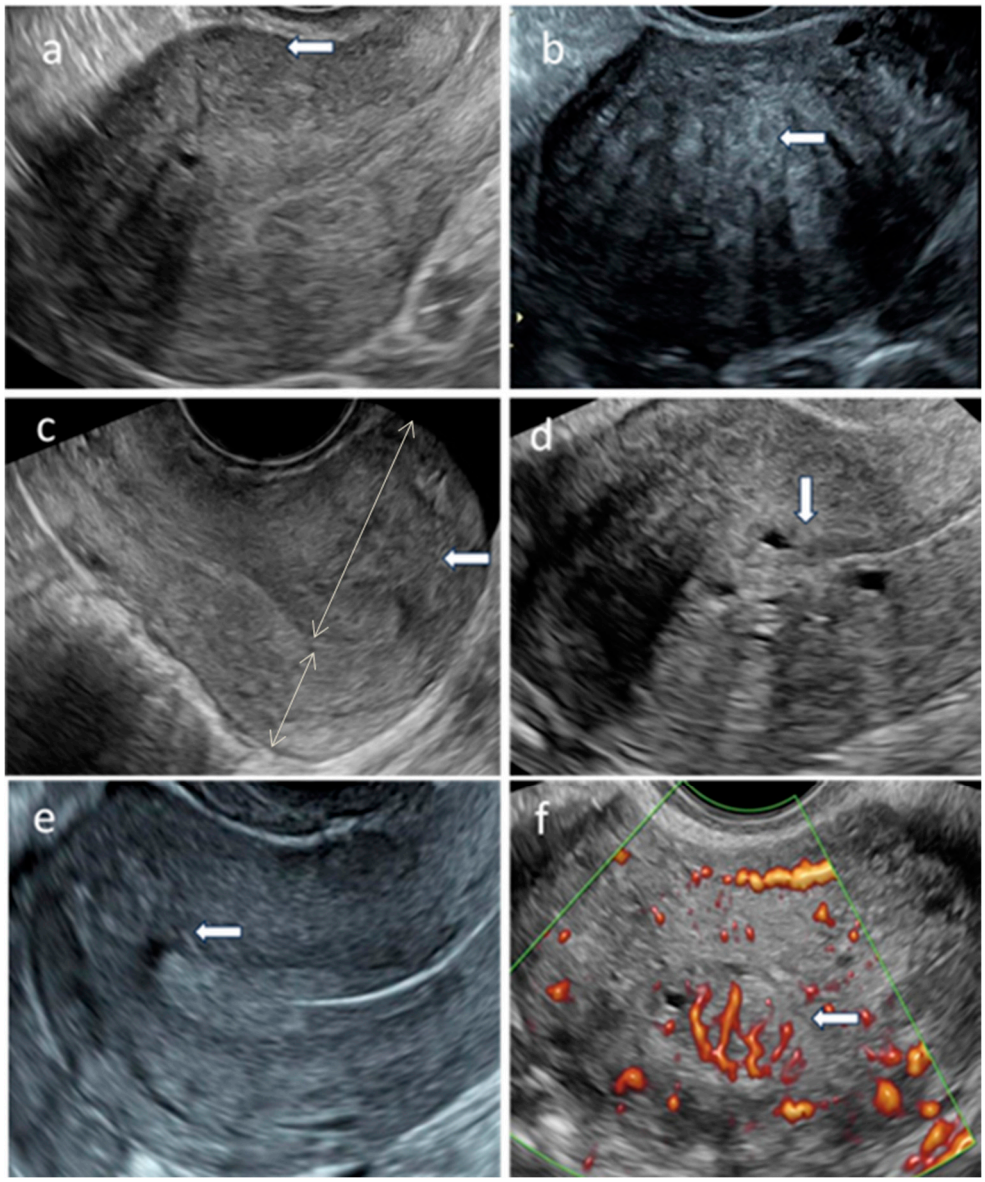

Figure 16. Indirect features of adenomyosis

Indirect features of adenomyosis on two-dimensional ultrasound images. The arrow indicates the particular feature. Some images may have several features. JZ= junctional zone. a) Globular uterus, b) fan-shaped shadowing, c) asymmetry, d) interrupted JZ, e) irregular JZ, f) translesional vascularity. Modified, with permission from Alson et al. (147).

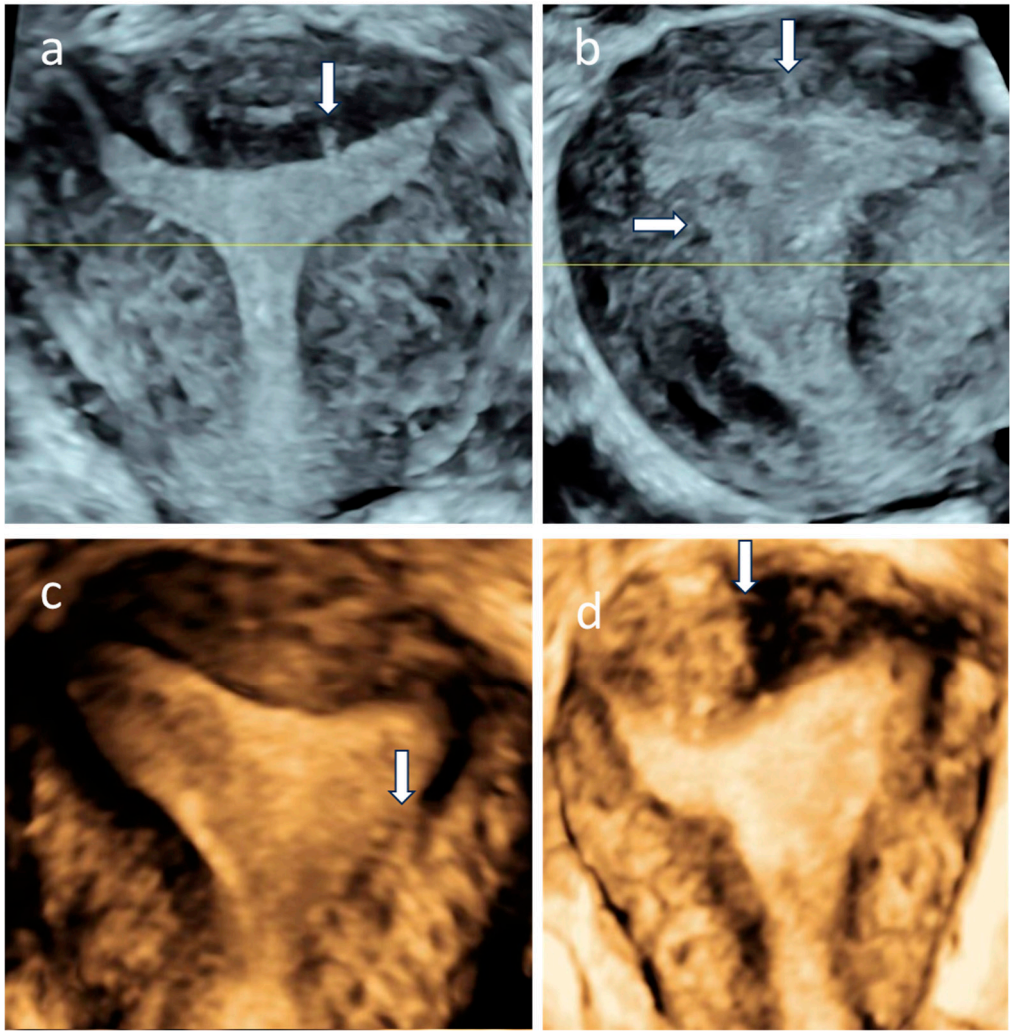

Figure 17. Indirect features of adenomyosis
Indirect features of adenomyosis on three-dimensional ultrasound images in the coronal plane of the uterus. The arrow indicates the particular feature. Some images may have several features. JZ= junctional zone. A) Irregular JZ due to lines and buds; b) irregular and interrupted JZ; c) interrupted JZ; d) interrupted JZ with infiltration and focal thickness.

The ultrasonographic characteristics and location of the different features of adenomyosis were reported, as described in Table 4.

Table 4. The ultrasonographic characteristics and location of the different features of adenomyosis that were evaluated at transvaginal ultrasonography.

Location	Type	Uterine layer involvement	Extent of disease
Anterior	Focal[a]	Inner myometrium (JZ)	Mild (<25%)
Posterior	Diffuse[b]	Middle myometrium	Moderate (25–50%)
Fundus	Mixed-type[c]	Outer myometrium	Severe (>50%)
Lateral right	Cystic		
Lateral left	Non-cystic		
Global			

JZ=Junctional zone,

[a] Normal myometrium surrounded >25% of the circumference of the lesion; [b] normal myometrium surrounded <25% of the lesion or it was difficult to differentiate focal from diffuse adenomyosis, [c] both focal and diffuse adenomyosis were present in different locations.

IVF/ICSI treatments

All women underwent ovarian stimulation according to either an agonist or antagonist protocol. We followed the European Society for Human Reproduction and Endocrinology (ESHRE) recommendations, that were updated during the study periods (148). Individual patient characteristics and preferences were taken into consideration when treatments were planned.

Protocols

When the first study was conducted (*cohort A*), the agonist protocol was more commonly used. However, when studies II-V were conducted (*cohort B*), the antagonist protocol had become standard procedure for the first IVF/ICSI treatment for most women. Generally, we used the antagonist protocol for women assessed to be high responders. The agonist protocol could be chosen for women assessed to be low responders or those downregulated with GnRH analogues (Synarela, Pfizer AB, Stockholm, Sweden). The agonist protocol was also offered to women with large endometriomas or severe pain suggestive of endometriosis-related inflammation.

Ovarian stimulation

For ovarian stimulation, we used individually set doses of FSH, either GONAL-f, (Merck-Serono, Darmstadt, Germany), Menopur, (Ferring, GmbH, Kiel, Germany) or Bemfola, (Gedeon Richter, Stockholm, Sweden) in both protocols. In *cohort A*, some women used Follitropin beta, (Puregon, Organon, Ireland Ltd), Urofollitropin, (Fostimon, Institut Biochimique SA (IBSA), Lugano, Switzerland) or Korifollitropin alfa, (Elonva, Merck Sharp & Dome, (MSD), New Jersey, USA). On day five or six in the antagonist protocol, we started subcutaneous injections with Fyremadel (SUN Pharmaceutical, Hoofddorp, Netherlands). We monitored follicle

development with TVUS. Ovulation was induced with subcutaneous human chorionic gonadotropin (Ovitrelle, Merck, KGsA, Darmstadt, Germany) when three or more follicles reached 17 mm in diameter. If imminent ovarian hyperstimulation, we used GnRH agonist (Suprefact, Ceplapharm Arzneimittel GmbH, Greifswald, Germany) for ovulation induction instead and total embryo freezing was preferred. In case of fewer than three mature follicles, treatments were either cancelled or converted to IUI. After 35-36 hours, transvaginal follicle aspiration was carried out.

IVF/ICSI treatment

Aspirated oocytes were assessed for maturity and either injected (ICSI) or inseminated (IVF) with sperm depending on the quality of the semen on the OPU day. The fertilization rate was assessed (the number of normally fertilized oocytes divided by the total number of mature oocytes retrieved). Embryos were assessed using the Gardner blastocyst grading scale (149). Embryos of good quality (GQE) were transferred either in cleavage stage (two or three days) or blastocyst stage (five days) after OPU. Single embryo transfer is clinical routine (150). Progesterone vagitories were given for two weeks after OPU as luteal phase support, (Crinone, (Merck AB, Solna, Sweden), for *cohort A* and Lutinus, (Ferring GmbH, Kiel, Germany) for *cohort B*. Any surplus embryos of good quality were cryopreserved 5-6 days after OPU. If there were any contraindications to fresh ET, we cryopreserved all GQEs. Depending on the woman´s ovulatory status, frozen-thawed embryo-transfers (FET) were carried out in either natural or hormone replacement cycles.

We used all fresh and frozen embryos from the same index treatment cycle until live birth (defined as the birth of a living child in gestational week >22) was achieved within two years after inclusion to the studies or no embryos remained. Therefore, some women did not use all their embryos whereas others underwent several ETs. IVF/ICSI outcomes were retrieved from medical journals. Miscarriages or extrauterine pregnancies were documented.

Developing an AI model

We used XGBoost to perform the modelling (138). First, the data set was divided into train- and test-set. We assigned 80% of the data for training and 20% as the test set. The train and test split were performed in a stratified fashion, which ensures that both datasets had the same distribution of the outcome variable. The training was performed using stratified 5-fold cross-validation, i.e., the training data was divided into 5 folds, where 4 folds were used to train a model, and the fifth was used as validation. This was then repeated 5 times, until every fold had been used once as the validation set (Figure 18).

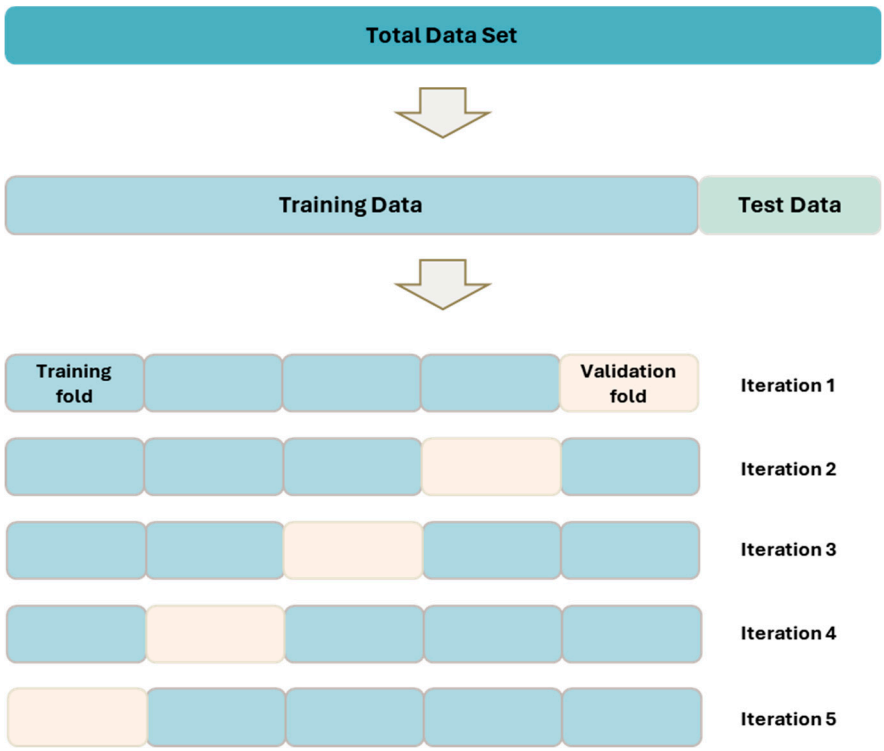

Figure 18. eXtreme Gradient Boosting modelling.

The hyperparameters of the XGBoost model, which are the parameters that specifies details of the learning process, were optimized using the open-source python library Optuna (151). This allows for automatic hyperparameter optimization. Optuna was set to optimize the average of the AUC from the validation sets. The XGBoost parameter "n_estimators" was set to a constant value of 500. To limit overfitting, the models were trained using early stopping when the validation score stops improving.

To predict the test set, an ensemble prediction approach was employed. This involves aggregating the predictions from five models created during cross-validation. The models that have the best performance during the cross-validation process are specifically selected. The final prediction for each patient in the test set was obtained by averaging the predictions generated by these selected models. Optuna was set to use Tree-structed Parzen Estimator, to sample the hyper-parameter space (152).

To reduce the dimensionality of the dataset, we needed to address unnecessary variables. Therefore, binary variables with less than 20 observations in one of the categories were removed. The second step was to find a suitable model and calculate the importance of the variables using SHAP-values (153). Variables that had a

negligible contribution to the model were considered for removal. This was the dataset used for the final model.

Statistical analyses

For statistical analyses, we used the statistical package IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY, USA.

Power

The statistical power of a study is a measure of its ability to detect a true effect or difference when it exists. In other words, it is the probability that the study will correctly reject a false null hypothesis (i.e., the probability of avoiding a Type II error). Several factors may influence the statistical power, such as the significance level (usually 0.05), the sample size of the examined population, the effect size, the variability, which is precision with which the data is measured, and the study design. Usually, the statistical power of a study is aimed at 80 or 90%, which means that there is an 80-90% probability of detecting a significant difference in the population.

To reach adequate power, the sample size for *cohort B* was calculated for the outcome CLBR in relation to features of adenomyosis. From a previous publication, we estimated that women with adenomyosis diagnosed at TVUS have a PR of 23.6% following IVF-treatment compared with 44.6% in women without adenomyosis (68). For an adequate power of 80% with a significance level of 0.05, we would need in total 158 women with adenomyosis to detect an equivalent difference. Assuming a prevalence of adenomyosis of 15% in our population (lower than the estimated 20% prevalence in a general, older, population) (27) and a calculated drop-out of 10%, we would need to recruit 1160 women.

Diagnostic tests

ROC-curves

To compare the predictive value of s-AMH, OSI and AFC in relation to chance of live birth, a receiver operator characteristic (ROC) – analysis was performed, and the AUC was calculated. The ROC curve is a diagram that is used in binary classification to evaluate the performance of a predictive model. The true positive rate (sensitivity) is plotted against the false positive rate (1 - specificity) for different threshold settings. The Area Under the ROC Curve is a measure of the overall performance of the model. A perfect model would have an AUC of 1, which equals 100% sensitivity and 100% specificity, while a random model would have an AUC of 0.5. The higher the AUC, the better the model's ability to distinguish between the two classes. Values below 0.5 mean that chance is better at predicting the outcome.

Association between exposure and outcome

Relative risk and odds ratio

In paper IV and V, we wanted to compare the outcome measure (CLBR) in different exposure groups (women with or without endometriosis or adenomyosis respectively). The association between exposure and outcome can be quantified using measures such as risk ratios, also known as relative risk (RR), and odds ratios (OR).

The risk is the probability of the outcome occurring, and the risk ratio provides a measure of how much more (or less) likely the outcome is in the exposed group compared to the unexposed group. The RR is calculated as the risk in the exposed group divided by the risk in the unexposed group. The OR is calculated as the odds of the outcome occurring in the exposed group divided by the odds of the outcome in the unexposed group. These measures provide insights into the strength and direction of the association between exposure and outcome. A RR or OR >1 indicates an increased risk or odds in the exposed group compared to the unexposed group, while a value < 1 suggests a decreased risk or odds. A RR or OR= 1 suggests that there is no association between the exposure and the outcome.

When the outcome is rare, the OR approximates the RR. If the outcome is common, the OR tends to overestimate the RR. In those situations, the RR is a more accurate measure of association.

Regression analyses

Logistic regression

Regression analyses are statistical methods used to examine the association between one or more independent variables (predictors) and a dependent variable (outcome). To predict the probability of a binary outcome, logistic regression is used. Logistic regression can be performed with or without backwards selection. This method aims to identify a subset of predictor variables that best explain the variation in the outcome variable. Starting with a full model, predictors are iteratively removed one at a time, starting with the one that has the highest p-value (least statistically significant) in the model. The process continues until no further improvement in model fit is observed, or until a predefined stopping criterion is met. In paper III, a logistic regression analysis with backwards selection was used to examine the odds for having any features of adenomyosis, before and after adjusting for potential confounders. However, the stepwise procedures have been criticised, as they can be influenced by random variation in the data. There is a risk of overfitting, selection bias and loss of information.

Modified Poisson regression analysis

A Poisson regression analysis can be used for comparing rates in different exposure groups, where the outcome variable represents the number of independently occurring events within a fixed time unit. However, for binary or count data, there may be concerns about overdispersion. Overdispersion occurs when the variance of the observed outcomes is greater that what would be expected under a Poisson distribution. This issue can be addressed using a Poisson regression analysis with robust error variance, also called a modified Poisson regression analysis. This allows for more flexibility in handling overdispersion. The model allows to control for potential confounders and can be used to analyse the RR. In paper IV and V, a modified Poisson regression analysis was used to estimate the RR for cumulative LB in women with endometriosis or adenomyosis respectively, as compared to women without the diseases, before and after adjusting for potential confounders.

Hypothesis testing

P-value

Significance tests are used to evaluate the strength of the evidence against a null hypothesis, which is an assumption that there is no significant difference, effect, or relationship in the population from which a sample is drawn. The p-value (probability value) is a measure to assess the evidence against the null hypothesis. The p-value indicates the probability of observing a result at least as extreme as the one observed, assuming that the null hypothesis is true. The significance level is often set at 0.05, which means that there is a 5% probability that we accept the null hypothesis. However, failing to reject the null hypothesis does not necessarily prove that the null hypothesis is true. It could also mean that there is not enough evidence in the sample data to support the alternative hypothesis.

A p-value between 0.005 and 0.05 have, by some, been suggested to be called “suggestive evidence” in explorative studies, to reduce the number of false positive findings in medical research. Others have proposed focusing less on fixed significance thresholds and instead interpret p-values as "continuous indices of the strength of evidence against the null hypothesis". Others have proposed focusing more on confidence intervals, and less on p-values (154).

Confidence intervals

A confidence interval (CI) is used to estimate the range within which a population parameter, such as a population mean or proportion, is likely to lie. It provides a measure of the uncertainty associated with estimating population parameters based on sample data.

The confidence level (often denoted as 1 - α, where α is the significance level) represents the probability that the true population parameter falls within the

confidence interval. Commonly used confidence levels are 90%, 95%, and 99%. In this thesis, we used a confidence level of 95%. This means that we are 95% confident that the true parameter of the population falls within the confidence interval.

Student´s t-test

The student's t-test is a parametric test used to compare the means of two independent groups, assuming that the data is normally distributed or that the groups are sufficiently large.

Mann-Whitney U-test

The Mann-Whitney U-test is the non-parametric equivalent of the student´s t-test, used for data that is not normally distributed. The test is based on ranks and determines if there is a significant difference between the distributions of two independent groups. The Mann-Whitney U test is robust, which means that it is less sensitive to extreme values or outliers than some parametric tests.

Chi-squared test and Chi-squared test for trend

The chi-squared test is a non-parametric statistic that is calculated based on the observed and expected frequencies of the categories in a contingency table. For small groups, Fishers exact test can be used instead.

To test for a linear trend for increasing LBR with higher s-AMH-levels (divided into three AMH-groups) against the null hypothesis of no trend, a chi-squared test for linear trend was performed in paper I. This test is appropriate for testing association between a nominal variable and an ordinal variable and can be used to assess the presence of a significant linear trend in proportions across ordered categorical data.

Prediction model

The prediction models were evaluated, and results presented as the area under the ROC curve and accuracy of the evaluation sets and test sets. The evaluation metrics were calculated based on the predictions of all patients whenever they were used as evaluation set during the cross-validation. The threshold to dichotomize the predicted probabilities was decided using Youden's J statistic based on the ROC curve for the evaluation set (155). Model performance was compared using the area under the ROC curve. Model interpretations were generated using SHAP by transforming model features into clinical variables and representing them as patient-specific visualizations.

Ethical considerations

The study protocol for paper I was approved by the Regional Ethical Review Board of Lund university, Lund, with a reference number 539/2008. Papers 2-5 were approved by the Regional Ethical Review Board of Lund university, Lund, Sweden, on September 11, 2018, with a reference number 2018/555.

All women were given oral and written information about the studies, and written informed consent was obtained from all women. Women that could not understand the information due to language difficulties were not included.

All women were informed about the possibility to withdraw from the study at any time and that their choice to participate or not participate would not affect their treatment. However, there is always a possibility that patients feel obliged to participate in a clinical study, especially when asked in a dependent situation. They come to the fertility clinic with great hopes and fears, and many would probably do anything their physician ask for, if they thought it would help them get pregnant. All women were reassured that choosing not to participate in a study would never affect their care. Almost all women were happy to participate, for different reasons. Some women chose to participate as the ultrasound examination was part of the work-up anyway. Therefore, any data needed for the study could just as well be saved. Most women were eager to help other couples in the same situation. Further, some women had long suspected that they had endometriosis but had never been offered any help. They were grateful for the opportunity of a thorough examination.

One ethical dilemma is that some women had never heard of endometriosis or adenomyosis. Suddenly they found themselves having a diagnosis they had never asked for. There is a risk that this knowledge would inflict a sense of guilt on them, that it was their "fault" that they could not conceive spontaneously. It felt suboptimal not being able to offer them many treatment options or being able to answer how the diagnosis would affect their chances of having a child. On the other hand, the study was carried out to increase our knowledge on this matter. Not trying to increase our knowledge because someone might get offended could also be considered unethical. The Word Medical Association declaration of Helsinki states that "Medical progress is based on research that ultimately must include studies involving human subject" (156). Our study did not inflict any harm or unnecessary physical discomfort as the examinations had to be done anyway. As a physician, I am obliged by law to inform the patient on all findings and to involve her in the care. This includes unexpected findings, such as cancer. As I performed all the ultrasound examinations, any pathologies were found regardless of study participance. Most women with findings of endometriosis were grateful to finally get a diagnosis and an understanding of the reason for the pain they lived with.

Methodological considerations

Bias

For this thesis, we carried out observational studies. Such studies are descriptive without intervention and measure associations between exposure and outcome.

Observational studies may be subject to bias, which is systematic errors in their design and methods. Bias may lead to misinterpretation of the results (lack of internal validity). The main categories of systematic errors in observational studies are selection bias, information bias and confounding. Selection bias occurs when the study participants are not representative of the population, particularly regarding the distribution of exposures. Information bias, or misclassification, is the result of inaccurate methods of measuring exposure or outcome. A confounder is a factor that, independently, is related to both the exposure and the outcome variables. It must not be on the casual pathway and inherently biases the measure of association between the exposure and outcome.

To minimize the effect of potential confounders, inclusion criteria can be strict and adjustments for those that are known can be undertaken. In regression models, potential confounders can be included as covariates. In our studies, we did not include smokers, women with BMI >30 kg/m^2 or age ≥ 40 years, which are factors known to potentially impact IVF/ICSI outcomes. In paper IV and V, when analysing IVF/ICSI treatment outcomes, adjustments were made for several potentially confounding factors. However, we did not adjust for male factors, which may represent a bias.

In paper I, women with irregular menstrual cycles were excluded. Some of these women probably had polycystic ovarian syndrome, which is associated with a high ovarian reserve. This may have affected the CLBR after ART. As not all women referred to RMC for ART were included in paper I, selection bias cannot be excluded. Perhaps more women with concurrent diseases that may affect fertility declined participation or were not asked by the doctor. Further, the reason for drop-outs is not known. For paper II-V, the same examiner included all women consecutively. Only 11 women declined participation and another 5 were not included due to language difficulties. This makes selection bias unlikely. The prospective design, with consecutive inclusion of a large cohort of women and well-defined diagnostic criteria, is another strength.

Counting the number of antral follicles in the ovaries adequately depends on the examiner and on the quality of the ultrasound machine. It is probably easier to count AFC if there are few antral follicles than if the ovaries are polyfollicular. A certain interobserver variability regarding AFC in paper I cannot be excluded.

We did not have any laparoscopic or histopathological confirmation of our findings in paper II-V. However, laparoscopy is not a part of the routine infertility work-up

and hysterectomy is not an alternative for our population. Moreover, even surgical, and histopathological findings are subject to interobserver variability, and no uniform diagnostic histopathological criteria exist. However, we cannot exclude that some women without visible endometriosis lesions at TVUS did in fact have superficial peritoneal lesions. Moreover, small endometriotic lesions on the peritoneum, vaginal wall or USLs were probably easier to detect when the bowel was empty, or when there was a small amount of fluid in the POD, which is more common after ovulation.

Not all women proceeded with IVF/ICSI treatment. For some women, this was due to spontaneous pregnancy. As this was equally common for women with or without endometriosis, it is unlikely that these drop-outs present a bias. However, offering IUI prior to starting IVF/ICSI treatment was more common to women without endometriosis or adenomyosis than to those with the diseases.

In paper I, IV and V, we used different IVF/ICSI protocols for different women. The agonist protocol has been associated with a higher oocyte yield than the agonist protocol, which subsequently may affect CLBR.

In cohort B, 23 same gender couples or single women were included. One could argue that these women do not fulfil the criteria for subfertility. However, as they were equally distributed among women with or without endometriosis or adenomyosis, they are unlikely to have introduced a bias. Likewise, one could argue that including women with secondary infertility may present a bias. Features of adenomyosis were more common among these women. The reason is that we included all women that were eligible for ART.

Backwards selection was used in regression analysis in Paper III. This method has been criticized for several reasons. As variables are iteratively selected or removed based on their statistical significance or contribution to the model fit, there is a risk of "overfitting", or an exaggeration regarding the model performance. Moreover, the variable selection does not necessarily incorporate knowledge about the relationships among variables. This can lead to the inclusion or exclusion of variables that do not make sense from a theoretical perspective.

Internal and external validity

The results of papers II – V may not be generalizable to all centres. High-end ultrasound equipment and expertise in the ultrasound diagnostics of endometriosis and adenomyosis may not be available at all clinics. A strength of the studies is having a single examiner for all women, which eliminates any interobserver variability and ensures consistency regarding ultrasound examinations and data collection. However, a certain inter-individual variation in interpreting ultrasound findings and MUSA definitions regarding indirect features is likely.

The cutoff-levels used to define "asymmetrical myometrial thickening" are only arbitrary (7). Transient uterine contractions can mimic globular uterus or asymmetry. As we used the MUSA definitions in this thesis, some indirect features may have been overdiagnosed. However, including only women that were not on current hormonal treatment is a strength, as this ensures that women that had successfully been treated for adenomyosis were not wrongly classified.

Another weakness of the MUSA definitions is that direct features of adenomyosis may simultaneously constitute indirect features, if located in the JZ. Therefore, the number of features of adenomyosis may be overestimated. This is a limitation of the MUSA definitions that we think should be reconsidered in a revised version. To overcome this, we evaluated indirect features before and after women with direct features had been excluded.

The questionnaire that we used to evaluate symptoms had not been validated in larger studies. To some women, it was unclear what was meant by "hormonal treatment" and why for example thyroid hormones was not what we meant. Moreover, the same questionnaire was used for all women, and some symptoms which may be more common in women with adenomyosis, such as abnormal uterine bleeding, were not included in the questionnaire.

Sample size and Type II errors.

For *cohort A*, no power calculation was performed. A lack of adequate sample size may increase the risk of type II error, which is a failure to reject the null hypothesis when it is false. However, this may be more of a concern when there is no statistically significant difference between groups. In our study, we found a weak association between AMH levels and CLBR. It is possible that the association would have been stronger had the sample size been larger. We performed a post hoc power calculation, showing that with the given sample size, the study had a statistical power of 0.4 to detect the differences in AMH levels between LB vs no-LB groups as found by us. A power of 0.4 means that there is a 40% chance of correctly detecting a true effect if one exists. Generally, a power of 0.8 or higher is considered acceptable, as it indicates a better ability to detect true effects.

The prevalence of adenomyosis was an estimated 15% for an adequate power for paper V. This prevalence was based on the original MUSA definitions. However, according to the revised MUSA definitions, only direct features of adenomyosis are considered as diagnostic for the disease. Direct features of adenomyosis were present in 9.8% of women in paper V. Therefore, the sample size may not have been adequate to detect differences between the groups.

Machine learning, sparse data, overfitting, and model complexity

Overfitting is a common problem in machine learning. This means that a model learns to perform well on the training data but fails to generalize to new, unseen

data. In other words, the model fits too closely to the training data, capturing noise or random fluctuations in the data rather than the underlying pattern or relationship. This can result in poor performance when the model is applied to new data. Overfitting typically occurs when a model is too complex relative to the amount and variability of the training data. To mitigate overfitting, early stopping was employed when our model was developed. This means monitoring the model's performance on a separate validation set and stopping the training process when the performance starts to degrade.

Datasets predominantly composed of categorical and binary variables, such as the one used in this thesis, may present challenges for predictive modelling. One of the main challenges encountered in paper V was the sparsity observed in the binary data, where some variables only had a few observations in one of the categories, such as “DE in the vaginal wall”. It’s important to note that sparsity does not necessarily imply that variables are undesired. Removing them solely due to sparsity may not be the most appropriate approach.

Given the limited size of the patient cohort in this study, we needed to address unnecessary variables to reduce the dimensionality of the dataset and simplify the model. To achieve this, we first removed very sparse binary variables, defined as variables with less than 20 observations in one of the categories. Instead of subgrouping different phenotypes of DE, they were grouped together as “DE”. The second step was to find a suitable model and calculate the importance of the variables using SHAP-values (153). Variables that had a negligible contribution to the model were considered for removal.

Results

Live birth rate in relation to ovarian reserve parameters

In total 454 women were included in *cohort A* (paper I). Of these, 162 (35.7%) women had a LB. The median (range) s-AMH was higher in women with LB [s-AMH 26.2, (0-137) pmol/l], compared to women without LB, [s-AMH 22.1, (0-154) pmol/L], p=0.035.

A similar pattern was observed for the 1191 women in *cohort B*. Women with LB had a higher median (range) s-AMH [21.4, (0.5 – 151) pmol/L] compared to women without LB, [median (range) s-AMH 15.3, (0.2 – 244) pmol/L], p<0.001.

When dividing *cohort A* into three AMH-groups representing women with expected low, normal, and high response to ovarian stimulation, CLBR increased with 8 %, (95 % CI: 2 -14), per AMH-group, p=0.015.

The ovarian reserve parameters in the three AMH-groups are presented in Table 5.

Table 5. Comparison of ovarian reserve parameters in different AMH-groups in cohort A

Parameter	Total Cohort n=454	AMH ≤10 n=83	AMH 10-<30 n=201	AMH ≥30 n=170
AFC[a]	16 (7)	10 (8)	14 (5)	20 (7)
Total dose FSH	1660 (760)	2470 (1070)	1630 (610)	1330 (420)
Oocytes	11 (6)	6 (4)	10 (5)	13 (7)
OSI	6.7 (6.1)	2.7 (2.5)	6.3 (6.6)	9.0 (5.6)
LBR	36 (48)	26 (44)	34 (48)	41 (49)

AMH= antimüllerian hormone (pmol/L), AFC= Antral follicle count (n), FSH= Follicle Stimulating hormone (IU), OSI= Ovarian sensitivity index, LBR= Live birth rate (%). [a] n=445 due to missing values. Data is presented as mean (±SD).

Predictive value of ovarian reserve parameters on live birth

The ability of s-AMH, AFC and OSI to predict LB was assessed by ROC curve. The overall LB prediction was low. For *cohort A*, the area under the ROC curve for s-AMH was 0.57 (95% CI, 0.51–0.62), for AFC 0.56 (95% CI, 0.51–0.62) and for OSI 0.63 (95% CI, 0.58–0.69), (Figure 19a).

For *cohort B*, the results were similar. The AUC for s-AMH was 0.61 (95% CI, 0.58–0.65), for AFC 0.62 (95% CI, 0.59–0.65) and for OSI 0.66 (95% CI, 0.63–0.69), (Figure 19b).

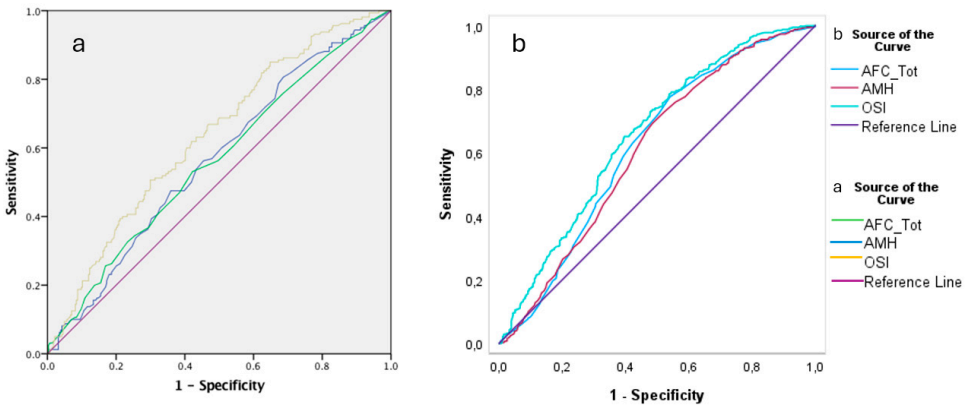

Figure 19. Receiver operating characteristics (ROC) Curve, demonstrating the predicitive value of s-AMH, AFC and OSI on live birth, presented as area under the curve.

ROC= Receiver operating characteristics curve; s-AMH= serum antimüllerian hormone; AFC= antral follicle count; OSI= ovarian sensitivity index. a) Cohort A, The AUC for s-AMH = 0.57, AFC = 0.56, and OSI 0.63, b) Cohort B (unpublished data); The AUS for s-AMH=0.61, AFC= 0.62; OSI= 0.66.

Prevalence of endometriosis and adenomyosis at ultrasonography

The baseline characteristics of the study population of *Cohort B*, based on the largest study group corresponding to paper II, are presented in Table 6.

Table 6. Baseline characteristics of the study population (cohort B).

Parameter	Total cohort, n=1191
Age (years)	32.0 (±3.9)
BMI (kg/m2)	23.6 (16.6 – 35.0)
Menstrual cycle length (days)	28 (18 – 150)
Length of infertility (years)	2.5 (0–16)
Main Indication for ART	
Unexplained	547 (45.9)
Male	357 (30.0)
Mixed	40 (3.4)
Tubal	87 (7.3)
Endometriosis	58 (4.9)
Oligo-/amenorrhea[a]	77 (6.5)
Other[b]	25 (2.1)
Previous childbirth	55 (4.6)
Previous extrauterine pregnancy	47 (3.9)
Previous termination of pregnancy	124 (10.4)
Previous surgery	257 (21.6)

BMI= Body Mass Index; ART= Assisted Reproductive treatment.
[a] Women with polycystic ovarian syndrome are included in this group; [b] Other= single women, same gender couples. Data is presented as mean (±SD), median (range) or n (%).

Data is presented as percentages of all women included in paper II or III, unless otherwise stated.

Prevalence of endometriosis

Out of 1191 women included in paper II, endometriotic lesions were present in 260 [21.8%, (95% CI, 19.5 – 24.2)] women. Endometrioma was present in 125 [10.5%, (95% CI, 8.8-12.2)] women and DE in 205 [17.2%, (95% CI, 15.1 – 19.4)] women. Concomitant DE and endometrioma were present in 70 [5.9%, (95% CI 4.5 – 7.2)] women. Only 63 (5.3%) women had previously confirmed endometriosis. The anatomical distribution of endometriosis lesions is presented in Figure 20.

Bowel lesions were most commonly located in the anterior rectum (n=58, 4.9%). All endometriotic lesions in the vagina and in the urinary tract were associated with endometriotic lesions in other locations. Lesions in the vaginal wall were associated with a diabolo-like nodule in 18 (1.5%) women. A negative sliding sign with POD obliteration was found in 57 (4.8%) women. Most women had one (n=121, 10.2%) or two (n=82, 6.9%) endometriotic lesions. More than three lesions were present in 57 (4.8%) women.

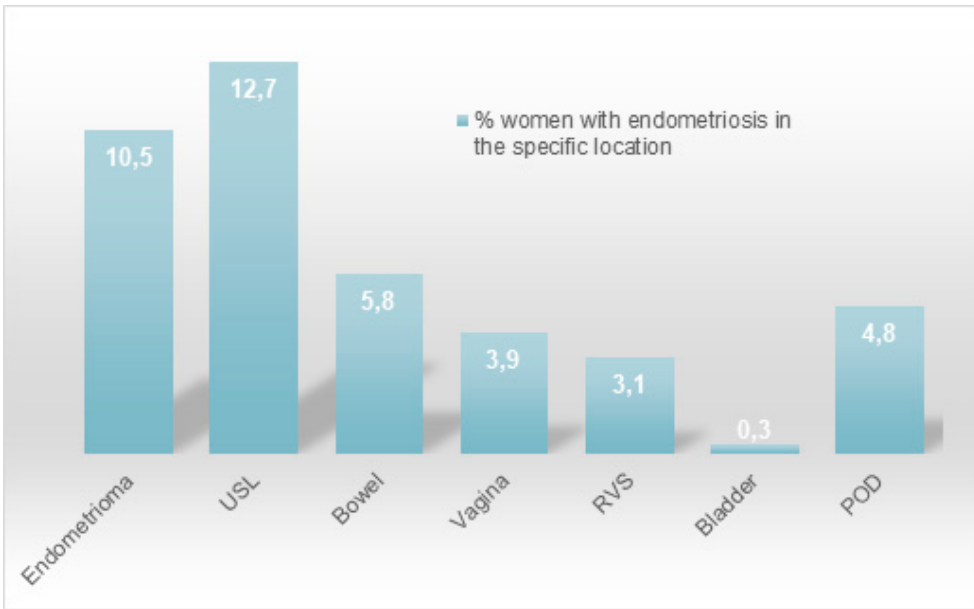

Figure 20. Distribution of endometriosis in different anatomical locations.
USL= Uterosacral ligaments; RVS= Rectovaginal septum; POD= Obliteration of the Pouch of Douglas. Data is presented as % of the total cohort of 1191 women. Some women may have had endometriosis lesions in several locations.

Prevalence of different features of adenomyosis

After excluding 31 women that were using hormonal treatment, 1160 women were included in paper III. At least one direct feature of adenomyosis was present in 111/1160 [9.6% (95% CI, 7.9 – 11.3)] women. The prevalence of at least one feature of adenomyosis (direct and/or indirect) was 272/1160 [23.4% (95% CI, 21.0 – 25.9)] women. The prevalence and distribution of different features of adenomyosis are presented in Figure 21.

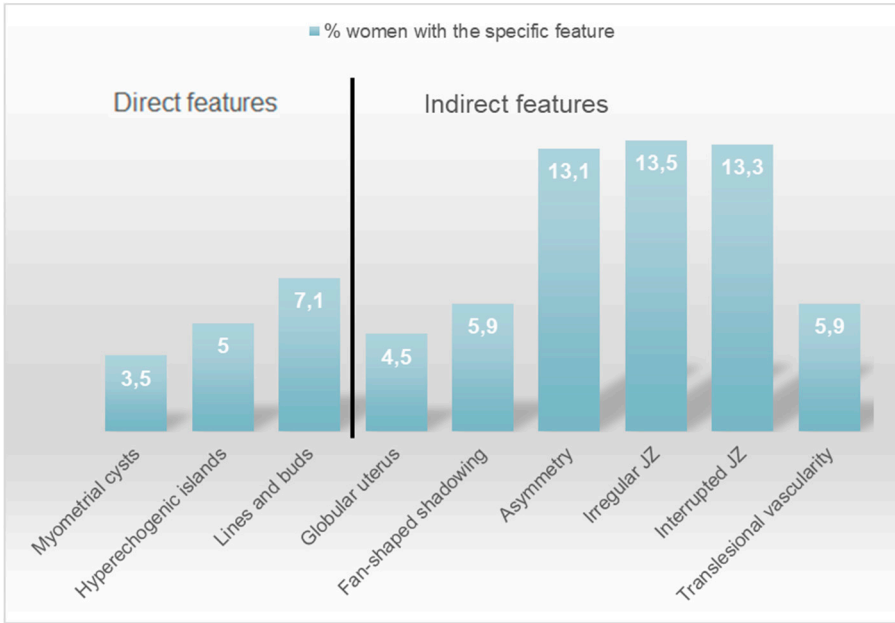

Figure 21. Distribution of different features of adenomyosis.
JZ= Junctional zone. Data is presented as % of the total cohort of 1160 women. Some women may have had several different features.

Direct features were visible only in the coronal plane on 3D TVUS in 56 [4.8% (95% CI, 3.6 – 6.1)] women and only on 2D TVUS in 7 [0.6%, (95% CI, 0.2 – 1.1)] women. Indirect features were visible only on 2D TVUS in 77 [6.6%, (95% CI, 5.2 – 8.1)] women and only on 3D TVUS in 62 [5.3%, (95% CI 4.1- 6.6)] women. The JZ was unassessable both on 2D and 3D TVUS in 33 [2.8% (95% CI, 2.0 – 4-0)] women.

The number of direct features increased with age. In women aged 25 – 29 years, 12 (3.5%) women had at least one direct feature, whereas 40 (8.0%) women aged 30-34 years and 59 (18.3%) women aged 35 years or older had at least one direct feature of adenomyosis.

Direct features mostly had a mild extent (n=34/111, 30.6%), were diffuse (n=57/111, 51.4%), and located in the inner to middle myometrium (n= 44/111, 39.6%) in the lateral walls of the uterus (n=78/111, 70.3%).

Concurrent endometriosis and at least one direct and/or indirect feature of adenomyosis were present in 95/1160 [8.2%, (95% CI, 6.6-9.8)] women. In total 44/111 (39.6%) women with direct features and 51/272 (18.8%) women with indirect features of adenomyosis simultaneously had visible endometriosis.

The odds for having any feature of adenomyosis for women with or without various demographic variables are presented in Table 7.

Table 7. The odds for having at least one direct and/or indirect feature of adenomyosis for women with different demographic variables.

	Direct features[a], n=111			Indirect features[b], n=156		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.2	1.1 - 1.3	<0.001	1.0	0.98 – 1.1	0.37
Childbirth	1.6	0.74 - 3.5	0.24	2.9	1.5 – 5.3	0.001
Miscarriage	0.97	0.55 - 1.7	0.90	1.2	0.76 – 1.9	0.43
Termination of pregnancy	1.9	1.1 – 3.3	0.03	0.81	0.45 – 1.4	0.47
Endometriosis	2.8	1.8 – 4.3	<0.001	1.9	1.3 – 2.8	<0.001

OR= Odds ratio; CI= Confidence interval; [a] Direct features with indirect features,[b] Indirect features without direct features.
OR was calculated using binary logistic regression analysis. P <0.05 is considered statistically significant.

Symptoms related to endometriosis and adenomyosis

Women with endometriosis on TVUS more frequently reported the presence of typical symptoms compared to women without endometriosis. The frequency of reported symptoms is presented in Figure 22.

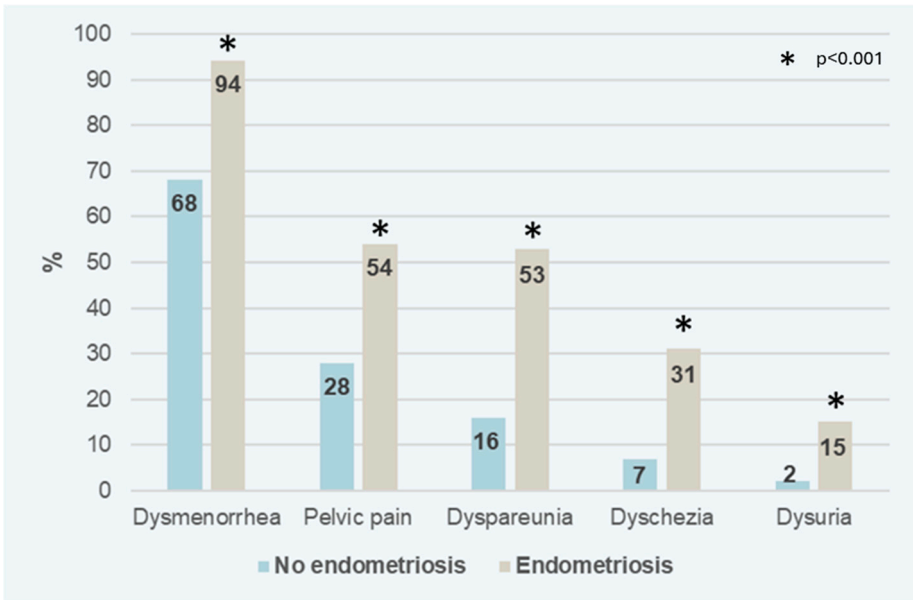

Figure 22. Frequency of symptoms reported by women with or without endometriosis.
Pelvic pain= chronic pelvic pain. Data is presented as % of women in each category. No endometriosis, n=931, Endometriosis, n=260. The asterisk * indicates statistically significant difference, p<0.001. Comparison within each group was made with the Chi2-test.

Women with direct features of adenomyosis more frequently reported dysmenorrhea than women without direct features. The frequency of reported symptoms in women with or without direct features of adenomyosis is presented in Figure 23.

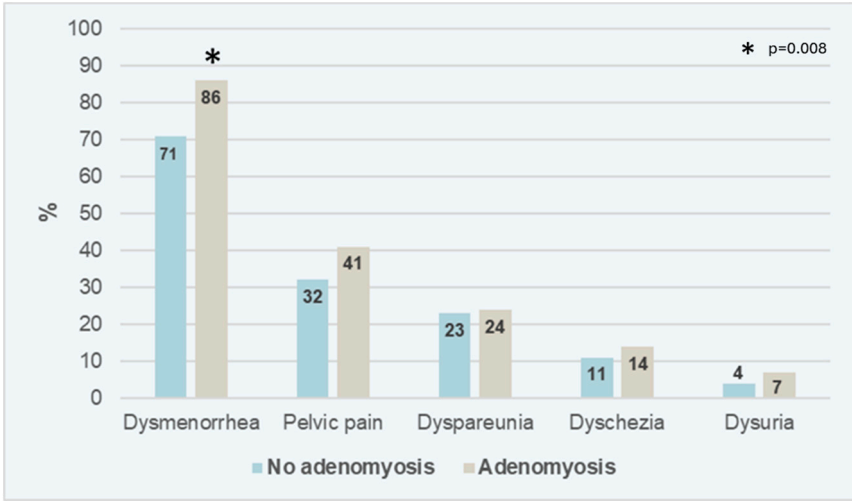

Figure 23. Frequency of symptoms reported by women with or without direct features of adenomyosis.
Data is presented as % of women in each category. No adenomyosis, n=1049, Adenomyosis (i.e. direct features of adenomyosis), n=111. The asterisk * indicates statistically significant difference, p=0.008. Comparison within each group was made with the Chi2-test.

Ovarian reserve parameters in relation to endometriosis and adenomyosis

Women with endometriosis (i.e. endometrioma and/or DE) or adenomyosis (i.e. direct features of adenomyosis) had lower AFC, s-AMH and OSI than women without the diseases, Table 8.

Table 8. Ovarian reserve parameters in women with or without endometriosis or adenomyosis

Parameter	No endo[a] n=806	Endo[a] n=234	p-value	No adeno[b] n=935	Adeno[b] n=102	p-value
Age	31.9 (4.0)	32.3 (4.0)	0.228	31.7 (3.9)	34.4 (3.8)	<0.001
s-AMH	19.0 (10-31)	17.0 (9.2-25)	0.034	19.0 (10-30)	14 (5-19)	<0.001
AFC	18 (11-26)	14 (12-27)	0.001	17 (10-25)	14 (12-26)	<0.001
OSI	6.0 (6.5)	5.2 (5.8)	0.004	6.1 (6.5)	4.4 (5.8)	0.003

[a]Total number of women in this cohort was 1040. [b]Total number of women in this cohort was 1037. Endo= endometriosis; adeno= adenomyosis; s-AMH= serum-antimüllerian hormone (pmol/L); AFC= antral follicle count (n); OSI= ovarian sensitivity index; Age (years). Data is presented as median (interquartile range) or mean (±SD).

Live birth rate in relation to endometriosis and adenomyosis

Data is presented as percentages of all women included in paper IV and V, unless otherwise stated.

Endometriosis

The main outcomes after the first IVF/ICSI treatment for women with or without endometriosis are presented in Figure 24.

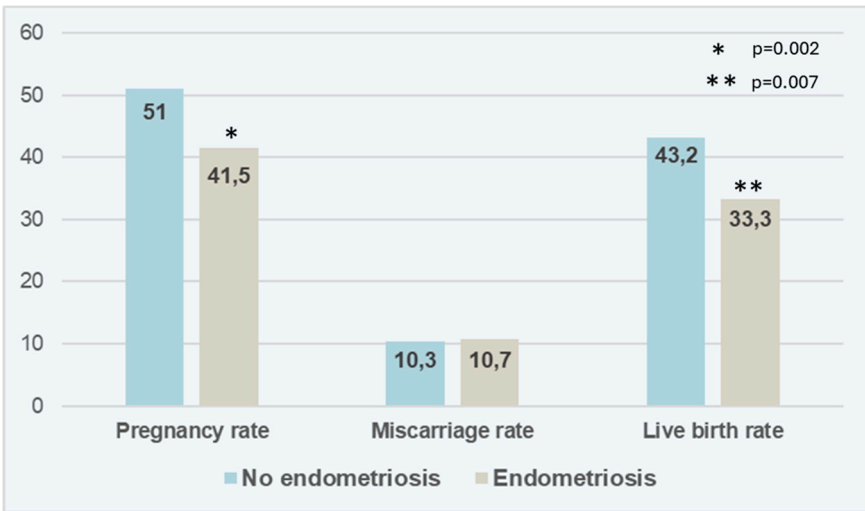

Figure 24. Main outcomes after the first IVF/ICSI treatment in women with or without endometriosis.
IVF= *in vitro* fertilization; ICSI= Intracytoplasmic sperm injection. Numbers are given as % of women with or without endometriosis at transvaginal ultrasonography. No endometriosis, n= 806, Endometriosis, n= 234. The asterisk * indicates statistically significant difference. Comparison within each group was made with the Chi2-test. Unadjusted cumulative data after the first treatment are shown.

Cumulative data for the main outcomes after the first IVF/ICSI treatment, with crude and adjusted relative risks for pregnancy, miscarriage, and CLBR, are presented for women with or without endometriosis in Table 9. Adjustments were made for age, BMI, s-AMH, stimulation protocol, FSH dose, number of stimulation days and ET day.

Table 9. Results of the first IVF/ICSI cycle in women with or without endometriosis at ultrasonography.

Parameter	Total cohort, n=1040	No endo n=806	Endo n=234	Crude RR	95% CI	p-value	Adjusted RR[a]	95% CI	p-value
Cumulative PR[b]	508 (48.8)	411 (51.0)	97 (41.5)	0.81	0.68–0.96	0.013	0.70	0.57-0.87	0.001
Cumulative pregnancy loss[b,c]	108 (10.4)	83 (10.3)	25 (10.7)	1.06	0.83-1.35	0.662	0.91	0.69-1.20	0.492
Pregnancy loss, no live birth	64 (6.2)	51 (6.3)	13 (5.6)	0.88	0.49-1.59	0.666	0.84	0.41-1.72	0.624
CLBR	426 (41.0)	348 (43.2)	78 (33.3)	0.77	0.63–0.94	0.010	0.63	0.48-0.82	<0.001

IVF= In vitro Fertilization; ICSI= Intracytoplasmic sperm injection; Endo= endometriosis; PR= Pregnancy rate, CLBR= Cumulative live birth rate; RR=Relative risk; CI= Confidence intervals. [a]Adjustments were made for age, serum- antimüllerian hormone, body mass index, protocol, stimulation days, Follicle stimulating hormone dose, and day for embryo transfer. [b]Cumulative PR/ pregnancy loss is calculated per woman. Some women may have had pregnancy or pregnancy loss after fresh as well as frozen embryo transfer. [c]Pregnancy loss was defined as extrauterine pregnancies and miscarriages before 22 gestational weeks.
Data is presented as n (%). An adjusted Poisson regression analysis was performed to estimate RRs, which are presented with 95% confidence intervals.

Women with endometriosis had a lower chance of CLB after the first IVF/ICSI treatment compared to women without, aRR 0.63, (95% CI, 0.48 – 0.82), p<0.001.

Of the total cohort of 1040 women included in paper IV, in total 426 [41.0%, (95% CI, 38.0 – 44.0)] women had a CLB after their first IVF/ICSI treatment. Women with endometriosis had a lower CLBR [78/234, 33.3%, (95% CI, 27.3 – 39.4]) compared to women without the disease [348/806, 43.2%, (95% CI, 39.8 – 46.6)], p=0.007. Women with endometriosis had a lower PR after fresh ET [71/176 (40.3%)] compared to women without endometriosis [306/588, (52.0%)], aRR 0.72 (95% CI 0.56-0.93), p=0.011, calculated as % of fresh ET cycles. PR after FET were similar between the two groups (37/96, 38.5% versus 122/306, 39.9%), aRR 0.76 (95% CI 0.50-1.15), calculated as % of FET cycles.

The CLBR for women with or without different phenotypes of endometriosis is presented in Figure 26. When stratifying for phenotype of endometriosis, women with DE but without endometrioma had similar CLBR compared to women without endometriosis, [44/119, 37.0%, (95% CI, 28.8 – 46.2), versus 348/806, [43.2%, (95% CI, 39.9 – 46.7)], p=0.201. The RR for CLB for women with DE compared to women without DE was 0.93 (95% CI, 0.75 - 1.15). Women with endometrioma without DE had a lower CLBR [12/49, (24.5%, 95% CI, 12.5 – 36.5)] compared to women without endometriosis, p=0.010. Their RR for CLB was 0.72, (95% CI 0.53 – 0.97).

There was no difference in the number of stimulation days, retrieved mature oocytes, fertilization rates or number of GQEs between women with or without endometriosis. Women with endometriosis more often had ET in cleavage stage compared to women without the disease [105/176, (59.7%) versus 293/588 (49.8%), p=0.02], calculated as % of ET cycles.

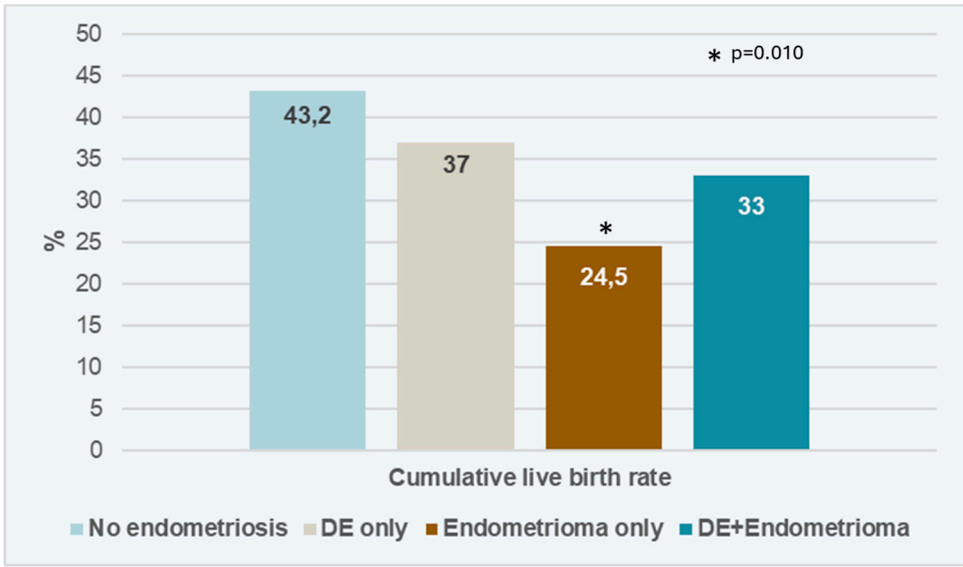

Figure 26. Cumulative live birth rates for women with different phenotypes of endometriosis. DE= Deep endometriosis. Data is presented as % of women in each category. No endometriosis, n=806, DE only, n= 119, Endometrioma only, n=49, DE+ Endometrioma, n=66. Comparison with the No endometriosis group was made with the Chi2-test. The asterisk * indicates statistically significant difference. Unadjusted cumulative data are shown.

Adenomyosis

In total 1037 women were included in paper V. The CLBR after the first IVF/ICSI treatment was 424/1037, [40.9%, (95% CI, 37.9-43.8)]. Women with direct features of adenomyosis had a lower CLBR, 25/102 [24.5%, (95% CI, 17.5-31-5)] compared to women without any direct feature, 399/935, [42.7%, (95% CI, 39.5-45.8)], $p<0.001$.

The main outcomes after the first IVF/ICSI treatment for women with or without direct features of adenomyosis are presented with unadjusted data in Figure 27.

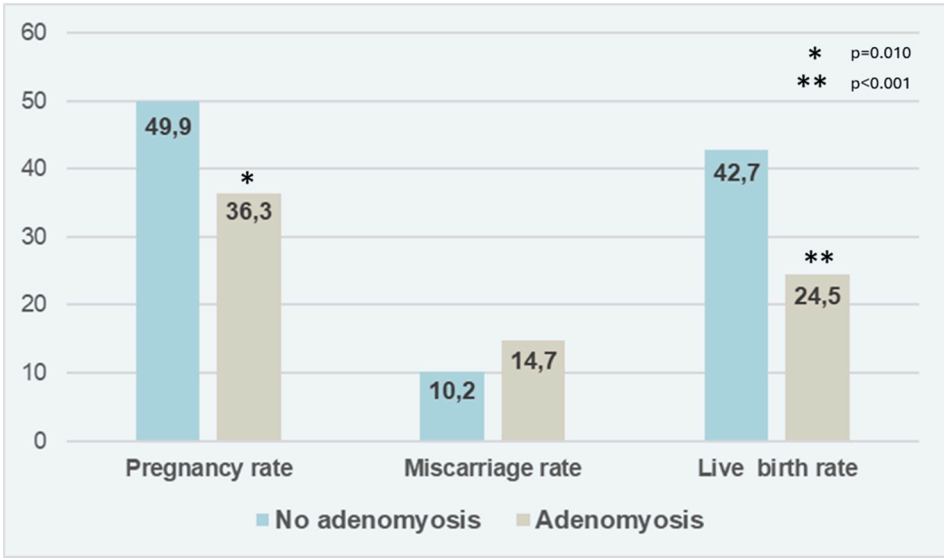

Figure 27. Main outcomes after the first IVF/ICSI treatment in women with or without direct features of adenomyosis.

IVF= in vitro fertilization; ICSI= Intracytoplasmic sperm injection. No adenomyosis (no direct features of adenomyosis), n= 935, Adenomyosis (direct features of adenomyosis), n=102 women. Data is presented as % of women with or without direct features of adenomyosis. Comparison within each group was made with the Chi2-test. The asterisk * indicates statistically singnificant difference. Cumulative, unadjusted data after the first treatment cycle are shown.

Cumulative data for the main outcomes after the first IVF/ICSI treatment for women with direct or indirect features of adenomyosis, with crude and adjusted relative risks for pregnancy, miscarriage, and CLBR, are presented in Table 10.

Women with direct features of adenomyosis had a similar chance of CLB as women without direct features, after adjustments were made for age, BMI, s-AMH, stimulation protocol, number of stimulation days, ET day and presence of endometriosis, [aRR 0.83, (95% CI, 0.56 – 1.22), p=0.361], (Table 10a). A similar pattern was found when comparing women with direct features of adenomyosis with women without any direct or indirect features, aRR 0.69, (95% CI 0.46 – 1.01), p= 0.056. However, women with indirect features of adenomyosis had a lower chance of CLB than women without, [aRR 0.64, (95% CI, 0.47 – 0.87), p=0.005], Table 10b.

Women with direct features of adenomyosis had an increased risk of miscarriage after FET [n=10/14, (71.4%)] compared to women without direct features of adenomyosis [n=29/145, (20.0%)], after adjusting for potentially confounding factors, [aRR 4.54, (95% CI 2.01 – 10.2), p<0.001].

Table 10. Cumulative results after the first IVF/IVSI cycle for a) women with or without direct features of adenomyosis or b) without direct features but with or without indirect features of adenomyosis at ultrasonography.

a Parameter	Total cohort n=1037	No direct features n=935	Direct features n=102	Crude RR	95% CI	p-value	Adjusted RR[a]	95% CI	p-value
Cumulative PR[b]	504 (48.6)	467 (49.9)	37 (36.3)	0.73	0.56–0.95	0.013	1.01	0.99-1.03	0.89
Cumulative pregnancy loss[b,c]	110 (10.6)	95 (10.2)	15 (14.7)	1.46	0.88-2.42	0.662	1.65	0.92-2.95	0.09
Pregnancy loss, no live birth	103 (9.9)	91 (9.7)	12 (11.8)	1.22	0.69-2.15	0.666	1.42	0.75-2.67	0.28
CLBR	424 (40.9)	399 (42.7)	25 (24.5)	0.58	0.41–0.82	0.010	0.83	0.56-1.22	0.36

b Parameter	No direct features n=935	No indirect feature n=747	Indirect features n=188	Crude RR	95% CI	p-value	Adjusted RR[a]	95% CI	p-value
Cumulative PR[b]	467 (49.9)	404 (54.1)	63 (33.5)	0.63	0.51–0.78	<0.001	0.70	0.55-0.91	0.006
Cumulative pregnancy loss[b,c]	95 (10.2)	79 (10.6)	16 (8.5)	0.81	0.49-1.35	0.42	0.78	0.42-1.45	0.44
Pregnancy loss, no live birth	25 (2.7)	22 (2.9)	3 (1.6)	0.81	0.49-1.36	0.43	0.75	0.39-1.45	0.40
CLBR	399 (42.6)	348 (46.6)	49 (26.1)	0.57	0.45–0.73	<0.001	0.64	0.47-0.87	0.005

IVF= In vitro Fertilization; ICSI= Intracytoplasmic sperm injection; PR= Pregnancy rate, CLBR= Cumulative Live birth rate; RR=Relative risk; CI= Confidence intervals. [a]Adjustments were made for age, serum- antimüllerian hormone, BMI, protocol, stimulation days, Follicle stimulating hormone dose, and day for embryo transfer. [b]Cumulative PR/ pregnancy loss is calculated per woman. Some women may have had pregnancy or pregnancy loss after fresh as well as frozen ET. cPregnancy loss was defined as extrauterine pregnancies and miscarriages before 22 gestational weeks.
Data is presented as n (%). An adjusted Poisson regression analysis was performed to estimate RRs, which are presented with 95% confidence intervals.

The only individual feature of adenomyosis that had an impact on CLBR was an interrupted JZ in the coronal plane on 3D TVUS. The crude RR for CLB for an interrupted compared to a regular JZ was 0.36, (95% CI, 0.23-0.58), p<0.001, and the adjusted RR 0.47, (95% CI, 0.22-0.61), p<0.001. None of the other MUSA features had an individual impact on CLBR.

Having at least one feature of adenomyosis located in the JZ lowered the chance for LB in comparison with other locations, [RR 0.39 (95% CI; 0.11-0.74)], p= 0.010. Conversely, having any feature of adenomyosis only in the outer myometrium increased the chance for LB in comparison with other locations, [RR 2.61 (95% CI, 1.42-4.8)], p=0.002.

AI prediction model

The best XGBoost model for prediction of CLBR resulted in an evaluation AUC of 0.69 and test AUC of 0.66. The model´s evaluation accuracy was 0.64, and the model´s test accuracy was 0.59, (Figure 28). The variables with the best predictive ability in relation to LB were s-AMH (mean SHAP 0.21) and a regular JZ (mean SHAP 0.13). An interrupted JZ at 3D TVUS was the most important MUSA feature (mean SHAP 0.06). The MUSA features were generally poor predictors of LB.

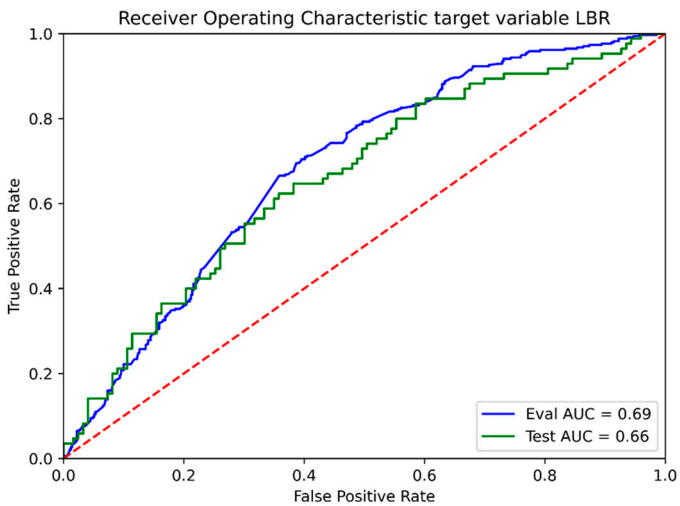

Figure 28. Receiver operating characteristics curves showing the area under the curve for prediction of live birth rate. LBR= Live birth rate; Eval = evaluation; AUC= area under the curve

The importance of the individual variables in the prediction model for LB are presented in Figure 29.

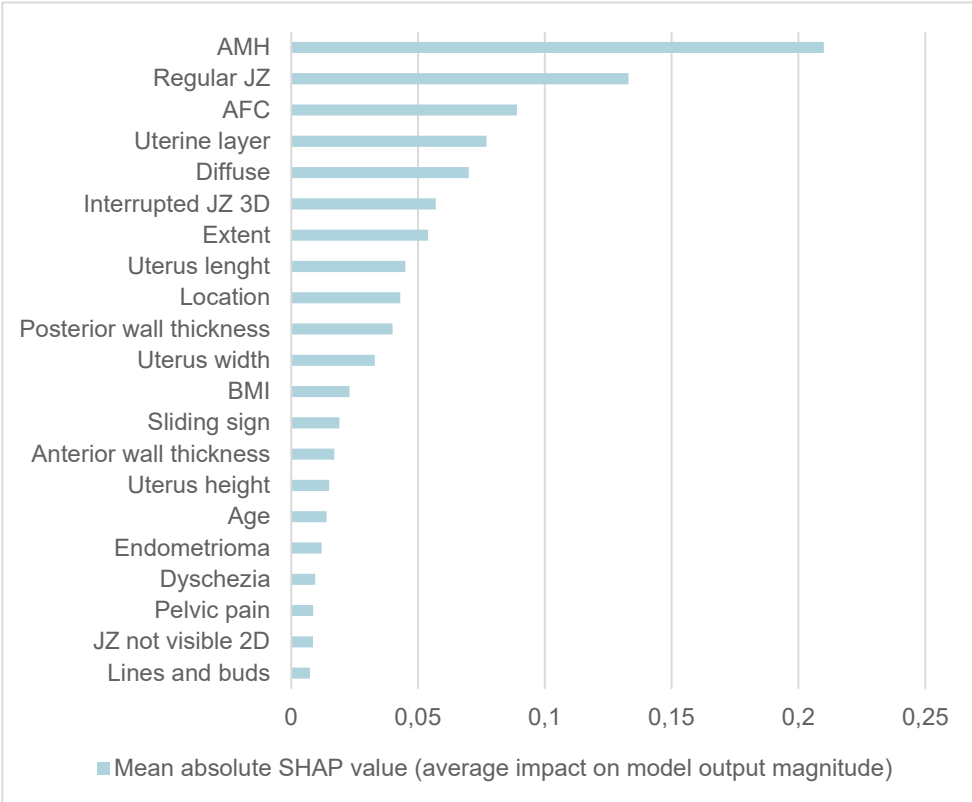

Figure 29. The importance of different variables in the prediction model for live birth
3D= Three-dimensional; JZ= junctional zone; 2D= two-dimensional; BMI= Body Mass Index; AFC= antral follicle count; AMH= antimüllerian hormone; pelvic pain= chronic pelvic pain.
The importance of each variable on the model, illustrated with the Shapley additive explanations algorithm (SHAP) variable importance. The most important variable has the highest mean of absolute SHAP values.

Discussion

This thesis was conducted with the overall aim of increasing the knowledge of endometriosis and adenomyosis, to improve the care and counselling for women that seek treatment for subfertility, particularly those with endometriosis or adenomyosis. Using systematic ultrasonography with standardized definitions, we have provided new knowledge regarding the prevalence of endometriosis and adenomyosis among these women. We have also increased our knowledge on how ovarian reserve parameters correlate with CLBR after IVF/ICSI treatment and how endometriosis and adenomyosis impact fertility treatment outcomes.

Our main findings were that even if ovarian reserve parameters correlate with LBR, the predictive ability of these parameters in relation to LB was poor. Further, we found that endometriosis was present in 22% of women with subfertility. A majority were previously undiagnosed despite typical symptoms and repeated examinations. Women with endometriosis had reduced s-AMH-levels and a lower chance of LB compared to women without the disease. We found that adenomyosis was present in one in ten women scheduled for ART. Adenomyosis was more prevalent in women with endometriosis and with increasing age. Even if women with adenomyosis had lower CLBR than women without the disease, they had in fact similar chances of having a LB after IVF/ICSI treatment as women without the disease, after adjustments were made for potentially confounding factors. Predicting LB in women embarking on ART is challenging, as various factors interact. S-AMH was the most important single variable for predicting LB, whereas MUSA features of adenomyosis were poor predictors. When using a machine learning algorithm, we were not able to build a clinically useful model for the prediction of LB after IVF/ICSI treatment.

In paper I, we found that s-AMH and AFC correlated with CLBR, but the predictive value of these parameters in relation to CLB was limited. Our findings are in line with previous studies, that concluded that s-AMH and AFC are correlated with LBR (28, 29, 30, 157, 158, 159). Several studies have disputed a predictive value of s-AMH, arguing that regardless of an association with LB, s-AMH does not offer any added predictive value to that of age or AFC (160, 161, 162). There is neither a lower threshold under which no woman achieves LB, nor is there an upper threshold above which all women succeed. This limits its predictive value, as concluded in a recent meta-analysis (163). However, the same meta-analysis found that s-AMH performed better in relation to CLBR than to LBR after first fresh ET, which was

attributed to the correlation between s-AMH and oocyte yield. These findings align with ours. Several women in this thesis with undetectable levels of s-AMH had a LB, whereas not all women with s-AMH above 100 succeeded. S-AMH may be used for counselling couples of their chances but should not be used as a sole variable to dissuade a woman from treatment.

In paper II, we found that 22% of women scheduled for ART had endometriosis on TVUS. Three quarters of these women were previously undiagnosed, and our findings explained their cause for subfertility. The substantial delay in time to diagnosis for most women with endometriosis is previously well known (42). What is concerning, however, is our finding that most women with endometriosis that seek help due to subfertility remain undiagnosed. This is despite having typical symptoms that affect their daily life, despite seeking help due to one of the cardinal symptoms of endometriosis and despite undergoing repeated ultrasonographic and pelvic examinations to find out the reason for their subfertility. This implies that symptoms suggestive of endometriosis may be neglected even among professionals, which is worrying for several reasons.

A recent study showed that women with endometriosis that were diagnosed *after* undergoing ART were 33% less likely to have a LB compared to women without endometriosis, despite undergoing more ART cycles (164). Women with undiagnosed endometriosis may be deprived of correct treatment. If they are diagnosed as having unknown cause for subfertility, they may undergo repeated cycles of IUI, which is usually not recommended for women with endometriosis (165). Postponing IVF/ICSI treatment may reduce the chances of a successful outcome (166). Moreover, regardless of ART results, endometriosis often has a major impact on affected women´s daily life (42, 167). Many women might benefit from hormonal treatment, surgery, or the specific management that can be offered at centres specialized in endometriosis treatment. Even if the risk of disease progression in asymptomatic women that are managed conservatively recently has been questioned (168, 169), women with endometriosis in our study were hardly asymptomatic. On the contrary, apart from having subfertility, women in our cohort more frequently reported the presence of dysmenorrhea, dyspareunia, dyschezia, pelvic pain and dysuria than women without endometriosis. Further, the presence of dyschezia and pelvic pain were variables that contributed to the prediction model for LB in paper V. Considering that women with endometriosis had lower s-AMH levels compared to women without endometriosis in this thesis, progressive damage to the ovarian reserve in untreated women cannot be ruled out. It is possible that expedited ART should be considered for women with endometriosis. Another aspect concerning a potential underdiagnosis of endometriosis, is that this hampers the interpretation of studies that assess whether subfertile women with endometriosis would benefit from specific treatment protocols or management. Having a correct diagnosis is a prerequisite for such studies.

The presence of endometriosis was associated with lower CLBR after the first IVF/ICSI treatment in paper IV. This is consistent with a previous retrospective study, in which women with endometriosis had 24% less likelihood of a LB when compared to those with unexplained subfertility (71). Likewise, endometriosis had the lowest chance of LB, when associated with other infertility diagnoses, in a retrospective population-based cohort study assessing the impact of endometriosis alone, or in combination with other infertility diagnoses, on IVF outcomes (170). Several recent meta-analyses have shown opposite results to ours, with similar LBR after IVF/ICSI treatment in women with or without endometriosis (73, 75, 171, 172). As mentioned earlier, some of the discrepancies may be attributed to heterogeneity in study design, particularly regarding the diagnostics of endometriosis. In some of the studies, the endometriosis diagnosis was made after laparoscopy and staged according to the rASRM classification, which does not consider DE in retroperitoneal structures (173). Moreover, considering that most women with endometriosis in this thesis were previously undiagnosed, it is likely that some of the women in the "non-endometriosis" groups in previous retrospective studies in fact had endometriosis.

After stratifying for different phenotypes of endometriosis, it appears as if the presence of endometriomas affected the CLBR after the first IVF/ICSI treatment more that the presence of DE. This is in alignment with a previous study that found significantly lower LBR or ongoing PR after IVF/ICSI treatment in women diagnosed with endometriomas at laparoscopy (LBR 18.8%), compared to women with tubal infertility or various stages of peritoneal endometriosis (LBR 30.5%) (174). A recent retrospective population-based cohort study found that the incidence rate of first LB was reduced by approximately half in women with subsequent surgical diagnosis of endometriosis compared to women with no such diagnosis (175). The fertility rate of parous women was lowest in the sub-cohort of endometriomas compared to those with peritoneal and deep endometriosis, which agrees with our results.

We found lower s-AMH levels and AFC in women with endometriosis compared to healthy women in paper IV, which aligns with data reported by others (94, 176, 177). Ovarian endometrioma seems to be associated with a faster decline of the ovarian reserve compared to healthy women (95), which in turn is associated with a shorter reproductive window (26). Several possible reasons for the accelerated decline have been suggested. The endometrioma may cause compression of the ovarian cortex, which in turn may impede circulation and cause a loss of follicles (178). An inflammatory, rather than mechanical, impact is another possible explanation. The endometrioma contains high concentrations of iron, that mediates the production of ROS. ROS may induce fibrosis in the ovarian cortex, with a subsequent loss of follicles (179) and damage to the quantity and/or quality of the remaining oocytes. In contrast to endometriomas, the impact of DE may be anatomical rather than inflammatory, with adhesions affecting the fallopian tubes.

It is also possible that some of the DE lesions found in our study consisted of fibrosis rather than active endometriosis lesions. This might explain the greater impact of endometriomas on s-AMH levels and CLBR than that of DE in paper IV.

Interestingly, we did not find any difference in LBR after FET between women with or without endometriosis. The difference in CLBRs was merely a consequence of differences in LBR after fresh ET. There are several possible explanations for this.

At first, frozen-thawed embryos are blastocysts and might be of superior quality to those transferred in cleavage stage. Women with endometriosis more often had ET in cleavage stage. However, as we adjusted for ET day in our analyses, this is unlikely to have affected the results.

Secondly, local intra-endometrial hypersecretion of oestradiol in women with endometriosis induces progesterone resistance (81, 88). This can lead to inadequate preparation of the endometrium, resulting in decreased endometrial receptivity. This, in turn, may impair the ability of the embryo to implant successfully and increase the risk of miscarriage. COS is associated with supraphysiologic levels of oestradiol and progesterone, which may interfere with endometrial receptivity in fresh cycles by enhancing development of the endometrium (180). Concerns have been raised that alterations of the eutopic endometrium in women with endometriosis may be exacerbated by COS (181). In FET cycles, however, embryos are transferred in a more physiological environment, with restored optimal endometrial receptivity. In line with this, a retrospective study that compared PR in women with endometriosis, when using either fresh ET or FET, found that cumulative PR in women with endometriosis were improved when employing deferred ET (181). Further, progesterone resistance may reduce the effectiveness of progesterone supplementation used during IVF cycles to support embryo implantation and early pregnancy development. It is possible that women with endometriosis or adenomyosis would benefit from tailored treatment regarding timing and dosage of progesterone supplementation (182).

In paper III, we found that the prevalence of adenomyosis in our population was 10%, when using strict criteria. This is lower than what has previously been suggested (57). However, different populations were examined in different studies, and findings of adenomyosis are likely to be more prevalent in older, symptomatic women scheduled for hysterectomy than in younger women with subfertility. It is also probable that adenomyosis has been overdiagnosed in previous studies, when indirect as well as direct features have been used for diagnosis (57, 183). In paper IV, indirect features of adenomyosis were indeed detected in almost a quarter of examined women, which corresponds to previous findings.

The presence of adenomyosis did not reduce the chances of LB in paper V. This is in alignment with several studies (72, 184, 185, 186), but opposite to recent meta-analyses (77, 187, 188). Contradictive results to ours may be explained by different criteria used to diagnose adenomyosis, as discussed above. Further, not all studies

have adjusted for potentially confounding factors (183, 189, 190). In this thesis, women with adenomyosis were older, had lower s-AMH and AFC and more often endometriosis compared to women without the disease. It is possible that the negative impact of adenomyosis on ART outcomes seen in previous studies is rather an effect of a reduced ovarian reserve and not of adenomyosis per se.

In paper V, women with direct features of adenomyosis had higher miscarriage rates after FET compared to women without adenomyosis. This is in line with a recent prospective study of 228 women with or without direct MUSA features of adenomyosis, undergoing oocyte donation treatment (185). Similar results have been reported by others (191). An impaired uterine environment, with hyperperistaltic contractions, inflammation and progesterone resistance may hamper gamete function and implantation in women with adenomyosis (44, 80).

Indirect features of adenomyosis were associated with reduced CLBR in paper V. An interrupted JZ was the only individual feature of adenomyosis that was associated with lower chances of a LB. Moreover, features of adenomyosis located in the JZ negatively correlated with LB, whereas the opposite was true for location in the outer myometrium. A regular JZ was one of the most important variables for predicting LB in the ML model. This aligns with evidence that the JZ is of vital importance for fertility and proper embryo implantation (192). As discussed above, a disrupted endometrial-myometrial interface may negatively impact local inflammatory factors, uterine peristalsis, sperm transport, decidualization, trophoblast invasion and angiogenesis (44, 193). Altogether, an interrupted JZ may compromise successful embryo implantation and pregnancy.

An altered JZ has previously been suggested to be a sign of endometriosis (194). Kunz et al found that 79% of women with pelvic endometriosis had irregular JZ thickening on MRI (46). Another study found that one third of young women with endometriosis had concurrent JZ alterations on MRI (195). JZ alterations were a common finding at 3D TVUS in s study of women with endometriosis (130). Ectopic endometrial cells in the myometrium may cause proliferation of smooth muscle cells in the JZ (194), which then appears irregular and thickened on TVUS (12). An altered JZ has previously been associated with implantation failure (194), possibly due to inflammation triggered by ectopic endometrium, and subsequent increased contractility of the uterus. Even if most women will have signs of adenomyosis with increasing age (196), data suggest that adenomyosis develops at an earlier age in women with endometriosis compared to healthy women (197). In this thesis, the odds for having at least one feature of adenomyosis were higher in women with endometriosis. Moreover, endometriosis or indirect features of adenomyosis reduced the chances of LB. One may speculate that indirect features of adenomyosis to some extent correlate with endometriosis. Shared pathophysiology between the two diseases has been suggested by Bulun et al (80). Perhaps direct features of adenomyosis are a late sign of the uterine ageing process, whereas indirect features, which might appear earlier in women with endometriosis,

are early manifestations of this ageing process (195)? It is possible that the presence of endometriosis affects the chances of conceiving more than the presence of adenomyosis in women with both diseases. The importance of indirect features in the diagnostics of early forms of adenomyosis and for reproductive counselling should be further evaluated.

In paper III, we found that direct features of adenomyosis were more often visualized on 3D TVUS than on 2D TVUS. This was not true for indirect features. However, most indirect features are only assessed on 2D TVUS, whereas the JZ is evaluated on 2D as well as 3D TVUS. The latter is superior for assessing the JZ in the coronal plane (12). A regular JZ was associated with a favourable outcome after ART, whereas an interrupted JZ was associated with poorer outcome. Our findings are in line with previous observations (45, 130) and indicate that 3D TVUS is an important complement to 2D TVUS in the diagnostics of different features of adenomyosis in subfertile women.

Predicting the chances of LB after ART would be valuable for several reasons. With adequate information regarding the chance of successful treatment, the individual couple can weigh the chance of having a child against potential risks with the treatment. Moreover, they can decide whether they are willing to accept the financial and emotional burden they might have to face.

Building a good prediction model for LB is challenging, as various factors may interact to affect the outcome. Male factors, such as semen quality parameters, are important aspects that were not considered in this thesis. In a previous study that used the same cohort of women as in paper I, we investigated the impact of sperm DNA fragmentation, expressed as % DNA fragmentation index (DFI), on the outcome after IVF/ICSI treatment (198). We found that the impact of high DFI on standard IVF was most pronounced if the woman had relatively low AMH levels. S-AMH is believed to be a quantitative and not a qualitative marker of the ovarian reserve (199). In this context, however, one may speculate that lower s-AMH levels reflect the potentially lower capacity of the oocyte to repair breaks of the sperm DNA strand, which are implicated by the high DFI. This, in turn, may impact the fertilization process. In this thesis, we found in papers I, IV and V that s-AMH is correlated with CLBR. Older age, or the presence of endometriosis, were associated with lower s-AMH-levels. Possibly, this may lead to a reduced reparative capacity of the gametes and hence lower CLBR. Nevertheless, male factors should probably be included in a model that aims at predicting LB after IVF/ICSI treatment.

Even if s-AMH is a poor predictor of LB after IVF/ICSI treatment, the ovarian reserve is one of the most important factors to achieve LB. In this thesis, s-AMH was the most important variable for predicting LB, when using a ML algorithm in paper V. Maybe evaluating s-AMH is as good as it can get?

Summary of findings

The main findings of this thesis are as follows:

I. S-AMH levels were associated with CLBR in patients undergoing their first IVF/ICSI treatment. The ovarian reserve markers s-AMH, AFC and OSI had an equally poor predictive ability in relation to CLBR.

II. Using the IDEA terminology, the prevalence of endometriosis at TVUS was 21.8% in subfertile women referred for their first ART. Three quarters of women with findings of endometriosis at our examination were previously undiagnosed.

III. Using the revised MUSA terminology, the prevalence of direct features of adenomyosis was 9.6% in subfertile women referred for their first ART. In total 23.4% women had indirect features of adenomyosis. Women with any feature of adenomyosis were older and more often had concurrent endometriosis than women without any features. 3D TVUS was an important complement to 2D TVUS in detecting direct features of adenomyosis.

IV. Women with endometriosis on TVUS had a 37% reduced chance of having a LB after IVF/ICSI treatment compared to women without the disease. The presence of endometrioma had a greater impact on CLBR than DE. Women with endometriosis had lower s-AMH levels and AFC than women without the disease.

V. The presence of direct MUSA features of adenomyosis did not correlate to the CLBR in women undergoing their first IVF/ICSI treatment, after adjustments were made for potentially confounding factors. However, the presence of indirect features reduced the chance of LB in comparison with women without any features. Women with adenomyosis were older and had a reduced ovarian reserve compared to women without the disease.

VI. A regular JZ was the best ultrasonographic variable in predicting LB, whereas s-AMH was the best clinical variable, confirmed by the XGBoost model. Overall, the predictive ability of MUSA features in relation to LB after IVF/ICSI treatment was poor. Many factors may interact to impact fertility treatment outcomes. Using a ML algorithm, we were not able to build a clinically useful model to predict IVF/ICSI treatment outcomes.

Conclusions

This thesis has contributed to an increased understanding of the disease panorama of endometriosis and adenomyosis. For many women, endometriosis may explain their cause for subfertility. For others, adenomyosis may increase the risk of miscarriage. Our results highlight the importance of a structured and detailed ultrasound examination in women who seek care for subfertility. Referral for specialized ultrasound examinations should be considered more often, particularly for women with symptoms suggestive of endometriosis or adenomyosis. A diagnosis at an earlier stage would enable individualized fertility counselling as well as an improved management in terms of hormonal treatment, pain relief, surgery or expedited IVF/ICSI treatment. Further studies examining if different treatment strategies would be beneficial for women with endometriosis or adenomyosis are needed. Our results will facilitate the design of such studies.

Even if s-AMH cannot be used as a sole parameter for predicting fertility treatment outcomes, it continues to be valuable for planning fertility treatments, as well as for counselling women embarking on ART.

Future perspectives

Most women that are unsuccessful on their first IVF/ICSI treatment will choose to undergo further attempts. In Sweden, women are entitled to up to three subsidized treatments, until the birth of a living child is achieved. Usually, subsequent treatment protocols are adjusted according to the first results. A natural next step would be to examine the CLBR after three IVF/ICSI treatments in women with endometriosis or adenomyosis. Could women with endometriosis achieve the same CLBR after repeated fertility treatments as women without the disease?

Previously, many women have been incorrectly classified as having unknown cause for subfertility. Improved ultrasonography has allowed for more women being diagnosed with endometriosis or adenomyosis. Specific treatment protocols for these women are scarce. Larger studies are needed that compare different treatment protocols. Could women with endometriosis or adenomyosis benefit from prolonged GnRH treatment prior to ART, deferred ET or individual dosing or timing of progesterone supplementation?

One weakness of our project is that the presence of superficial endometriotic lesions was not assessed, hence its effect on CLBR is unknown. SonoPODography should be carried out, to evaluate the presence of peritoneal endometriosis (122).

Women with endometriosis and particularly those with ART use, have been suggested to be a subgroup with increased risk of adverse pregnancy outcomes such as preterm birth, antepartum haemorrhage, and placenta praevia (200). Similarly, women with adenomyosis are believed to have an increased risk of small for gestational age, preterm birth, and preeclampsia (64, 66, 201). However, previous studies may be biased as many women may have undiagnosed endometriosis, which we have seen in this thesis. Further, the criteria used to diagnose adenomyosis may vary. A natural next step forward is to study the obstetric outcomes for women in our cohort. Are there any differences between women with or without endometriosis and/or adenomyosis regarding obstetric outcomes?

Further, it would be interesting to carry out a pilot study to evaluate whether different JZ alterations could be associated with alterations in the uterine artery blood flow in the second trimester of pregnancy. Are there any alterations that could be correlated to the development of preeclampsia or intrauterine growth restriction?

Our results indicate that endometriomas impact IVF/ICSI outcomes more than DE. Further research regarding the composition of the follicular fluid surrounding the oocytes should be carried out, to elucidate whether levels of inflammatory parameters or molecular markers differ between women with or without endometriosis, or between women with different phenotypes of endometriosis. Could women with endometriosis benefit from oocyte cryopreservation for fertility preservation? Should this be considered in the individualized fertility counselling of these women? Likewise, endometrial samples from women with or without different features of adenomyosis or endometriosis should be examined.

Features of adenomyosis were correlated with increasing age and previous pregnancy. It would be of interest to examine our cohort of women 5 and 10 years after the initial examination, regarding disease progression, appearance of the JZ and presence of new features of adenomyosis. Are there any differences between women with or without pregnancy and childbirth? Do ART results or the appearance of the uterus differ between women with or without typical symptoms, if they were disease-free on the index examination? Has endometriosis developed in some women that initially had severe symptoms? Has direct features of adenomyosis developed in women who had indirect features of adenomyosis on the initial examination?

Artificial Intelligence is upcoming but has so far had limited use in ultrasound diagnostics of endometriosis, adenomyosis and reproductive medicine. Could artificial neural networks or deep machine learning models be better than experienced examiners at pattern recognition, to detect clinically useful alterations in internal genital organs?

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Appendix I

1. Använder du hormonbehandling/preventivmedel? Ja Nej

Om ja, vilken? _____

Hur länge har du använt denna behandling?_____

2. Har du använt hormonbehandling/preventivmedel tidigare? Ja Nej

Om ja, vilken behandling använde du senast? _____

När slutade du med senaste behandlingen: _____

Hur länge har du använt senaste behandlingen:_____

Ange andra hormonbehandlingar som du har använt, samt hur länge du använde dem:

_____

Skatta dina besvär i frågorna nedan genom att markera med ett streck på linjen, t.ex.

3. Har du ont vid mens? Ja Nej

Utan hormonbehandling

Ingen _____ Maximalt

Med hormonbehandling

Ingen _____ Maximalt

4. Har du ont i magen eller i bäckenet? Ja Nej

Hur ofta har du ont i magen? Varje dag 1-3 ggr/v 1-3 ggr/mån

Utan hormonbehandling

Ingen _____ Maximalt

Med hormonbehandling

Ingen _____ Maximalt

5. Har du ont vid samlag? Ja Nej

Var har du ont vid samlag? Vid slidöppningen Djup smärta Annat:_____

Utan hormonbehandling

Ingen _____ Maximalt

Med hormonbehandling

Ingen _____ Maximalt

6. Har du ont när du kissar? Ja Nej

Om ja, när har du ont? Bara vid mens Ej mensrelaterat Alltid

Utan hormonbehandling

Ingen _____ Maximalt

Med hormonbehandling

Ingen _____ Maximalt

Har du haft blod i urinen? Ja Nej

Om ja, när har du haft blod i urinen? Bara vid mens Ej mensrelatetat

7. Har du ont när du bajsar? Ja Nej

Om ja, när har du ont när du bajsar? Bara vid mens Ej mensrelaterat Alltid

Utan hormonbehandling

Ingen _____ Maximalt

Med hormonbehandling

Ingen _____ Maximalt

Har du haft blod i avföringen? Ja Nej

När har du haft blod i avföringen? Vid mens Ej mensrelaterat Alltid

8. Tar du smärtstillande mediciner? Ja Nej

- Om ja, var god fyll i tabellen

	Kryssa om du behöver smärtstillande	Vilken medicin tar du? Skriv styrka och hur många du brukar ta per dag.
Varje dag		
Varje vecka		
Vid ägglossning		
Bara under mens		
Veckan före mens och vid mens		
Vid mens, samt veckan före och efter		

9. Vad tycker du om effekten av den smärtstillande medicinen du tar?

Ingen effekt _____ Utmärkt effekt

SARA ALSON works as an obstetrician and gynaecologist at Skåne university hospital. Her research interest is ultrasound diagnostics. This thesis focuses on endometriosis and adenomyosis diagnosed by ultrasonography in women with subfertility, and the correlation with fertility treatment outcomes.

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