Chapter 1
General introduction
Purpose and motivation

It is generally acknowledged that an estimated 10% of all women during their reproductive years are affected by endometriosis [1]. Various theories have been promulgated to explain the pathogenesis of endometriosis, but the “retrograde menstruation theory” postulated by Sampson in 1927 is still the most widely accepted [2]. However, not all women with “retrograde menstruation” develop endometriosis and the theory cannot explain all locations of endometriotic lesions. Therefore, the origin of endometriosis remains a continuing debate.

There is a significant diagnostic delay of endometriosis, because symptoms are not easily recognized and a non-invasive test for diagnosis is not available. The gold standard for diagnosis of pelvic endometriosis is visual inspection by laparoscopy [3]. However, laparoscopy is limited for the evaluation of deep infiltrating endometriosis (DIE) as patients diagnosed with DIE often show extensive pelvic adhesions. Also, the infiltration depth and extent of DIE lesions infiltrating under the peritoneum cannot be evaluated. Therefore, imaging techniques are necessary for mapping of disease extent. Accurate assessment is helpful to decide whether surgical intervention is indicated and to choose an adequate surgical technique.

Transvaginal sonography (TVS) and magnetic resonance (MR) imaging are both used for the evaluation of endometriosis [4-6]. TVS is often used for screening and MR imaging is in general performed in patients referred, because of suspected DIE.

The main emphasis of this thesis is to gain new insights into MR imaging of (deep infiltrating) endometriosis. We aim to describe the MR imaging appearance of DIE lesions and correlate imaging findings to histopathology, where possible. We will also focus on the value of MR imaging in endometriosis located in the abdominal wall, a common location of extrapelvic endometriosis. Furthermore, our aim is to explore advanced imaging techniques, including diffusion-weighted MR imaging and 3DT2-weighted imaging with a high sampling efficiency technique (SPACE), for their role in diagnosis and the preoperative assessment of DIE lesions. Only a minority of patients undergo surgical therapy for DIE. For the majority of patients therefore, a combination of clinical findings and surgery reports were used as standard of reference.
General Introduction

Endometriosis is characterized by ectopic growth of endometrial glands and stroma [7]. Patients present with a broad spectrum of symptoms, including dysmenorrhoea, dyspareunia, dyschezia, dysuria and non-cyclical pelvic pain. Moreover, endometriosis is associated with infertility. The highest prevalence rates of endometriosis are found in infertile couples, with a prevalence varying from 5% to 50% [7]. The impact of this disease affects both a woman’s physical and mental well being, the latter even more due to the frequent delay from the onset of symptoms to a confirmed diagnosis [8]. The mean time interval between first symptoms and diagnosis is reported to be 8–12 years [9].

Pathogenesis

Regarding the pathogenesis of endometriosis, different theories have been raised. Although no single theory can explain all cases of endometriosis, the retrograde menstruation theory has gained the widest acceptance [2, 10-13]. This theory proposes that viable endometrial tissue is refluxed through the fallopian tubes during menstruation and implants on peritoneal surface or pelvic organs [2]. Most endometriotic deposits are found in the pelvis (ovaries, peritoneum, uterosacral ligaments and pouch of Douglas). An asymmetric distribution of lesions has been recognized, probably related to the anatomical difference between the left and right hemipelvis and the flow of peritoneal fluid [12]. Retrograde menstruation occurs in 76% to 90% of women [14]. Not all of these women will develop endometriosis. The much lower prevalence of endometriosis suggests that additional factors determine susceptibility to endometriosis. Various theories have been put forth to explain the susceptibility to develop endometriosis. First, a strong familial component is recognized and recently Painter et al identified a locus on chromosome 7p15.2 significantly associated with the risk of endometriosis in women of European ancestry [15]. Secondly, a growing body of evidence suggests that eutopic endometrium from women with endometriosis exhibits fundamental differences compared to eutopic endometrium from women without this disorder [16, 17]. Furthermore, environmental factors and alterations in immune and endocrine functions are believed to play a significant role in the establishment and maintenance of endometriosis [18].
**Superficial endometriosis, deep infiltrating endometriosis and extrapelvic endometriosis**

Endometriosis can be divided into superficial (peritoneal) endometriosis, deep infiltrating (pelvic) endometriosis (DIE) and extrapelvic endometriosis.

**Superficial endometriosis**

Superficial endometriosis has been described as deposits of endometrial glands and stroma on the peritoneal surface and ovaries. Endometrial cysts of the ovaries (endometriomas) usually contain a dense, brown, chocolate-like fluid, but may also contain watery fluid occasionally. They originate from invagination of endometriosis within the ovarian cortex, forming pseudo cysts [19, 20]. Adhesions are usually associated with ovarian endometrial cysts and attach them to nearby pelvic structures. Although endometrial cysts of the ovary are classified as superficial disease, a significantly higher proportion of women with endometrial cysts will have DIE when compared to women without endometrial cysts [21].

**Deep infiltrating endometriosis (DIE)**

DIE has been described as endometrial glands and stroma infiltrating under the peritoneum. Histologically, DIE often takes the form of a nodular lesion consisting of smooth muscle and fibrosis with active glands and scanty stroma [22]. DIE lesions are found retrocervical (eg. fornix posterior and torus uterinus), infiltrating the bowel, bladder wall, uterosacral ligaments, ureters, intestines and rectovaginal septum. The latter is a rare location of DIE, although previous studies sometimes refer to the rectovaginal septum in cases that are anatomically defined as posterior vaginal fornix or the retrocervical area [23, 24]. Reduced Douglas pouch depth and volume in women with deep endometriosis suggest that such lesions develop not in the rectovaginal septum but intraperitoneally and that burial by anterior rectal wall adhesions creates a false bottom, giving an erroneous impression of extraperitoneal origin [25, 26]. As lesions extend from the serosa to the luminal side of the bowel, most lesions reach out into the muscular or submucosal layer of the bowel or bladder wall, while the mucosa is rarely and only focally involved. It has also been reported that lesions infiltrating the bowel preferentially extend along the nerves [27].
Extrapelvic endometriosis
Extrapelvic endometriosis is characterized by endometrial glands and stroma at distance from the genital organs, including the abdominal wall (e.g. abdominal scars, hernias and the umbilicus), diaphragm and upper abdomen.

Adenomyosis
Adenomyosis is classified as the benign invasion of endometrial glands and stroma under the level of the endometrium into the myometrium, surrounded by hypertrophic myometrium. A junctional zone thickness of more than 12mm is thought to indicate adenomyosis [28]. In previous literature, there is no consensus yet on the definition of adenomyosis. Adenomyosis is considered a distinct and different clinical entity from endometriosis, because its pathogenesis, symptoms, and epidemiology differ from those of endometriosis [29, 30]. However, endometriosis and adenomyosis regularly coexist in the same patient.

Diagnosis
Diagnosis of endometriosis is challenging, as patients present with a broad spectrum of symptoms. Moreover pain symptoms relate to the site of disease [31], but stage of disease is not consistently related to pain symptoms [32, 33]. Physical examination is not sufficient for diagnosis, but may be valuable for screening, when performed by an experienced gynecologist [34]. Blood tests, more specific CA-125 levels, have no diagnostic value for diagnosis of endometriosis [35], but may be used in patients suspected of ovarian malignancy. Visual inspection by laparoscopy is used as gold standard for diagnosis of pelvic endometriosis. The most widely used staging system for endometriosis is the Revised American Society for Reproductive Medicine classification of endometriosis: 1996 [36]. However, in case of deep infiltrating endometriosis, the value of laparoscopy is limited, as lesions hidden under dense pelvic adhesions are difficult to detect during laparoscopy. Previously, visual diagnosis of endometriosis was demonstrated to be inaccurate [37, 38]. Imaging techniques are therefore fundamental for diagnosis of (deep infiltrating) endometriosis and preoperative mapping of disease extent. In cases of severe DIE, or in case of extrapelvic disease, in which hormonal therapy
does not relieve symptoms, complete surgical excision of endometriosis has been demonstrated to decrease pain symptoms and increase quality of life [39,40]. In patients with DIE infiltrating the bowel wall, surgical excision may be performed by segmental bowel resection or in cases in which infiltration of endometriosis is limited to the serosa of the bowel or in case of minimal infiltration of the muscular layer, other surgical techniques, including the shaving technique or discoid resection, [41] may be used.

**Colonoscopy**
Colonoscopy with biopsies may be used, although lately less frequently, to confirm endometriosis infiltrating the bowel and/or exclude malignancy or other sources of bleeding [42, 43]. However, in endometriosis infiltrating the bowel, mucosal involvement is very rare and usually focal, and therefore diagnosis by colonoscopy may be inaccurate.

**Imaging**
Imaging modalities used in the analysis of endometriosis include, transvaginal sonography (TVS), transrectal sonography (TRS), rectal endoscopic sonography (RES), magnetic resonance (MR) imaging and computed tomography (CT). In our opinion CT should not be used to diagnose endometriosis, because of its lack of contrast resolution and its radiation exposure.

**TVS / TRS / RES**
TVS is usually the first imaging modality used for screening of patients with pelvic pain symptoms and can be used to diagnose or suspect (deep infiltrating) endometriosis.

On TVS, DIE lesions appear as hypo to iso-echogenic irregular nodules. Previously, TVS performed by an experienced investigator, showed accurate diagnosis of DIE infiltrating the rectum and bladder wall [5]. Furthermore, TVS accurately predicted endometriotic infiltration of the serosal and muscular layer of the bowel wall in a group of 43 patients [44].

Transrectal sonography (TRS) and rectal endoscopic sonography (RES) have also been assessed for the diagnosis of bowel wall involvement in endometriosis. In previous literature TRS and TVS showed similar degrees of accuracy for
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predicting rectal wall involvement [45], and TVS showed a higher accuracy for diagnosis of DIE at specific locations compared to RES [46]. TVS is less invasive and also performs well for diagnosis of ovarian endometrial cysts and associated DIE lesions of the anterior pelvic compartment (eg. bladder).

**MR imaging**

MR imaging has previously demonstrated accurate diagnosis of DIE [4]. In a previous study of Bazot et al [4] diagnosis of DIE was based on signal intensity and morphologic abnormalities. The signal intensity abnormalities included tissue areas that corresponded to fibrosis, with signal intensities close to that of pelvic muscle on T2- and T1-weighted imaging with or without foci or cavities. Morphologic abnormalities, in case of the anterior wall of the rectum and sigmoid, included disappearance of the fat tissue plane lying between the uterus and rectum and sigmoid colon. In case of bladder endometriosis, these included a nodule or mass at the level of the vesicouterine pouch, extending through the bladder wall, with involvement of the muscular layer (obliteration of the hypointense signal of the wall on T2-weighted images) or protruded into the lumen with invasion of the mucosal layer.

MR imaging has the advantage, over other methods of investigation, of making a survey of the anterior and posterior compartments of the pelvis at one time [47], including the retroperitoneal space. This is important as endometriotic lesions may be found infiltrating the sigmoid, while TVS is limited in the evaluation of this site, since it is too far from the probe. Moreover, the retroperitoneal space is not evaluated by (diagnostic) laparoscopy for pelvic pain/ endometriosis. MR imaging on the other hand is able to diagnose endometriosis retrocervical, infiltrating the bladder, infiltrating the bowel (including sigmoid) and may also be valuable for detection of hydroureter nephrosis as a consequence of endometriosis. Ureteral involvement is a silent, serious complication that must be suspected in all cases of DIE [48].

A standard MR imaging protocol for analysis of (deep infiltrating) endometriosis, includes T2- and fat suppressed T1-weighted images in different planes (axial, sagittal and coronal), with or without vaginal or rectal gel opacification. T2-weighted images are used for detection and anatomical localization of disease, while fat suppressed T1-weighted images are useful to facilitate detection of
hemorrhagic implants of endometriosis. Some previous studies have used vaginal or rectal gel opacification in the evaluation of DIE infiltrating the bowel on MR imaging [4, 49], but no consensus is reached yet on the value of vaginal or rectal gel opacification for diagnosis of DIE.

**MR Diffusion-weighted imaging**

Due to advances in imaging techniques, diffusion-weighted MR imaging (DWI) is increasingly used in body MR imaging. DWI can demonstrate abnormal signals emitted by pathologic foci based on differences in molecular diffusion [50]. The degree of restricted water diffusion in biological tissues has been shown to inversely correlate to the tissue cellularity and integrity of cell membranes [51]. Previously, studies reported decreased ADC values for a variety of malignant lesions [50, 51, 53]. However, due to a considerable overlap of ADC values in benign and malignant lesions, quantitative DWI alone is limited in the differentiation between them. In a previous study, ADC values in endometrial cysts were decreased and a low correlation was found between ADC values, T1- and T2- ratios [54]. In the latter study authors concluded that diffusion-weighted imaging may be a valuable diagnostic tool for the evaluation of protein and/or blood concentration within cystic lesions.

**3DT2-weighted MR imaging**

The standard imaging protocol for DIE includes a 2DT2-weighted sequence in three orthogonal planes. This sequence is relatively time-consuming. It may be possible to achieve a large time saving by reconstructing T2-weighted images in all three planes after the accelerating acquisition of a single volumetric data set with the recently proposed SPACE sequence. Moreover, this SPACE sequence (Sampling perfection with application optimized contrasts using different flip angle evolutions) allows retrospective free alignments of images according to anatomic/pathologic structures [55]. Previously, 2DT2-weighted and 3DT2-weighted imaging TSE (turbo spin echo) MR imaging were compared for local staging of rectal cancer at 3T. Author’s concluded that 3DT2-weighted MR imaging cannot replace 2D MR imaging for local staging of rectal cancer, but 3D MR imaging can be used for visualization of the complex pelvic anatomy for treatment planning purposes [56].
References


