ENZIAN-score: Classification of Deep Infiltrating Endometriosis

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Endometriosis is a condition with a highly variable clinical presentation. The attempt to fully describe and classify ("Classification of endometriosis. The American Fertility Society," 1979) the different manifestations of the condition (Beecham, 1966) (Kistner, Siegler, & Behrman, 1977) (Buttram, 1978) ("Classification of endometriosis. The American Fertility Society," 1979) has been ongoing for many years (Acosta et al., 1973; Alabau Lacomba, 1956). Classification systems of endometriosis, developed by several professional organizations, traditionally have been based on lesion appearance, pelvic adhesions, and anatomic location of disease. The division of endometriosis into different grades of severity serves firstly to record the extent of the disease and secondly to provide information about the correlation between the stage of the disease and the symptoms, and in particular to allow an assessment of the patient’s fertility.

In 1979 ("Classification of endometriosis. The American Fertility Society," 1979) and in 1985 the American Fertility Society (AFS) published a classification ("Revised American Fertility Society classification of endometriosis: 1985," 1985). This was revised in 1997 ("Revised American Society for Reproductive Medicine classification of endometriosis: 1996," 1997) and is now the most frequently used classification both in clinical practice and in international publications. The corresponding staging process is performed by means of either a diagnostic laparoscopy or a laparotomy. The classification evaluates the intraperitoneal distribution of the disease (peritoneum, ovary). The emphasis of the AFS classification is primarily on the correlation between the score and the fertility of the patient. The score also takes into account the extent of adhesions, which is of great importance for the fertility of the patient. However, adhesions are not just caused by endometriosis and they can also conceal deeper foci.

The AFS score is particularly useful in the treatment of the infertile patient.

Endometriosis is a disease which invades and proliferates the affected tissue structures and organs, causing inflammation and destruction. For many patients this leads to severe pain, as well as to disturbed function of the affected organs, with corresponding clinical, physical and psychological consequences for the patient.

While the correlations between score and symptoms are used to evaluate the efficacy of therapeutic interventions all these systems do not respect pelvic pain, response to medications, disease recurrence, risks for associated disorders, quality of life measures, and other endpoints important to women and health care providers for guiding appropriate therapeutic options and prognosis (Johnson et al., 2016).
Different forms of endometriosis with different symptoms:

Endometriosis shows different clinical presentations depending on its localisation. The classification differentiates between peritoneal endometriosis, ovarian endometriosis and deep infiltrating endometriosis.

What is DIE?

Deep infiltrating endometriosis (DIE) is a variable and poorly reproducible term, which is unsatisfactory for clinicians as well as researchers.

While deep endometriosis was originally described by Reich (Reich, McGlynn, & Salvat, 1991) as deep fibrotic nodules, the concept was developed into the deep lesions being either those infiltrating from the peritoneal surface (Koninckx, Oosterlynck, D'Hooghe, & Meuleman, 1994) or developing from a deeper origin as ‘adenomyosis externa’ (Koninckx & Martin).

The commonest definitions relate simply to (arbitrary) depth of extension beneath the peritoneal surface. For practical purposes this definition would encompass almost all lesions that either involve or cause anatomical distortion of vital structures (bowel, ureters, and bladder), as well as rectovaginal lesions. However the most useful definition should include a surgical description that reflects anatomical functional deficit in addition to the depth of extension beneath the peritoneal surface – hence the statement, based on what was judged to be weak evidence, that ‘deep endometriosis should be defined as lesions extending deeper than 5mm under the peritoneal surface’.

In the literature, the sites are specified in different ways. In particular, endometriosis deep in the pelvis (Pouch of Douglas, sacrouterine ligaments, cardinal ligaments, parametria, pararectal fossae, bowel infiltration, bladder infiltration, ureteric involvement, pelvic wall involvement) are considered to be DIE and are the cause for the patient’s extensive symptoms and change in quality of life.

The rapid development of minimally invasive surgery now makes possible the adequate resection even of severe endometriosis and to thereby enormously improve the patient’s quality of life once more. Even severe findings such as extragenital endometriosis can be adequately resected with the appropriate expertise. (Keckstein & Wiesinger, 2005b) (Donnez et al., 1997) (Donnez & Squifflet, 2010)
The involvement of the bowel, bladder and ureter sometimes necessitates a multidisciplinary approach.

However, each therapy involves the risk of side effects and complications. Thus, a small nodule in the pouch of Douglas is relatively easy to remove, whereas when the endometriosis has infiltrated the pouch of Douglas to involve the vagina, uterus and bowel, its removal represents a significant challenge for the surgeon.

Occasionally a small nodule is found associated with prominent pain symptoms; on the other hand large bowel nodules can be found with only minor symptoms.

Foci of endometriosis in the extraperitoneal space, extragenital endometrial foci (bowel, bladder, ureter, etc.) and extensive adenomyosis, however, are not adequately depicted by the AFS score which is standardly utilised ("Revised American Society for Reproductive Medicine classification of endometriosis: 1996," 1997).

In a study of 63 patients (Landeskrankenhaus [Regional Hospital] Villach) with DIE including recto-sigmoid endometriosis, 21% were found to have only Stage 1 or 2 according to the revised AFS Score (Wustlich) (Figure: 1).

![Figure 1: Staging of endometriosis with r-AFS score in 63 Patients with DIE and bowel involvement](image)

Haas confirms these data in 160 patients with DIE (Haas, Shebl, Shamiyeh, & Oppelt, 2013).
The lack of knowledge about the extent of the disease and the inadequate staging is of enormous consequence for the patient and the clinician:

1. Foci of endometriosis which are not demonstrated during laparoscopy lead to the diagnosis of a lower stage of the disease.
2. The therapeutic intervention is then either wrong or inadequate.
3. The value of the scientific studies, discussions and conclusions is called into question by this inadequate staging.

It is therefore desirable to achieve a better knowledge of this disease through a better assessment of the anatomical changes and the pathological structures.

ENZIAN Score

In order to better describe deep infiltrating endometriosis and also to evaluate the therapeutic interventions appropriately, the Stiftung Endometriose Forschung, (SEF, Endometriosis Research Foundation, Germany) created the ENZIAN Score in 2002. The idea for this score originated from the controversial discussions in the literature as well as at congresses, regarding the definition and meaning of DIE and its correct treatment.

Particularly for the extragenital form of DIE, with involvement of the bowel, ureter and other pelvic structures, we need the following information pre-operatively, intra-operatively and post-operatively:

1. Demonstration of the DIE by means of palpation, US, MRI and CT
2. Follow up of findings
3. Correlation between DIE and symptoms
4. Choice of therapy
5. Surgical technique
6. Planning and execution of the operation
7. DIE and surgical complications
8. Post-operative follow up

The score was developed by a working group of the SEFin 20002 as part of the first Weissensee Meeting in Carinthia, Austria.

SEF Members at the meeting:
Initiators: Prof. J. Keckstein, Prof. K.-W. Schweppe
P.D. Dr. M. Sillem, Prof. Dr. R. Greb, Dr. R. Mangold, Dr. N. Reeka, Dr. O. Richter, Prof. V. Terruhn, Prof. H.-R. Tinneberg, Prof. U. Ulrich, Prof. M. Possover, Prof. K. Neis, Prof. A. E. Schindler, P.D. Dr. Buchweitz, Dr. Frank Tuttlies

The term ENZIAN derives from the name of the hotel for the congress (Hotel Enzian, Neusach, Weissensee, Austria).

Enzian was first described in 2003 by Keckstein (Keckstein, Ulrich, Possover, & Schweppe, 2003b) (Keckstein & Wiesinger, 2005b) (Keckstein & Wiesinger, 2005a)and also 2005 by Tuttlies and
Keckstein (Tuttles et al., 2005). It was revised in 2010 and again in 2011 also by the SEF group during further annual “Weissensee-Meetings. (Stiftung Endometriose Forschung) (Keckstein, 2013). The latter revision was designed to reduce complexity and thus gain wider acceptance and also to resolve unintended partial overlap with r-ASRM (Keckstein et al., 2003b) (Haas, Wurm, et al., 2013).

The guidelines of the German, Austrian and Swiss national specialist societies recommend using the score (Ulrich et al., 2014). The certification process for centres of excellence for endometriosis in these countries requires that the score is used (Ebert et al., 2013).

In the meantime, the ENZIAN score is becoming increasingly recognised not just among surgeons but also among diagnosticians (Di Paola et al., 2015; Haas, Chvatal, et al., 2013; Haas, Oppelt, et al., 2013; Haas, Wurm, et al., 2013; Pellegrino et al., 2015) (Vanhie et al., 2016) (Johnson et al., 2016).

**Background to the ENZIAN score:**

Designed to complement the r-ASRM classification, Enzian is a system which allows more accurate description of severe endometriosis and registers all lesions. It describes the involvement of retroperitoneal structures with deep endometriosis, and thus provides a morphologically descriptive classification of deep endometriosis and endometriosis involving other organs, including the cul-de-sac, vagina, cervico-uterine ligaments, bladder, ureter, bowel and uterus.

In order to assess the full extent of the disease intraoperatively, a complete exploration of all structures and organs is necessary.

In many cases staging by diagnostic laparoscopy alone is inadequate, because of the foci which lie extraperitoneally.

Here the exposure and potentially the excision of extraperitoneal structures becomes necessary.

For various reasons, this is neither desired nor possible in every operation.

Imaging procedures (US, MRI) can assist in demonstrating these structures and enabling correct staging even during diagnostic operations (Di Paola et al., 2015).

**ENZIAN Score: based on the TNM classification!**
Based on the TNM (tumour/node/metastasis) classification system familiar (Figure 2) to those staging breast cancer and cervical cancer, Enzian identifies organs (bladder, ureter, bowel, vagina, uterus) as well as the cul-de-sac and uterine ligaments. The pelvis is divided into three compartments extending from the central pouch of Douglas. These are defined by the three directions of extension of the disease (Figure 3)

Figure 2. The cul-de-sac as the centre of the pelvis (left). Three dimensions of the staging system. A= (craniocaudal) cul-de-sac, rectovaginal septum, vagina. B= (mediolateral) uterosacral lig., cardinal lig., pelvic side wall, extrinsic ureteric involvement, C= (mediodorsal) rectum, rectosigmoid.
ENZIAN 2012

Classification of Deep Infiltrating Endometriosis (according to the Endometriosis Research Foundation, NFI)

Compartment
A, B or C

Level
1
< 1 cm
2
1 - 3 cm
3
> 3 cm

Figure 3: Graphical representation of the ENZIAN classification. http://www.endometriose-sef.de/dateien/ENZIAN_2013_web.pdf
Compartments A, B, and C (Figure 3 and 4):
The Enzian score encompasses three axes or levels (Figure 2) in compartments A, B, and C, and classifies the presence of endometriosis in each of these. Figure 2b illustrates the Enzian classification diagrammatically.

A: Pelvic compartment A comprises the rectovaginal space and vagina;

B: Pelvic compartment B comprises the uterosacral ligaments, cardinal ligaments, pelvic sidewall and extrinsic ureteric compression;

C: Pelvic compartment C comprises the lower bowel (rectum and sigmoid colon).

Grades of severity (Figure 5):
are identified for each compartment (thus excluding apparently minor peritoneal lesions) as follows:

Grade 1 invasion <1cm,

Grade 2 invasion 1-3cm,

Grade 3 invasion >3cm.
Organ involvement and other lesions (F), (Figure 6):

Deep invasion of endometriosis beyond the lesser pelvis and deep invasion of the organs is also recorded separately in the Enzian classification as follows: FA = adenomyosis; FB = bladder involvement; FU = intrinsic ureteric involvement; FI = bowel disease cranial to the rectosigmoid junction (upper sigmoid, tranverse colon, coecum, appendix, small bowel); FO = other locations such as abdominal wall or diaphragmatic endometriosis.

The prefix ‘c’ is used in cEnzian to denote a lesion suspected clinically, on imaging, or from operative findings. Once a histological diagnosis of endomtriosis has been confirmed, the ‘c’ prefix is lost and it is described as Enzian. The letter that follows marks the location of the affected compartment, followed by a number that describes the size of the lesion. Two similar letters representing the ‘same’ compartment signifies bilateral disease.

Figure 6: Uterine and other extragenital deep infiltrating endometriosis with the prefix F according to the localisation of the lesion.
## Cases:

### Case 1: (Figure 7 and 8)

The 29 years old patientin with severe dysmenorrhoea, dyspareunia and dyschezia. During laparoscopy the endomeriosis was not visible completely. The rectosigmoid was attached to the posterior part of the uterosacral ligament (Figure 7). While palpation of the nodule seemed to be bigger than the visible lesion. The preoperative assessment showed a deep nodule in the lateral rectal wall (> 3 cm) and a nodule between the rectum and the pelvic sidewall. After dissection of the nodule in two halves, the extent of the disease became visible (figure 8). There was a deep infiltrating nodule in the rectum, > 3 cm, **ENZIAN C3** and a nodule to the pelvic sidewall was also > 3 cm, **ENZIAN B3**. Only by preoperative assessment, palpation and dissection, the complete disease became visible. Classification **ENZIAN C3, B3**.

![Figure 7: Deep infiltrating endometriosis between the rectum and the uterosacral ligament right.](image)

**Figure 7**: Deep infiltrating endometriosis between the rectum and the uterosacral ligament right.
Figure 8: (after dissection of the endometriosis). Uterosacral Lig. (B3), rectum (C3)
Final score: ENZIAN B3, C3
Case 2 (Figure 9):

A patient with extreme pelvic pain and lower abdominal cramping on the left side during the menstruation. The colonoscopy showed a stenosis in the upper sigmoid. Lower pelvis did not show any intestinal endometriosis. This nodule could be also be demonstrated by the transvaginal sonography because the loop lies very close to the vagina.

Classification: ENZIAN FI.

Figure 9: Endometriosis in the sigmoid: ENZIAN FI
Case 3: (figure 10)

35 years old patient with chronic pain in the upper abdomen on the left side close to the diaphragm. She suffers from periodically problems with inspiration. The laparoscopy view showed a nodule on the left diaphragm (Figure 10).

Classification: ENZIAN FO.

Figure 10: Endometriosis on the left diaphragm. ENZIAN FO (others)
Case 4: (Fig. 11, 12):

30 years old patient with deep infiltrating endometriosis in the cul de sac. The lesion was also visible during the preoperative inspection of the posterior fornix. The transvaginal ultrasound showed a nodule > 4 cm in the fornix and the space between the vagina and the rectum (septum rectovaginale). The rectal wall was not involved. The laparoscopic view showed the same nodule (Figure 11). The nodule is already mobilized from the septum rectovaginale, the vagina is still intact.

The nodule was dissected en bloc. The figure 12 shows the open posterior fornix with the uterus manipulator.

The isolated localisation of this nodule involves the compartment A

Classification ENZIAN A3.

Figure 11 and 12: Endometriosis in cul de sac. After dissection the extend (4 cm) of the nodule between the vagina and the septum rectovaginale. The rectum is not involved. ENZIAN A3
Case 6: Figure 13:  Intrinsic endometriosis in the right ureter. ENZIAN FU

30 years old patient with hydronephrosis on the right side.
The patient had a deep infiltrating endometriosis in the cardinal ligament (ENZIAN B3) on the right side and in the anterior rectal wall ENZIAN C3.
During laparoscopy the complete fibrotic tissue in the cardinal ligament was removed. The nodule in the rectum was left behind (no symptoms). The ureter was mobilised and the infiltration of the ureteral wall became visible. A segmental resection of the ureter was performed.
Classification: ENZIAN B3, C3, FU (intrinsic ureteral infiltration)
Case 7: (Figure 14):

28 years old patient with cyclic bleeding out of the umbilicus. The nodule has been identified by ultrasound and clinical examination. Classification of deep infiltrating endometriosis outside of the pelvis.

Classification: ENZIAN FO.

Figure 14: Endometriosis umbilicus. ENZIAN FO
Case 8: (Figure 15, 16, 17)

38 years old patient with deep infiltration of the cul de sac. In figure 15 the infiltration of the cul de sac, the rectal anterior wall, the backside of the uterus and the ligamentum sacrouterinum on the left side is obvious. The preoperative assessment showed also a deep lesion in the vagina and in the anterior rectal wall > 3cm. According to the size of the lesion it was dissected in two pieces. Figure 16 shows the anterior wall of the rectum with a big nodule invading the muscularis > 3 cm (ENZIAN C3). The left uterosacral ligament has been already been removed.

On the backside of the uterus a piece of adenomyosis was also dissected.

Figure 17 demonstrates the open vagina after the removal of the vaginal nodule (ENZIAN A3).

Classification ENZIAN A3, B2, C3, FA.
Figure 15, 16, 17: Deep Endometriosis in the cul de sac including the vagina (A3), uterus (FA), uterosacral ligament (B2) and rectum (C3). ENZIAN A3, B2, C3, FA
Case 9 (Figure 18, 19, 20)

35 years old patient with chronic dysuria and haematuria during menstruation. A preoperative ultrasound assessment showed a nodule on the backside of the bladder wall close to the uterus (Figure 18). In Figure 19 the cystoscopic view confirmed the ultrasound picture with an intravesical proliferated process.

Laparoscopic dissection and removal of the nodule out of the posterior wall of the bladder (Figure 20). Classification: ENZIAN FB

Figure 18, 19, 20: Endometriosis in the bladder wall. ENZIAN FB
Case 10: (figure 21, 22, 23)

25 years old patient with longlasting extreme dysmenorrhea, hypermenorrhea and sterility (longer than 3 years).
The clinical examination showed an enlarged uterus with a thickened anterior wall.
Figure 21 shows the anterior wall of the enlarged uterus during laparoscopy.
MRI shows the typical lesion of an intramural adenomyosis of the anterior wall (Figure 22).
Due to the big nodule the laparoscopic intervention has been changed to laparotomy. The sagittal incision of the anterior wall is seen in Figure 23. The complete adenomyotic nodule has been removed and the uterus reconstructed.

Classification: ENZIAN FA

Figure 20 (above left), 21 (a. right), 22 (below): Adenomyosis, EZIAN FA
**Validation of ENZIAN:**

The validation of the score has been described by the SEF group in a retrospective study of 460 women allowing 187 women undergoing surgery (including a total of 270 lesions) to be analysed for the revised Enzian classification (Haas et al., 2013a) and 156 women to be scored preoperatively based on clinical examination findings, and imaging findings in transvaginal ultrasound and MRI (Mutuku and Keckstein, 2014).

Where deep endometriosis is present, Enzian gives a more complete description of endometriosis, when used as an adjunct to r-ASRM (Haas et al., 2013a). Previously Enzian tended to duplicate classification, thus 'over-scoring' women with deep endometriosis in whom both r-ASRM and Enzian were used. However, the revised Enzian classification has been shown to complement the r-ASRM score better and to avoid this duplication (Haas et al., 2013b).

Enzian may be used preoperatively based on clinical findings, transvaginal ultrasound and MRI. Thus, surgical planning can be improved by more accurate prediction of both the extent of deep endometriosis and predicted duration of the surgical procedure (Haas et al., 2013c).

In an analysis of 156 patients with DIE and bowel involvement Mutuku und Keckstein (2014) (Mutuku, 2015) showed a clear association between preoperative and intraoperative ENZIAN findings. A significant relationship was noted between these findings and presence of dyspareunia. However, there was no significant correlation between the extent of the disease and the dysmenorrhoea and bowel symptoms which occurred.

Bilateral involvement of compartment B is associated with a significantly higher complication rate after bowel surgery (p=0.002). Advanced surgery may be required for complete intraoperative staging.

Preoperative use of the Enzian score for correct diagnosis of DIE with MRI and Ultrasound is of great interest. Di Paola (Di Paola et al., 2015) compared MRI-ENZIAN score and histopathological-ENZIAN score. The overall sensitivity, specificity, accuracy, and positive and negative predictive values relating to presence/absence of deep endometriosis were calculated for each patient. The concordance between histopathological and MRI ENZIAN score was excellent (k=0.824). MRI correlates with the ENZIAN score and is highly accurate in the detection and localization of deep endometriosis, thus minimising false negative results (4%) in patients with deep endometriosis and allowing correct preoperative staging.

Pellegrino describes the use of ENZIAN to evaluate the Robotic Shaving Technique Deep Infiltrating
Endometriosis of the Rectovaginal Space. (Pellegrino et al., 2015)
**Summary and recommendation:**

ENZIAN is anatomically logical and easy to use. The significant association between preoperative and postoperative ENZIAN findings leads to a unified and clear classification of DIE. Thus conservative and surgical treatments, planning of therapy, and follow up are all considerably easier. The score can be used to further investigate the known associations between extent of disease and some symptoms with a view to improving correlation.

If the r-ASRM classification is to be used, the Enzian classification system should be employed when deep endometriosis is also present to give a complete description of the operative findings (Johnson et al., 2016). Enzian may be used preoperatively based on clinical findings, transvaginal ultrasound and MRI. (International statement on the classification of endometriosis through systematic appraisal of evidence and a consensus process by the WES).

It is also recommended by the CORDES statement on recording of deep endometriosis surgery to use the ENZIAN classification(Vanhie et al., 2016).
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