DEEPLY INFILTRATIVE ENDOMETRIOSIS: CLINICAL OUTCOME AFTER SURGERY IN ADULTS AND PATHWAYS TO POTENTIAL PREVENTION IN ADOLESCENTS
Thesis submitted in partial fulfillment of the requirements for the degree of «Doctor of Biomedical Sciences»
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Searching to understand human nature, I became a medical doctor. Being amazed about the origin of human life, I specialised in Obstetrics and Gynaecology and further on in reproductive medicine. Hazard (being in the right place at the right moment) and apparently having the appropriate skills made me become a reproductive surgeon. The miraculous experience of being pregnant and delivering two wonderful daughters reinforced my motivation of trying to help women with fertility problems. In this manuscript I laid down all the ideas which came progressively into my mind during 20 years of operating women with fertility problems. I hope that my younger co-workers will consider it as a base to further refine the surgical treatment of female fertility problems, and of endometriosis, this enigmatic disease disturbing the quality of life and the pregnancy wish of so many women.

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their endless love. They made me go to the top of the mountain. I wanted to show them that one can get whatever one wants by just never giving up and always continuing till the end. I hope that they understand the example I wanted to give them.
List of Abbreviations

AAGL  American Association of Gynaecologic Laparoscopists
ASRM  American Society of Reproductive Medicine
BSRM  Belgian Society for Reproductive Medicine
CASP  Critical Appraisal Skills Programme
CPP   Chronic Pelvic Pain
COCs  Combined Oral Contraceptives
DIE   Deeply Infiltrative Endometriosis
ESGE  European Society for Gynaecologic Endoscopy
ESHRE European Society of Human Reproduction and Embryology
GnRH  Gonadotropin-Releasing Hormone
ICSI  Intracytoplasmic Sperm Injection
IEC   International Endogene Consortium
IVF   In Vitro Fertilisation
IVP   Intravenous Pyelogram
ISGE  International Society for Gynaecologic Endoscopy
LLCS  Lower Limb Compartement Syndrome
LUFc  Leuven University Fertility Center
MESH  Medical Subject Hearing
MFR   Monthly Fecundity Rate
NSAIDs Non Steroidal Anti-Inflammatory drugs
OCP   Oral Contraception Pills
OR    Operating Room
PID   Pelvic Inflammatory Disease
QOL   Quality Of Life
rAFS  revised American Fertility Society
RCTs  Randomized Controlled Trials
RVE   Rectovaginal Endometriosis
TVU   Transvaginal Ultrasound
VVOG  Flemish Society of Obstetrics and Gynaecology (Vlaamse Vereniging voor Obstetrie en Gynaecologie)
WES   World Endometriosis Society
Chapter 1

General Introduction and Objective of the PhD project
General Introduction: Endometriosis

Definition
Endometriosis is a gynaecologic disorder defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic inflammatory reaction. Endometriosis predominantly affects women of reproductive age (10%) (D’Hooghe et al., 2003) and is associated with pelvic pain (dysmenorrhea, chronic pelvic pain, deep dyspareunia, dyschesia, dysuria) and/or infertility (Burns and Schenken, 1999; Gupta et al., 2008) but can be asymptomatic.

Localization and Clinical Appearance
The endometrial stray tissue is found most frequently in the pelvis, affecting the peritoneum and the pelvic organs.

Three clinical presentations have been described: peritoneal endometriosis, endometriomas (ovarian endometriotic cysts) and deeply infiltrative endometriosis (DIE) (Donnez et al., 2003). The ectopic endometrium can appear as superficial ‘powder-burn’ or ‘gunshot’ lesions on the peritoneum, serosal surfaces and ovaries. Typical peritoneal lesions are black, dark-brown, or bluish puckered lesions, nodules or small cysts containing old haemorrhage and surrounded by a variable extent of fibrosis. Atypical or ‘subtle’ lesions are also common, including red implants (petechial, vesicular, polypoid, hemorrhagic, red flame-like) and clear vesicles. Other appearances are white plaques or scarring and yellow-brown peritoneal discoloration. Ovarian endometriotic cysts (endometriomas) usually contain thick tar-like fluid (old blood). Located in the ovary (inclusive) or between ovary and ovarian fossa (invaginating) coexisting with adnexal adhesions, they are often densely adherent to the peritoneum of the ovarian fossa and the surrounding fibrosis and/or adhesions may involve the tubes (affecting fertility) and bowel (causing bowel function related pain symptoms). DIE is characterized by the invasion of anatomical structures and organs deeper than 5 - 6 mm beyond the peritoneum (Koninckx and Martin, 1994; Vercellini et al., 2004) and affects about 20 - 35% of the women with endometriosis (Chapron et al., 2001). DIE mainly involves the uterosacral ligaments, followed by the rectosigmoid colon, the vagina and the bladder (Jenkins et al., 1986).
The extent of the disease varies from a few, small lesions, limited to the superficial peritoneum, in an otherwise normal pelvis (peritoneal endometriosis) to large endometriotic cysts (endometriomas) and/or extensive fibrosis and adhesion formation causing an important distortion of the pelvic anatomy. This is merely the case when the endometriotic lesions are covered by adhesions between the posterior wall of the vagina, cervix or uterus and the front wall of the recto-sigmoid or between the anterior wall of the uterus and the bladder, causing a complete obliteration of the cul-de-sac and/or the vesico-uterine fold (DIE).

During laparoscopy or laparotomy, the degree of endometriosis is scored and staged as minimal, mild, moderate or severe disease according to the revised American Fertility Society (rAFS) classification system of the American Society for Reproductive Medicine (ASRM) (rAFS, 1997). The disease score (minimal, mild, moderate, severe) increases with the degree of peritoneal and ovarian involvement and with the extent of adnexal and cul-de-sac adhesions.

Pathogenesis
The pathogenesis of endometriosis can be explained by ectopic implantation of endometrial cells following retrograde menstruation via the Fallopian tubes into the pelvis (Sampson, 1927). Although this retrograde menstruation theory is the most widely accepted one, other theories are not mutually exclusive and have been proposed to explain the pathogenesis of endometriosis.

The coelomic metaplasia theory, proposed by Meyer in 1919, suggests that the coelomic cavity contains cells able to differentiate into endometrial tissue under the influence of unknown factors (Meyer, 1919). This theory is supported by the description of cases of endometriosis in which retrograde menstruation does not occur (Rokitansky-Küster-Hauser syndrome) and therefore cannot be explained by Sampson’s theory.

The induction theory (Merril, 1966) proposes that the menstrual endometrium produces substances that induce peritoneal tissues to form endometriotic lesions.

The embryonic remnants theory (Nisolle and Donnez, 1997) suggests that endometriosis results form pluri-potent embryonic stem cells, which could differentiate into functioning endometrium.
The lymphatic and vascular metastasis theories (Halban, 1925; Javert, 1951) propose a dissemination of endometrial cells through lymphatic and blood vessels and explain the development of endometriosis outside the pelvis.

The direct transplantation theory is the probable explanation for endometriosis developing in episiotomy, caesarean section, and other scars after surgery.

Etiology
Whichever mechanism is responsible for the development of endometriosis, despite years of research it remains unclear which additional factors influence the probability of women to become affected.

Genetic factors probably influence an individual's susceptibility to endometriosis (Bischoff and Simpson, 2000; Campbell and Thomas, 2001; Thomas and Campbell, 2000). The possibility of a familial tendency for endometriosis has been recognized for several decades. If a woman has endometriosis, a first-degree relative has a 7 percent likelihood of developing the disorder as compared with 1 percent in unrelated persons (Simpson et al., 1980). Concordance in twins has also been observed (Bischoff and Simpson, 2000).

Multiple genes which may interact with each other and the environment to confer disease susceptibility and produce the phenotype have been proposed (Kennedy, 2003) and several genetic polymorphisms associated with endometriosis have been identified (Bedaiwy et al., 2006).

Nowadays, there is evidence pointing to a complex interplay between susceptibility genes and the environment as being one of the most important effects. The International Endogene Consortium (IEC) recently published (Painter et al., 2011) the results of their genome-wide association study, which identifies variations in the DNA of women that predispose them to developing endometriosis. Two regions on chromosomes 7 and 1 associated with endometriosis have been identified by the IEC. Not only is this the first genome-wide association study to give robust evidence of variations in the DNA of women with endometriosis, but it has also shown that moderate-to-severe endometriosis is significantly more genetically driven than minimal-to-mild disease.
**Symptoms**

The **pain symptoms** of endometriosis are aspecific, with a considerable overlap with other conditions such as Irritable Bowel Syndrome and Pelvic Inflammatory Disease. Based on clinical and patient experience, it is known that complaints such as severe dysmenorrhea, chronic pelvic pain, deep dyspareunia, ovulation pain, cyclic or perimenstrual symptoms (e.g. bowel or bladder associated) with or without abnormal bleeding, often associated with chronic fatigue and a reduced Quality Of Life (QOL) (Gao et al., 2006; Jones et al., 2001a) can be caused by endometriosis. Clinical experience demonstrates however that there is no correlation between the rAFS score and the type or severity of pain symptoms (Vercellini et al., 2007) with exception of deeply infiltrative endometriotic lesions where the type and severity of symptoms appears to be related to the anatomical location (Fauconnier et al., 2002) and the depth of infiltration (Chapron et al., 2003; Koninckx et al., 1991; Porpora et al., 1999). The predictive value of any symptom or set of symptoms remains uncertain as each of these symptoms can have other causes. As a result, there is often a delay of several years between pain symptom onset and definitive diagnosis (Arruda et al., 2003; Hadfield et al., 1996; Husby et al., 2003). Moreover, a significant proportion of affected women are asymptomatic. In these women, endometriosis remains undiagnosed or is diagnosed at laparoscopy for another indication.

The association between endometriosis and **subfertility** is clinically recognized (D’Hooghe et al., 2003; de Ziegler et al., 2010; Gupta et al., 2008). When endometriosis is moderate or severe (rAFS, 1997), it usually involves the ovaries and results in adnexal adhesions that by reducing tubo-ovarian motility impede ovum pick-up function. In this situation, a causal relation between endometriosis and subfertility is likely. When endometriosis is minimal to mild, a causal relation is controversial. The following arguments point in the direction of causality: an increased prevalence of endometriosis in sub fertile women when compared to the prevalence in women of proven fertility (D’Hooghe et al., 2003), a reduced monthly fecundity rate and cumulative pregnancy rate after donor as well as husband sperm insemination in women with minimal-mild endometriosis when compared to those with a normal pelvis (Hughes, 1997; Nuojua-Huttunen et al., 1999; Omland et al., 1998), an increased monthly fecundity rate and cumulative pregnancy rate after surgical removal of minimal to mild endometriosis as shown in a multicentre randomized trial (Marcoux et al., 1997), a negative correlation between the rAFS stage of endometriosis and the cumulative
pregnancy rate after surgery (Adamson et al., 1993; Guzik et al., 1997; Osuga et al., 2002). One can conclude that fertility problems in endometriosis are multi-factorial, likely related to anatomical distortion due to adhesions and ovarian endometriotic cysts in women with moderate to severe endometriosis, and possibly related to inflammatory, immunological or endocrine factors in women with minimal-mild endometriosis without effect on tubo-ovarian anatomy.

While there seems to be a positive correlation between severity of endometriosis and degree of infertility, such a correlation is largely absent between severity of endometriosis and pelvic pain (Kennedy et al., 2005).

**Clinical Signs**

Findings during clinical examination like pelvic tenderness, a fixed retroverted uterus, tender utero-sacral ligaments or enlarged ovaries are suggestive of endometriosis (Kennedy et al., 2005). The diagnosis is more certain if deeply infiltrative nodules are found on the utero-sacral ligaments or in the pouch of Douglas, and/or visible lesions are seen in the vagina or on the cervix. However, a normal clinical examination does not rule out the possibility of endometriosis.

Deeply infiltrative nodules are most reliably detected when clinical examination is performed during menstruation (Koninckx et al., 1996) as at that moment of the menstrual cycle they are maximally swollen.

**Diagnosis**

Because of the aspecific symptoms and the not always conclusive clinical examination, the optimal way to diagnose endometriosis is by direct visualization of the implant(s) (Kennedy et al., 2005) and should ideally be confirmed by histological examination of excised lesions. Laparoscopy is the preferred technique for diagnosis since endometriosis is located primarily on the pelvic peritoneum and organs.

Imaging studies are rarely helpful for diagnosis or determining extent of disease because they lack adequate resolution for visualizing adhesions and superficial peritoneal/ovarian implants (Albrao et al., 2007). Gynaecological ultrasound is accurate for the diagnosis of ovarian
endometriotic cysts (Kennedy et al., 2005), but this also depends on the quality of the operator and his/her ultrasound equipment.

If there is clinical evidence of DIE, then the possibility of urethral, bladder, and bowel involvement should be assessed (Kennedy et al., 2005). Ultrasound (transrectal and/or transvaginal) is the first choice imaging technique to map the extent of disease (Bazot et al., 2007; Bazot et al., 2009; Faccioli et al., 2008; Goncalves et al., 2010; Hudelist et al., 2009a; Hudelist et al., 2009b; Piketty et al., 2009, Van Holsbeke et al., 2010). The choice of supplementary test(s) to evaluate the impact of DIE on the non-gynaecologic pelvic organs depends upon individual and local circumstances.

**Prevalence**

The prevalence of endometriosis is difficult to determine because symptoms are diverse and nonspecific, and because some women are asymptomatic. Moreover, laparoscopy, by far the gold standard for definitive diagnosis of endometriosis (Kennedy et al., 2005), is an invasive procedure and the sensitivity varies with the experience and the interest of the surgeon.

Although laparoscopy is the gold standard for the diagnosis of endometriosis, shifts have occurred over the last 40 years in the diagnosis and classification of endometriosis and results regarding incidence and prevalence of endometriosis need to be interpreted with caution (Koninckx, 1998). Firstly, technical amelioration of the optic instruments used in laparoscopic surgery has allowed a progressively better recognition of abnormalities on the pelvic peritoneum and anatomic abnormalities within the pelvis. Secondly, the recognition that subtle peritoneal lesions can also be a manifestation of endometriosis (Martin et al., 1989) has led to an increased diagnosis of endometriosis in women whose pelvis would have been classified as normal before the mid-eighties. Thirdly, it has been realized only in the last 20-25 years that DIE with obliteration of the cul–the-sac can laparoscopically appear as minimal or mild disease, or may not be recognized at all (Koninckx, 1998).

Therefore, little is known about the overall prevalence of this disorder (D’Hooghe et al., 2003).

The prevalence of endometriosis among women of reproductive age has been estimated to be as high as 10% (D’Hooghe et al., 2003). However, the prevalence is estimated to be higher in infertile women [35%, (D’Hooghe et al., 2003)] and in women suffering from pelvic pain
Among women with endometriosis, minimal-mild disease was observed in 37% and moderate-severe disease was found in 67% of the whole Icelandic population over a 20 year period (Gylfason et al., 2010). However, in a subfertility population (Calhaz-Jorge et al., 2003; D’Hooghe et al., 2003), the proportion of women with minimal-mild endometriosis was higher (68 - 74%) than those with moderate-severe endometriosis (24 - 32%), suggesting that the degree of endometriosis observed is largely dependent on the population studied. The distribution between different stages of endometriosis is of course also dependent on the indications and reimbursement system for laparoscopy that may vary between countries.

Treatment
Clinical manifestations of endometriosis fall into three general categories: pelvic pain, infertility and pelvic mass. The goal of therapy is to relieve these symptoms and to prevent recurrence taking into account that in most women with endometriosis, being of reproductive age, preservation of reproductive function is desirable. As the etiology of endometriosis is unclear, despite seemingly adequate medical and/or surgical treatment of the disease, the results of treatment are often temporarily with recurrence of pain. For many women, endometriosis becomes a chronic disease affecting QOL due to incapacitating pain, emotional impact of subfertility, anger about disease recurrence, and uncertainty about the future regarding repeated surgeries or long term medical therapies and their side-effects. Therefore, there is a need to look at endometriosis, at least in a subset of highly symptomatic women, as a chronic disease. QOL issues should therefore be addressed (Colwell et al., 1998; Jones et al., 2001).

As estrogen is known to stimulate the growth of endometriosis, hormonal therapy has been designed to suppress estrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding. Withdrawal of estrogen stimulation causes cellular inactivation and degeneration of endometriotic implants but not their disappearance.

Empirical treatment for pain symptoms presumed to be due to endometriosis without a definitive diagnosis includes counselling, adequate analgesia, progestins, combined oral contraceptives (COCs) and nutritional therapy.
In case of confirmed disease, non-steroidal anti-inflammatory drugs (NSAIDs) may be effective in reducing endometriosis associated pain (Kauppila et al., 1979; Kauppila et al., 1985; Ylikorkala and Viinikka, 1983).

Suppression of ovarian function for 6 months reduces endometriosis associated pain. The hormonal drugs investigated - COCs, danazol, gestrinone, medroxyprogesterone acetate and GnRH agonists - are equally effective but their side-effects and cost profiles differ (Davis et al., 2007; Prentice et al., 2000a; Prentice et al., 2000b; Selak et al., 2007). Evidence also suggests that the levonorgestrel intra-uterine-device reduces endometriosis associated pain (Petta et al., 2005; Vercellini et al., 1999) with symptom control maintained over 3 years (Lockhat et al., 2004; Lockhat et al., 2005). Treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief (Hornstein et al., 1995). Treatment with a GnRH agonist for up to 2 years with combined estrogen and progestin 'add-back' appears to be effective and safe in terms of pain relief and bone density protection; progestin only 'add-back' does not protect against bone-demineralization (Sagsveen et al., 2003). However, careful consideration should be given to the use of GnRH agonists in women who may not have reached their maximum bone density.

Most women with symptomatic endometriosis experience pain relief throughout treatment as shown in several prospective, randomized, placebo-controlled, double-blind studies (Davis et al., 2007; Prentice et al., 2000a; Prentice et al., 2000b; Selak et al., 2007). The effect lasts for a variable time after cessation of therapy. As progestins, COCs, danazol, gestrinone and GnRH agonists are equally effective, the choice of treatment is guided by cost and side effects.

Although medical therapy will improve symptoms in most of the patients, one has to take into account possible side effects of medication and a high recurrence rate of pain after discontinuation of therapy. Treatments involving suppression of ovulation also exclude the possibility of pregnancy during the treatment period. Moreover, medical interventions neither enhance fertility nor diminish endometriomas or adhesions (Hughes et al., 2007; Kennedy et al., 2005). Therefore, women with suspected endometriomas and advanced stages of disease, or infertility, are more appropriately managed surgically.
When endometriosis causes mechanical distortion of the pelvis, surgery should be performed if reconstruction of normal pelvic anatomy can be achieved. The goal of surgery is to excise or coagulate (to eliminate) all visible endometriotic peritoneal lesions, endometriotic ovarian cysts, DIE and associated adhesions, and to restore normal anatomy and normal function of pelvic organs as good as possible. The surgical technique has to be designed to realize the lowest possible complication rate and recurrence rate as QOL and fertility have to be optimized.

Conservative surgery preserves the uterus and as much ovarian tissue as possible. A laparoscopic approach offers advantages over laparotomy, including a shorter duration of hospitalization, anaesthesia, and recovery (Crosignani et al., 1996) as well as a decreased risk of adhesion formation postoperatively. Importantly, optical magnification provides better visualization of implants with the laparoscope than with open procedures.

The effectiveness of surgical ablation of endometriosis-associated pain has been convincingly shown in two randomized controlled trials where the control group underwent a laparoscopy without surgical ablation of lesions. The treated group had a significant reduction of symptoms that persisted for 12 months (Abbott et al., 2004) and 18 months (Sutton et al., 1994; Sutton et al., 1997). Furthermore, ablation of endometriotic lesions plus adhesiolysis improves fertility in women with minimal-mild endometriosis effectively compared to diagnostic laparoscopy alone (Jacobson et al., 2002).

Superficial ovarian lesions can be coagulated, vaporized or excised. The primary indication for extirpation of an endometrioma is to ensure it is not malignant. Small ovarian endometriomas (< 3 cm diameter) can be aspirated, irrigated, and inspected for intra-cystic lesions. Their interior wall can be coagulated or vaporized to destroy the mucosal lining. Ovarian endometriomas larger than 3 cm should be removed completely (Chapron et al., 2002). In cases where excision is technically difficult without removing a large part of the ovary, a two-step procedure (marsupialisation and rinsing followed by hormonal treatment and surgery 3 months later) should be considered (Donnez et al., 1996). Although as little as one-tenth of an ovary may be enough to preserve function and fertility, at least for a while, there is increasing concern that ovarian cystectomy with concomitant removal or destruction of normal ovarian tissue may reduce ovarian follicle reserve and reduce fertility (Loh et al., 1999). Therefore, it has been proposed to replace cystectomy by fenestration and coagulation.
of the inner cyst wall (Hemmings et al., 1998). However a case-control study (Saleh and Tulandi, 1999) and a randomized controlled trial (Beretta et al., 1998) have demonstrated that pain and subfertility (Beretta et al., 1998; Chapron et al., 2002; Kennedy et al., 2005), related to ovarian endometriomas, were improved more by cystectomy than by fenestration/drainage/coagulation. Therefore, based on the current evidence, ovarian cystectomy seems to be the method of choice (Chapron et al., 2002) with a significantly decreased risk of cyst recurrence (Hart et al., 2005; Kennedy et al., 2005; Vercellini et al., 2003).

Medical management of DIE, based on suppression of the symptoms, is not curative and is often associated with significant side effects (Marana et al., 1994; Telimaa, 1988; Vercellini et al., 2009). It is not clear if this approach prevents disease progression, especially in more severe cases of endometriosis. In addition, discontinuation of this therapy commonly results in recurrence (Jatan et al., 2006). Moreover, as intestinal endometriosis often undergoes fibrotic changes, it can be resistant to hormonal therapy, which makes surgical therapy the only option for treatment (Lewis and Nezhat, 2007).

Because of the relative ineffectiveness of medical therapy (Donnez et al., 2004; Olive, 2003), it is widely agreed that surgical management is the primary treatment for more severe forms of endometriosis, such as symptomatic DIE with colorectal involvement (Emmanuel and Davis, 2005; Garry, 2004). Intestinal involvement has been estimated to occur in 3 - 37% of cases of DIE (Collin and Russell, 1990; Coronado et al., 1990; Graham and Mazier, 1988). The rectum and rectosigmoid junction together account for 70% to 93% of all intestinal endometriotic sites (Bailey et al., 1994; Coronado et al., 1990). In addition to the rectosigmoid junction, the most common intestinal sites are the appendix (2 - 18%), the distal ileum (2 - 16%) and the caecum (< 2%) (Zwas and Lyon, 1991).

The term “bowel endometriosis” is used when endometrial-like glands and stroma infiltrate the bowel wall reaching at least the subserous fat tissue or adjacent to the neurovascular branches (subserous plexus) (Remorgida et al., 2007). As initially suggested by Chapron (Chapron et al., 2003), endometriotic foci located on the bowel serosa should be considered to be peritoneal and not bowel endometriosis (Remorgida et al., 2007). Bowel endometriosis can cause severe symptoms which may affect QOL, such as bowel cramping, abdominal bloating,
diarrhoea, constipation, dyschesia and cyclical rectal bleeding (Garry et al., 2000; Redwine and Wright, 2001).

A positive correlation exists between the extent of endometriosis resection and the degree of postoperative improvement (Chapron et al., 2004). Laparoscopic segmental excision of the rectum and other types of colorectal surgery, such as discoid excision and superficial shaving, have become increasingly popular but the appropriate surgical approach for DIE with involvement of the bowel remains controversial as little is known about the impact of the different types of surgery in the treatment of DIE involving the bowel on complications, pain, the patients’ QOL, reintervention/recurrence rate and pregnancy rate or fertility.

During reproductive age, radical excision of endometriosis combined with pelvic reconstruction appears to be the best option. DIE is usually multifocal and complete surgical excision must be performed in a one step surgical procedure, in order to prevent more than one surgery (Chapron et al., 2003). Complete removal of deep pelvic endometriosis has been reported to improve QOL and potentially fertility, but may be associated with a high risk of postoperative complications (Abbott et al., 2003; Adamson and Nelson, 1997; Coronado et al., 1990; Hughes et al., 1993; Redwine and Wright, 2001) such as bowel perforations with resulting peritonitis (Koninckx et al., 1996).

The risk of recurrences is significantly correlated to the age of the patients. The younger the patients are at the moment of the diagnosis, the higher the risk of recurrence. Higher recurrence rates in younger patients seem to justify a more radical treatment in this group (Fedele et al., 2004). Moreover, surgery resulted in pain relief in 80% of patients with severe disease who did not respond to medical therapy (Sutton and Hill, 1990).

It is commonly accepted that DIE, which involves intestines and/or bladder and ureters, is a challenging condition. This approach requires expertise, available in specialist centers (Emmanuel and Davis, 2005; Kennedy et al., 2005; Perry, 2005; Redwine and Wright, 2001) with multidisciplinary surgical approach, involving gynaecological surgeons, bowel surgeons and urologists. These severe cases should be handled by centers with special expertise (D’Hooghe and Hummelshoj, 2006; Kennedy et al., 2005). On the other hand, there is a lack of long term follow-up data on complication rate, cumulative recurrence and cumulative
pregnancy rate, pain, QOL and sexual satisfaction after radical but fertility-sparing laparoscopic excision of endometriosis.

Neither Randomized Controlled Trials (RCTs) nor meta-analyses are available to answer the question whether surgical excision of moderate to severe endometriosis enhances pregnancy rate (Kennedy et al., 2005). Based upon three studies (Adamson et al., 1993; Guzick et al., 1997; Osuga et al., 2002) there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was only reached in one study (Osuga et al., 2002). On the other hand, in recently published work (Stepniewska et al., 2009) the influence of bowel endometriosis on fertility was evaluated by comparing the postoperative pregnancy rate, time to conception and monthly fecundity rate between three groups of infertile patients. Group A (60 women) consisted of patients who underwent surgery for endometriosis with colorectal segmental resection. In group B, 40 patients with evidence of bowel endometriosis underwent endometriosis removal without bowel resection. Group C consisted of 55 women who underwent surgery for moderate or severe endometriosis with at least one endometrioma and DIE but without bowel involvement. The monthly fecundity rates (MFR) in groups A, B and C were 2.3, 0.84 and 3.95%, respectively. The difference in the MFR between groups was significant (p = 0.05). According to this study (Stepniewska et al., 2009) the presence of bowel infiltration by endometriosis seems to negatively influence the reproductive outcome in women with endometriosis-associated infertility and complete removal of endometriosis with bowel segmental resection appears to improve fertility.

**Assisted Reproduction in Endometriosis**

Endometriosis can impair female reproduction in nearly every process during attempted conception (Germeyer et al., 2005).

Treatment with intra-uterine insemination (IUI) improves fertility in minimal-mild endometriosis: IUI with ovarian stimulation is effective but the role of un-stimulated IUI is uncertain (Tummon et al., 1997).

In Vitro Fertilization (IVF) is an appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed. On the other hand, IVF pregnancy rates are lower in patients with endometriosis (lower embryo
implantation, fertilization and pregnancy rates, as well as fewer oocytes retrieved) than in those with tubal infertility (Barnhart et al., 2002).

Treatment with a GnRH agonist for 3 - 6 months before IVF or ICSI should be considered in women with endometriosis as it increases the odds of clinical pregnancy fourfold. However, the authors of the Cochrane review stressed that the recommendation is based on only one properly randomized study and called for further research, particularly on the mechanism of action (Sallam et al., 2006).

Risk of recurrence is no reason to withhold IVF therapy after surgery for endometriosis stage III or IV since cumulative endometriosis recurrence rates are not increased after ovarian hyperstimulation for IVF (D’Hooghe et al., 2006).

Laparoscopic ovarian cystectomy in patients with unilateral endometriomas between 3 and 6 cm in diameter before IVF/ICSI can decrease ovarian response without improving cycle outcome (Demirol et al., 2006). Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥ 4 cm in diameter is present to confirm the diagnosis by means of histological examination, reduce the risk of infection, improve access to follicles and possibly improve ovarian response. The patient should be counselled regarding the risks of reduced ovarian function after surgery and eventually the loss of an ovary. The decision should be reconsidered if she has previously under ovarian surgery.

**Endometriosis in Adolescents**

The most common presenting symptom in adolescents with endometriosis is cyclic pain. Less commonly, acyclic pain, dyspareunia, gastrointestinal symptoms, irregular menses, urinary symptoms and vaginal discharge are described (Bai et al., 2002, Ballweg, 2003; Goldstein et al., 1980). On the other hand, similar presenting symptoms occur in adolescent patients evaluated for pelvic pain with and without endometriosis (Laufer et al., 1997; Reese et al., 1996).

To investigate whether the clinical history, particularly of the adolescence period, contains markers of DIE, 229 adults operated on for endometriosis were evaluated (Chapron et al., 2010). Endometriotic lesions were confirmed by means of histological examination as non-DIE (superficial peritoneal endometriosis and/or ovarian endometriomas) (n = 131) or DIE
(n = 98). Patients with DIE had significantly more positive family history of endometriosis and more absenteeism from school during menstruation. The OCP use for treating severe primary dysmenorrhea was more frequent in patients with DIE. Duration of OCP use for severe primary dysmenorrhea was longer in patients with DIE. There was a higher incidence of OCP use for severe primary dysmenorrhea before 18 years of age in patients with DIE. In a recent case control study (Treloar et al., 2010) investigating the association between early menstrual characteristics, before symptom onset, and later diagnosis of endometriosis in women with surgically confirmed moderate to severe endometriosis (cases, n = 268) and women without endometriosis (controls, n = 244), an increased risk of endometriosis was found in women with an early history of dysmenorrhea.

Endometriosis lesions can be detected frequently in adolescent patients with chronic pelvic pain. Prevalence rates of endometriosis in adolescent patients undergoing laparoscopy for chronic pelvic pain range from 19% to 73% (Emmert et al., 1998; Goldstein et al., 1980; Hassan et al., 1999; Kontoravdis et al., 1999; Laufer et al., 1997; Reese et al., 1996; Vercellini et al., 1989). Because dysmenorrhea is very common in adolescents not all young women with pelvic pain can be subjected to invasive diagnosis by laparoscopy. However, if combination hormone therapy (such as OCP) or non-steroidal anti-inflammatory drugs fail, 35 - 73% of adolescents do have endometriosis at the time of laparoscopy (Laufer et al., 1997; Reese et al., 1996; Stavroulis et al., 2006).

Minimal to mild endometriosis according to the rAFS classification are the most common stages of the disease in adolescents. Gynaecologic surgeons should pay special attention to red, clear or white lesions which were reported to be more prevalent in adolescents as opposed to adults who have endometriosis (Bai et al., 2002; Davis et al., 1993; Emmert et al., 1998; Goldstein et al., 1980; Hassan et al., 1999; Laufer et al., 1997; Marsh and Laufer, 2005; Reese et al., 1996; Vercellini et al., 1989).

Treatment algorithms for management of adolescent endometriosis are based upon pathophysiologic principles and extrapolation of data from adult endometriosis. Physicians treating adolescents with endometriosis should adopt a multidimensional approach: surgery, hormonal manipulation, pain medication, mental health support, complementary and alternative therapies, and education in self management strategies are useful components.
**Objective of the PhD project**

The PhD project, entitled ‘Deeply Infiltrative Endometriosis: Clinical Outcome after Surgery in Adults and Pathways to Potential Prevention in Adolescent’ has 2 aims.

*The first aim (Chapter 2)* was to provide a clinical outcome assessment of CO₂ laser laparoscopic radical excision of DIE with extension to bowel and/or bladder, in order to monitor the quality of care of the multidisciplinary surgical team developed at the LUFc over the last 15 years.

*The second aim (Chapter 3)* was to address ways of preventing the development of DIE by documenting the need for early diagnosis and treatment of endometriosis in adolescents and young women with significant menstruation-associated pelvic pain.
Reference List


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Chapter 2

Deeply Infiltrative Endometriosis:
Clinical Outcome after Surgery in Adults
2.1 Study approach

The Leuven University Fertility Centre (LUFc) has an ISO 9001-2000 certification (since 2004) for multidisciplinary quality management of patients with fertility problems and is a tertiary referral centre for endometriosis. In that context, fertility exploration and treatment as well as the management of endometriosis are performed according to a commonly agreed and yearly reviewed/updated protocol.

Since 2003, clinical data of all patients consulting the LUFc are available in an electronic file. This file is completed by a staff member of the LUFc at the first out-patient visit and includes a detailed gynaecological history including endometriosis related pain symptoms (dysmenorrhea, chronic pelvic pain and deep dyspareunia) as well as information with respect to previous surgery and reproductive wishes. Laparoscopic explorations in patients with infertility with or without pain are performed by or under the supervision of one fertility surgeon with experience in laparoscopic diagnosis and treatment of endometriosis since 1989. The status of the pelvis is encoded in the electronic file immediately after surgery by the main fertility surgeon. Detailed information about cycles of medical assisted procreation as well as information about every contact with the patient at outpatient clinic can also be found in the electronic file.

Therefore, the LUFc meets two conditions necessary to decrease the heterogeneity in research on the prevalence of endometriosis: endometriosis surgery by or under supervision of one fertility surgeon (CM) and a systematic and detailed electronic patient file (Guo and Wang, 2006). In view of this background, our centre has all necessary conditions to perform a study on the prevalence of endometriosis in women with infertility. For 15 years it has been standard practice at the LUFc to propose a hysteroscopic and laparoscopic investigation to all women with infertility for at least one year, with a regular cycle (variation 21 – 35 days), whose partner has a normal semen analysis, allowing the prevalence of endometriosis in women with unexplained infertility to be explored (Chapter 2.2). In an answer to two ‘Letters to the Editor’ the statements made in the discussion of the resulting paper, are more profoundly argued.
The guidelines for the diagnosis and treatment of endometriosis of the European Society of Human Reproduction and Embryology (ESHRE) were summarized in the Dutch language (Chapter 2.3).

At the LUFc, advanced endometriosis with colorectal wall invasion and/or invasion of the wall of the bladder and ureters is treated laparoscopically by a multidisciplinary team. The gynaecologist (CM), trained in reproductive (endoscopic) surgery, defined as surgery performed to diagnose, conserve, correct and/or improve reproductive function (Zegers-Hochschild et al., 2009), performs a radical (but fertility sparing) excision of endometriosis with a CO₂ laser and afterwards a urologist and a colorectal surgeon, both also adept at laparoscopy, evaluate the integrity of the wall of the ureters/bladder, and the intestines respectively. An injury of the ureter or a bladder perforation due to segmental resection for bladder endometriosis is laparoscopically sutured by the urologist (B. Van Cleynenbreugel). If necessary, the urologist performs a re-implantation of a ureter in the bladder (Boarry plasty). The colorectal surgeon (A. D’Hoore) evaluates the integrity of the rectosigmoid colon and takes the final decision to either suture the bowel wall (minor seromuscular injury: reinforcing suture / small transmural lesions of the wall of the rectum (but not the sigmoid): suture) or to resect the bowel segment (with primary reanastomosis) that had been involved in the endometriotic nodule and was previously cleaned from all visible and palpable endometriosis by the gynaecologist. The treatment of bowel endometriosis depends on the type of the lesion and its extension and is performed laparoscopically, following the basic rules of bowel surgery. The following conditions can be considered as indications for bowel resection and reanastomosis: large direct full-thickness trauma to the colorectal wall, extensive lesion to the bowel wall musculature, and extensive lateral dissection compromising the colorectal wall vascularity and/or innervation. Perforation of the vagina due to segmental resection of the posterior wall is laparoscopically sutured by the gynaecologist. Endometriosis is scored and staged according to the revised ASRM (former American Fertility Society) classification of endometriosis (rAFS, 1997). A histological examination is performed on all resected tissue specimens.

As part of a quality control program related to the ISO 9001-2000 certification of the LUFc for the management of reproductive problems, a continuous clinical outcome assessment of the surgical program of the LUFc was set up. The following outcome variables were prospectively assessed: complications, recurrence of endometriosis, pain, fertility and QOL.
including sexual function. This assessment was based on a structured report of relevant clinical data obtained from patient files before, during and after admission for surgery, and on patient-centred reporting of the outcome variables mentioned above using visual analogues scales for pain assessment (dysmenorrhea, deep dyspareunia, chronic pelvic pain), and standardized questionnaires to record QOL (Jones et al., 2001), sexual function (Jones et al., 2001; Thirlaway et al., 1996) and health-economic variables before and after surgery. This method was used prospectively (2006 - 2008, Chapter 2.8) and was also applied in 2 retrospective cohort studies (1996 - 2004, Chapter 2.4; 2004 - 2006, Chapter 2.6).

In a first pilot study (Chapter 2.4) feasibility and safety of the above described multidisciplinary approach was demonstrated in all patients with DIE and colorectal extension operated in a multidisciplinary way between 1996 and August 2004 (n = 56) as well as improved QOL, pain, sexual function, high pregnancy rate and low postoperative complications and recurrence rate. In a Letter to the Editor, we react against the wrong presentation of data from our pilot study in an opinion paper published in the “Journal of Minimally Invasive Gynecology” (Koninckx et al., 2010).

In addition, a strategy to prevent the compartment syndrome, a complication we encountered during long lasting multidisciplinary endoscopic surgery, (2004 - 2008, Chapter 2.5) was evaluated.

The second study (Chapter 2.6) was executed as a validation of these previously good results, focusing on the group of women with DIE with colorectal wall invasion who underwent multidisciplinary CO₂ laser laparoscopic radical excision and segmental bowel resection and reanastomosis between September 2004 and September 2006. QOL, pain, sexual function, pregnancy rate, postoperative complications and recurrence rate were assessed. This subgroup was chosen because it is important to report clinical outcome after segmental bowel resection and reanastomosis, since this technique possibly increases the risk of complications when compared to discoid excision (Fanfani et al., 2010; Landi et al., 2008; Mohr et al., 2005; Ret Davalos et al., 2007; Roman et al., 2010).
Moreover, in a systematic review paper, we concluded that very few long-term follow-up data are available regarding QOL, cumulative pregnancy rate or cumulative recurrence rate after this type of surgery (Chapter 2.7). Based on the need to establish completeness and uniformity of the data collected during outcome studies evaluating the impact of surgery for DIE with colorectal extension, a checklist similar to the CONSORT guidelines concerning randomized trials for non-pharmaceutical interventions (Boutron et al., 2008b; Boutron et al., 2008a), was proposed. The checklist contains 32 items that should ideally be taken into account when designing a study for the surgical treatment of DIE and reporting the results of that study. More specifically, the checklist provides details on the description of participants, interventions, follow-up period, pain measurement, QOL measurement, and how to report data on histological confirmation, complications, additional interventions, fertility rate and recurrence rate. Based on the insights obtained during this systematic review (Chapter 2.7) and during our outcome studies (Chapters 2.4 and 2.6), we submitted a letter to the editor of ‘Human Reproduction’, as part of a post publication peer review process (Anderson, 1999), to highlight a number of limitations of a recently published prospective clinical outcome studies after conservative surgery by the shaving technique for deep rectovaginal endometriotic (RVE) nodules (Donnez and Squifflet, 2010). In this letter, in line with our systematic review (Chapter 2.7), we underline why international agreement on terms and definitions to assess clinical outcome after endometriosis surgery is needed.

Proposed guidelines for study design, proposed in our systematic review based on the CONSORT guidelines (Chapter 2.7), were applied for the first time in our prospective follow-up study after surgery in women with moderate to severe endometriosis (Chapter 2.8). Out of all patients operated between 1 September 2006 and 30 September 2008 and prospectively followed-up, we selected, for clinical outcome assessment, those patients with moderate to severe endometriosis (classified as rAFS III and IV) and compared the group who underwent bowel resection and reanastomosis with the group without this procedure to prospectively evaluate our operative procedure of radical but fertility sparing resection of all visible endometriosis with restoration (as good as possible) of normal anatomy and normal function of reproductive organs in a three step operative procedure by a multidisciplinary team of three surgeons of different specialties, all adept at laparoscopy.
A standardized questionnaire to record health-economic variables before and after surgery, used in the prospective follow-up of all patients operated between September 2006 and September 2008, allowed quantifying the non-health care costs associated with endometriosis in a sample of Belgian patients over a 30-month period (Chapter 2.9). The findings provide insight into the most important component of the economic burden associated with endometriosis.
Reference List


2.2. High Prevalence of Endometriosis in Infertile Women with Normal Ovulation and Normospermic Partners

Christel Meuleman M.D., Birgit Vandenabeele M.D., Steffen Fieuws Ph.D., Carl Spiessens Ph.D., Dirk Timmerman M.D., Ph.D., Thomas D'Hooghe M.D., Ph.D.

Fertility and Sterility, Volume 92, Issue 1, July 2009, Pages 68-74

Letter to the Editor

High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners

Krithiga Ilangavan M.R.C.O.G and Emmanuel Kalu M.R.C.O.G.

Fertility and Sterility, Volume 93, Issue 3, February 2010, Page e10

Letter to the Editor

Endometriosis: is laparoscopy justified without previous ultrasonogram and magnetic resonance imaging (MRI)?

Jean Belaisch M.D.

Fertility and Sterility, Volume 93, Issue 3, February 2010, Page e11

Reply of the Authors

Endometriosis: is laparoscopy justified without previous ultrasonogram and magnetic resonance imaging (MRI)? & High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners

Christel Meuleman M.D., Carla Tomassetti M.D., Dirk Timmerman M.D., Ph.D., Thomas D'Hooghe M.D., Ph.D.

Fertility and Sterility, Volume 93, Issue 3, February 2010, Page e12
High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners

Christel Meuleman, M.D., a Birgit Vandebroek, M.D., a Steffen Fieuws, Ph.D., a Carl Spiessens, Ph.D., b Dirk Timmerman, M.D., Ph.D., b and Thomas D’Hooghe, M.D., Ph.D. a

a Leuven University Fertility Centre, Department of Obstetrics and Gynecology; b Department of Obstetrics and Gynecology, University Hospital Leuven; and c Biostatistical Centre, University of Leuven, Leuven, Belgium

Endometriosis is a gynecological disorder defined by the presence of endometrial glands and stroma outside the uterus that primarily affects women during their reproductive years. It is associated with pelvic pain and infertility but can be asymptomatic. The stray endometrial tissue is found most frequently in the pelvis, where it can be limited to the superficial peritoneum or infiltrate deeply into the bladder, the ureters, the intestines, or the cul-de-sac. The degree of endometriosis can be staged laparoscopically according to the classification of the American Society of Reproductive Medicine (ASRM) (1). Endometriosis can cause a complete obliteration of the cul-de-sac when covered by adhesions between the posterior wall of the vagina, cervix, or uterus and the front wall of the rectosigmoid. Endometriosis in these locations can account for symptoms of deep dyspareunia and dyschezia and reduces the patient’s quality of life, sexual activity, and fertility (2). Ectopic endometrial tissue can develop into endometriotic cysts filled with old blood, which are named endometriomas when they are located in the ovary or between the ovary and ovarian fossa. Although there is a reasonable body of evidence to demonstrate an association between endometriosis and infertility, a causal relation between endometriosis and infertility is likely but remains controversial, especially with respect to minimal or mild endometriosis (1, 3, 4). Moreover, surgical treatment of endometriosis in infertile women improves their pregnancy rate (5, 6).

The diagnosis of endometriosis is made after laparoscopic inspection of the pelvis and should be confirmed by histological examination of the excised lesions (7). Since laparoscopy is the gold standard for the diagnosis of endometriosis, shifts have occurred over the last 25 years in the diagnosis and classification of endometriosis, and results regarding the incidence and prevalence of endometriosis need to be interpreted with caution (10). First, technical amelioration of the optic instruments used in laparoscopic surgery has allowed a progressively better recognition of abnormalities on the pelvic peritoneum and anatomic...
abnormalities within the pelvis. Second, the recognition that subtle peritoneal lesions can also be a manifestation of endometriosis (11) has led to an increased diagnosis of endometriosis in women whose pelvis would have been classified as normal before the mid-1980s. Third, it has been realized only in the last 10–15 years that deeply infiltrating endometriosis with obliteration of the cul-de-sac can laparoscopically appear as minimal or mild disease or may not be recognized at all (10).

At the Leuven University Fertility Centre (LUFC), all laparoscopic explorations in patients with infertility with or without pain have been performed by or under the supervision of one fertility surgeon (first author C.M.) with experience in laparoscopic diagnosis and treatment of endometriosis since 1989. The goals of reproductive surgery at the LUFC are to excise all lesions, to restore normal anatomy, and to confirm the visual diagnosis of endometriosis by histological examination. Since 2003, clinical data of all patients consulting the LUFC are available in an electronic file, which is completed by a staff member of the LUFC at the first outpatient visit and includes a detailed gynecological history including dysmenorrhea and deep dyspareunia. Therefore, the LUFC meets two conditions necessary to decrease heterogeneities in research on the prevalence of endometriosis: endometriosis surgery by or under supervision of one fertility surgeon and a systematic and detailed electronic patient file (12). Furthermore, the LUFC has an ISO 9001-2000 certification for multidisciplinary quality management of patients with fertility problems and is a tertiary referral center for endometriosis. In that context, fertility exploration and treatment as well as the management of endometriosis are performed according to a commonly agreed-on protocol at the LUFC. For 10 years, it has been standard practice at the LUFC to propose a hysteroscopic and laparoscopic investigation to all women with infertility for at least 1 year who have regular cycles (variation, 21–35 days) and whose partners have a normal semen analysis. In view of this background, our center has all necessary conditions to perform a study on the prevalence of endometriosis in women with infertility.

No information is available in the literature regarding the prevalence of histologically proven endometriosis in a subset of infertile women with a regular cycle (21–35 days) whose partner has normal semen analysis. We hypothesized that the prevalence of endometriosis in this subgroup is as high as 50% and justifies the need for an endoscopic exploration (hysteroscopy and laparoscopy) with surgical treatment of endometriosis and all other fertility-reducing pelvic pathologies before starting any other fertility treatment.

MATERIAL AND METHODS

At the LUFC Department of Obstetrics and Gynecology of the University Hospital Leuven, Belgium, a retrospective case series based on an electronic search of patient files was performed, after obtaining approval from the Ethics Committee of Leuven University Hospital (see also ClinicalTrials.gov ID: NCT00461439).

The standard infertility investigation in our center includes male medical history, clinical examination, sperm analysis (two separate samples with at least a 1-week interval and an interpretation according to World Health Organization [WHO] criteria) (13), with optional additional ultrasound and hormonal blood analysis, as well as female medical history, clinical examination, gynecological ultrasound, and day 3 blood analysis for reproductive hormones and thyroid function. In women with anovulation, tubal patency and uterine cavity are usually investigated by hysterosalpingography. In couples with severe male factor infertility, tubal patency is not assessed and hysteroscopy is done before IVF treatment. Women with infertility for at least 1 year with regular cycles (variation, 21–35 days) whose partners have a normal semen analysis receive a hysteroscopic and laparoscopic investigation, during which a search is made for endometriosis as a possible cause of infertility.

The availability of an electronic file system (Astraia, Munich, Germany) has allowed us to manage all medical and relevant social data of the couples attending the LUFC since 2003. By means of the “query” function of the program, it is possible to select a group of patients with specific properties, that is, patients with regular cycles (variation, 21–35 days) whose partners have a normal semen analysis.

In this study, the electronic files of all patients who consulted the LUFC since 2003 were searched to select women with at least 1 year of infertility and a regular cycle (variation, 21–35 days) whose partners have a normal semen analysis according to WHO criteria and without a history of tubal ligation (n = 304). After exclusion of 83 (27.3%) patients with a previous laparoscopic diagnosis of endometriosis before referral to our center, 221 (72.7%) infertile women were included in our study. These patients had a regular cycle (variation, 21–35 days), a partner with normal semen analysis, and no previous surgical diagnosis of endometriosis. According to our policy, they all underwent a diagnostic laparoscopy at the LUFC to determine the presence of endometriosis and other fertility-reducing factors (tubal and uterine) and to surgically treat endometriosis and all other fertility-reducing pelvic pathologies before starting any other fertility treatment.

All laparoscopies were performed by or in the presence of (supervised by) the first author. All surgical reports of these laparoscopies were written by the first author or were supervised by her in cases in which the report had been written by a colleague who was trained and supervised by her during the operation. During laparoscopy, endometriosis was scored and staged according to the revised American Fertility Society (rAFS) classification system of the ASRM (1). Although individual endometriotic lesions were not described in detail with respect to type or localization, endometriotic implants on the peritoneum or ovaries were scored according to diameter and depth, whereas the scoring of adhesions took into account the density and degree of enclosure. Total rAFS scores (implants and adhesions) from 1 to 5, 6 to 15, 16 to 40, and 41 to 150 corresponded to minimal (stage I), mild (stage II), moderate (stage III), and severe (stage IV) endometriosis.
respectively (14). Radical excision of endometriosis with CO₂ laser by the gynecologist included resection of endometriotic adhesions and endometriotic cysts, wide excision of diseased peritoneum, radical nodulectomy, and reconstruction of pelvic anatomy. This procedure was monitored visually and by touching indurations present with the rinsing/aspiration probe. A histological examination was performed on all resected tissue specimens. Patients were classified into the “endometriosis” group only if endometrial glands and stroma were found during histological examination of the resected specimens.

The study patients were analyzed for age, body mass index (BMI), duration and type of infertility (primary or secondary), prevalence of pain (dysmenorrhea and dyspareunia), the presence of hyper-echogenic ovarian cysts and/or nodules that were labeled as positive for endometriosis on the report of preoperative transvaginal ultrasound (TVU) carried out 3.4 ± 3.1 months before surgery, laparoscopic and histological evidence of endometriosis, and endoscopic evidence of uterine problems and tubal problems.

Statistical analysis included the calculation of 95% exact confidence intervals for percentages. Fisher’s exact test and the Kruskal-Wallis test were used to compare, respectively, proportions of endometriosis and of tubal pathology and continuous variables (age, BMI, duration of infertility) between groups. A multivariable logistic regression model was used to predict endometriosis based on the following clinical parameters: pelvic pain, type of infertility (primary/secondary), age, duration of infertility, and ultrasound data. Restricted cubic splines were used to allow flexible nonlinear relations and to avoid the a priori assumption of a linear relation (on the logit scale) between a continuous predictor and endometriosis (15). A receiver-operator curve (ROC) curve was constructed. The diagnostic performance of the logistic models was summarized by the c-index, which represents the area under the ROC curve. The c-indices of 0.5 and 1 correspond to no predictive power and perfect prediction, respectively. P < .05 was considered statistically significant. All reported P-values were two-sided.

RESULTS

An overview of the results is presented in Table 1. The overall prevalence of endometriosis was 47% (95% confidence interval [CI], 40%–54%), including mostly (63%) stage I–II endometriosis. Women with endometriosis had a shorter duration of infertility (P = .023) and were significantly younger (P = .005) than women without endometriosis, that is, 41 ± 68 (60%) of the women aged 25–30 had endometriosis, compared with 59/143 (42%) of the women older than 35. The prevalence of endometriosis was also significantly higher (P = .0003) in women with primary infertility (56%; 82/147) than in women with secondary infertility (30%; 22/74).

The overall prevalence of pelvic pain (dysmenorrhea or dyspareunia) was 51% (113/221) and was higher (P = .043) in women with endometriosis (59%; 61/104) than in women without endometriosis (44%; 52/117). On the other hand, the presence of endometriosis was comparable in patients with (54%, 61/113) and without (44%, 43/100) pelvic pain (P = .059). Not surprisingly, the predictive value of pelvic pain for the diagnosis of endometriosis remains rather low, with a sensitivity of 59% (CI, 48.6%–68.2%), a specificity of 56% (CI, 46.1%–64.7%), a positive predictive value of 54% (CI, 44.4%–63.4%), and a negative predictive value of 57% (CI, 50.2%–63.6%). The c-index equals 0.571. The predictive performance could be increased by adding other sources of information, that is, age, duration of infertility, and primary infertility, in a multivariable logistic regression model to predict endometriosis. The ROC curve obtained from this model is shown in Figure 1. The c-index equals 0.752 and yields a sensitivity of 65% and a specificity of 73%, using 0.52 as a cutoff for the predicted probability. Although this prediction was clearly improved compared with the use of pelvic pain alone, it is still far from optimal and not useful in clinical practice. A comparable diagnostic performance (c = 0.756) is obtained when a multivariable model with the same set of predictors is applied for the prediction of rAFS III–IV endometriosis.

A preoperative TVU examination was performed in 147 (67%) of 221 patients (Table 2). Endometriosis was suspected in only 20 patients (20/147 = 14%), but three women with a hyperechogenic ovarian cyst at TVU did not reveal any endometriosis at laparoscopy. The other 17 patients had rAFS I–II endometriosis (n = 1) or rAFS III–IV endometriosis (n = 16). In patients without anatomical abnormalities (hyperechogenic cysts or nodules) suggestive of endometriosis at preoperative TVU, the prevalence of endometriosis was 46% (58/127). Endometriosis was not visualized by preoperative TVU in 98% (43/44) of patients with rAFS II–III endometriosis or in 48% (15/31) of patients with rAFS III–IV endometriosis at laparoscopy. Among the patients who underwent a TVU, the information from the TVU increased the diagnostic performance of the multivariable model to predict rAFS III–IV endometriosis from c = 0.766 to c = 0.871. However, the TVU information only had a negligible impact on the diagnostic performance of the multivariable model (increase of the c-index from 0.763 to 0.797) for the prediction of endometriosis rAFS I–II.

The number of patients with fertility-reducing nonendometriotic pelvic pathology is presented in Table 3. Fertility-reducing nonendometriotic pelvic pathology was observed in 29% of all patients and included uterine pathology (submucous uterine myoma, endometrial polyp, endometritis, uterine septum, diethylstilbestrol [DES] malformation; 9%), nonendometriotic tubal pathology (hydrosalpinx, adnexal adhesions compromising tubal pick-up, and occlusion of the oocyte; 19%), and combined uterine/nonendometriotic tubal pathology (1%). In women without endometriosis, the prevalence of a fertility-reducing pathology of the uterus and/or the tubes was 40% (Table 3) and comparable in women with pain (39%, 20/52) and in women without pain (42%, 9/21).
Furthermore, 31% (36/117) of patients without endometriosis had nonendometriotic tubal pathology, which was caused by a previous pelvic infection (Table 3). Among patients with endometriosis, 8% (8/104) had nonendometriotic tubal pathology, which was caused by a ruptured appendix (n = 3), abortion (n = 2), or pelvic inflammatory disease (n = 3; Table 3). In our group of 221 patients, we found five women with a Mullerian anomaly (septum). In four (80.0%) of them we diagnosed endometriosis.

### DISCUSSION

In this study, we were able to confirm our hypothesis that the prevalence of endometriosis is about 50% (47% to be exact) in a well-defined group of patients consulting our center, that is, women with infertility of at least 1 year, regular cycles, and partners with normal semen analysis. To the best of our knowledge, our study is the first to document the prevalence of endometriosis in this well-defined population. This prevalence is higher than the overall prevalence of endometriosis in infertile women, which is estimated to be about 30% (4, 12).

However, the proportion of women in our study with stage I–II endometriosis (63%) and stage III–IV endometriosis (36%) was comparable to data in the literature (68% and 32%, respectively) (4).

Several possible sources of bias that may affect the interpretation of our data exist and include referral bias, recall bias, and selection bias. In our study, patients were referred to our center because they had infertility of at least 1 year, regular cycles, and partners with normal semen analysis. This selection bias may have led to an overestimation of the prevalence of endometriosis in our study. Additionally, the high prevalence of endometriosis in our study may be due to the fact that our patients were recruited from a single center, which may not be representative of the general population of infertile women. Finally, the high prevalence of endometriosis may be due to the fact that our patients were referred to our center because they had infertility of at least 1 year, regular cycles, and partners with normal semen analysis. This referral bias may have led to an overestimation of the prevalence of endometriosis in our study.

### TABLE 1

<table>
<thead>
<tr>
<th>Description of the study population.</th>
<th>Patients without endometriosis (n = 117)</th>
<th>Patients with endometriosis (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age, years</td>
<td>32.4 ± 4.3 (19–42)</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>22.8 ± 4.2 (17–39)</td>
</tr>
<tr>
<td></td>
<td>Cycle length, days</td>
<td>28 (24–42)</td>
</tr>
<tr>
<td></td>
<td>Duration infertility, years</td>
<td>2.4 (1–15)</td>
</tr>
<tr>
<td></td>
<td>Primary infertility (%)</td>
<td>65 (56)</td>
</tr>
<tr>
<td></td>
<td>Pelvic pain (%)</td>
<td>52 (44)</td>
</tr>
<tr>
<td></td>
<td>Only dysmenorrhea</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Only dyspareunia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>9</td>
</tr>
</tbody>
</table>

Note: Mean ± SD (range) or median (range) is indicated for continuous variables. P-values are based on Kruskal-Wallis tests and χ²-tests.

**Meuleman. Endometriosis prevalence in infertile women. Fertil Steril 2009.**

### FIGURE 1

ROC curve for prediction of endometriosis, using pelvic pain, type of infertility, age, and duration of infertility as sources of information (sens = sensitivity, spec = specificity).

**Meuleman. Endometriosis prevalence in infertile women. Fertil Steril 2009.**

### TABLE 2

| Relationship between the presence of endometriosis and the result of TVU. |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| TVU                        | No endometriosis | rAFS I–II | rAFS III–IV | Total |
| Negative                   | 69               | 43        | 15          | 127   |
| Positive                   | 3                | 1         | 16          | 20    |
| Total                      | 72               | 44        | 31          | 147   |

Note: A positive TVU is defined as the presence of anatomical abnormalities, including hyperechogenic cysts or nodules, suggestive of the presence of endometriosis.

**Meuleman. Endometriosis prevalence in infertile women. Fertil Steril 2009.**
bias, and physician bias during medical history taking at the initial patient visit.

Referral bias can be a possible limitation of our study, even when taking into account our efforts to exclude women with a previous laparoscopic diagnosis of endometriosis. Indeed, it can be argued that the referral pattern of the LUFC, known as a tertiary reference center for endometriosis offering the possibility of advanced fertility surgery and multidisciplinary endometriosis surgery by means of CO2 laser laparoscopy (2), probably differs somehow from the referral pattern of fertility centers without expertise in reproductive/endometriosis surgery. The coexistence of infertility with pelvic pain, as occurred in half of our patients studied, is likely to facilitate the referral to a reproductive surgery/endometriosis surgery expert center. Referral bias to a fertility center can also explain why the highest prevalence of endometriosis was found in our study in the group of patients between 25 and 30 years of age, whereas literature data suggest an age-dependent increase in the prevalence of endometriosis (12, 16, 17). However, referral bias does not explain why 40% of the patients without pain symptoms had endometriosis. The high prevalence of endometriosis in this subgroup of patients without pain and with infertility that cannot be explained by ovulatory problems or male factors leads us to the hypothesis that endometriosis is the most important cause of infertility in this population, as has been argued before (4, 12). Of course, endometriosis also occurs in women with irregular anovulatory cycles (18, 19) and in women with male factor infertility (20), but these subgroups have not been studied extensively, and the exact impact of endometriosis on the fertility status of the couple is unclear owing to the obvious coexisting fertility-reducing factors.

Recall bias in patients reporting pain is possible. The referral to an academic hospital for further treatment in itself may have artificially inflated their recollection of the frequency and intensity of pain symptoms. Or perhaps the opposite: fear of over-investigation in a tertiary center may have influenced patients to trivialize their pain symptoms.

Physician bias during medical history taking at the first patient visit may seem unlikely since all patient files were completed in a systematic fashion by a staff member of the LUFC, but it is still possible. Indeed, the medical history was taken by several staff members with variable levels of seniority and not by the same trained interrogator. In our study, pain was not assessed in a more objective way using a validated questionnaire.

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with uterine, tubal, or combined uterine-tubal pelvic pathology.</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Other pelvic pathology (%)</td>
</tr>
<tr>
<td>Uterine pathology:</td>
</tr>
<tr>
<td>Endometritis</td>
</tr>
<tr>
<td>Septate uterus</td>
</tr>
<tr>
<td>Polyp</td>
</tr>
<tr>
<td>Submucous myoma</td>
</tr>
<tr>
<td>Congenital (DES)</td>
</tr>
<tr>
<td>Tubal pathology:</td>
</tr>
<tr>
<td>Endometriosis</td>
</tr>
<tr>
<td>Nonendometriotic</td>
</tr>
<tr>
<td>Adhesions</td>
</tr>
<tr>
<td>Tubal obstruction</td>
</tr>
<tr>
<td>Both:</td>
</tr>
<tr>
<td>Endometriotic tubal</td>
</tr>
<tr>
<td>Nonendometriotic tubal</td>
</tr>
<tr>
<td>Adhesions</td>
</tr>
<tr>
<td>Tubal obstruction</td>
</tr>
<tr>
<td>Uterine:</td>
</tr>
<tr>
<td>Endometritis</td>
</tr>
<tr>
<td>Septate uterus</td>
</tr>
<tr>
<td>Polyp</td>
</tr>
<tr>
<td>Submucous myoma</td>
</tr>
<tr>
<td>Congenital</td>
</tr>
</tbody>
</table>

In our study, the presence of pain (i.e., dysmenorrhea or dyspareunia) was only weakly associated with the presence of endometriosis during laparoscopic investigation. Indeed, about one (46%) out of two patients with pain did not have endometriosis. Even when pain was combined with multiple other clinical parameters in our prediction model, the results were clinically irrelevant. These data are in line with recent data (21) questioning the association between the degree of pain and the stage of endometriosis.

The results from our study confirm that superficial peritoneal endometriosis, ovarian endometriosis, and endometriotic adhesions as seen in endometriosis rAFS I and II are not detectable by TVU (8). The limited prediction of endometriosis rAFS III and IV by TVU observed in our study is also in accordance with the literature. In a controlled prospective study of 142 women with symptomatic endometriosis (22), TVU was accurate for the diagnosis of intestinal and bladder endometriosis but less accurate for uterosacral, vaginal, and rectovaginal septum involvement. Moreover, endometriosis infiltrating the wall of the sigmoid and endometriosis situated between the sigmoid and left adnexa/left round ligament is situated out of range for the probe used at TVU.

The high prevalence of nonendometriotic tubal and/or uterine fertility-reducing factors (submucous uterine myoma, endometrial polyp, uterine septum, hydrosalpinx, and adnexal adhesions compromising tubal pick-up and/or transport of the oocyte) in patients with (15%) and without (40%) endometriosis supports the rationale for performing a diagnostic/operative laparoscopy in all infertile patients with a regular ovulatory cycle whose partners have a normal semen analysis. Obviously, tubal function is one of the key factors that determines the spontaneous pregnancy rate or the pregnancy rate after ovarian stimulation with or without IUI. According to the National Institute for Clinical Excellence (NICE), tubal surgery may be more effective for women with mild tubal disease than no treatment; in centers at which appropriate expertise is available it may be considered as a treatment option (23). Indeed, during surgery, it is possible to restore tubal ovum pick-up function and transport capacity and to remove a dysfunctional tube. Other fertility treatment including controlled ovarian hyperstimulation (COH) combined with intercourse or with IUI is considered to be useless without at least one functioning tube. Furthermore, the pregnancy rate of IVF is negatively influenced by the presence of a hydrosalpinx (24).

The results of our study need to be confirmed by other research groups. If our data are confirmed, it may be advisable to adapt the NICE guideline that women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathologies can be assessed at the same time (23). Based on the results of our study, we propose the following clinical guideline. Women with at least 1 year of infertility, regular cycles (variation, 21–35 days), and male partners with a normal semen analysis should receive a diagnostic laparoscopy and hysteroscopy so that tubal and other pelvic pathologies can be assessed and treated at the same time, since endometriosis or other clinically relevant pelvic comorbidities are present in at least 40% of cases, regardless of the presence of dysmenorrhea or dyspareunia and regardless of the absence of anatomical abnormalities suggestive of the presence of endometriosis (hyperechogenic cysts or nodules) at TVU. A diagnostic laparoscopy with the collection of biopsies for histological examination is the only examination that allows the confirmation of the presence or absence of endometriosis and has been recommended as ideal practice in the European Society of Human Reproduction and Embryology guidelines (8). A radical resection of all visual abnormal endometriotic tissue and an effort to restore normal anatomy in the same procedure, leading to amelioration of the infertility, has also been recommended in existing guidelines for the management of endometriosis (5, 8, 23). The role of surgical treatment of moderate and severe endometriosis in infertility has not been confirmed by randomized controlled trials but is carried out often (4, 8) and is recommended in the NICE guidelines (23). Patients without endometriosis also benefit from a laparoscopic exploration of the pelvis since in our study population one-third of them demonstrated significant tubal problems. In view of the high prevalence of pelvic, tubal, and uterine problems, a hysterosalpingography is not justified in women meeting the criteria of our study. However, we also realize that a surgical risk or cost-effectiveness assessment is needed for this policy in our patient population with a prevalence rate of approximately 50% for endometriosis and 40% for comorbidities.

The added value of laparoscopic excision of endometriosis before IUI is a matter of debate. Although the clinical pregnancy rate after ovarian stimulation and IUI has been reported to be lower in women with minimal to mild endometriosis than in women with unexplained infertility, we recently showed that surgical treatment of minimal and mild endometriosis before starting COH and IUI restores the cycle pregnancy rate and reduces the time to pregnancy (6) to the same level as in women with unexplained infertility. However, in a prospective randomized reallocation study evaluating the role of laparoscopy in patients scheduled for IUI (25), the at random allocation of patients with unexplained, cervical, or mild male factor subfertility to IUI or to laparoscopy did not show any difference in pregnancy rates or pelvic pathology with therapeutic implications. To resolve this issue, a randomized study should be performed to test the hypothesis that surgical excision of endometriosis before IUI increases the pregnancy rate during IUI treatment when compared with diagnostic laparoscopy alone.

In conclusion, our study confirmed our hypothesis that the prevalence of histologically proven endometriosis in this well-defined patient population group of infertile women consulting our center, that is, those with at least 1 year of infertility, regular cycles (variation, 21–35 days), and partners with a normal semen analysis, is about 50%. To our surprise, the prevalence of endometriosis in the above-mentioned study population was as high as 40% in the absence of dysmenorrhea or dyspareunia. Moreover, in 48% of the patients with rAFS III–IV endometriosis, neither hyperechogenic cysts

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nor nodules were visualized at a preoperatively performed TVU. Nonendometriotic fertility-reducing tubal and/or uterine pathology was found in 40% of women without endometriosis. Collectively, these data justify the following policy for all infertile women admitted to our center. Women with at least 1 year of infertility with regular cycles (variation, 21–35 days) whose male partners have a normal semen analysis should receive a diagnostic laparoscopy and hysteroscopy so that endometriosis and other pelvic pathology can be assessed and treated at the same time, since endometriosis or other clinically relevant pelvic comorbidities are present in at least 40% of cases, regardless of the presence of dysmenorrhea or dyspareunia and regardless of the absence of anatomical abnormalities suggestive of the presence of endometriosis (hyerechogenic cysts or nodules) at TVU. More research is needed to find out whether these findings can be expanded to other fertility centers.

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High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners

To the Editor:

We read with interest the article by Meuleman et al. (1). The high incidence of endometriosis (47%) and other pelvic pathology (29%) in this cohort makes a strong case to offer laparoscopy and hysteroscopy to couples with “unexplained infertility” (a diagnosis of exclusion). This diagnosis, however, requires confirmation of tubal integrity, and the issue is whether laparoscopy should be the first line investigation to establish tubal patency. The investigators did not say how many women in their cohort had a completely normal pelvis after laparoscopy and hysteroscopy.

Their data put in another way showed that 53% of the women who underwent laparoscopy did not have endometriosis. It is in an effort to minimize the risks and costs associated with laparoscopy that the National Collaboration Centre for Women’s and Children’s Health (2) recommends that hysterosalpingogram be considered as first-line test for tubal patency and laparoscopy be considered only for women with comorbidity. Although the definition of comorbidity is fairly wholly and nonspecific, it generally refers to women whose clinical history may suggest the presence of potential pelvic pathology. This includes those who have had previous pelvic infection, previous ectopic pregnancy (EP), and known endometriosis. By limiting laparoscopy to this cohort, fewer women are exposed to the risks associated with this procedure and its potential cost implications.

Also, as interesting as it is to know that laparoscopy revealed a high incidence of endometriosis and other “fertility-reducing pathologies” among the cohort of women studied, the investigators failed to discuss the outcome of the treatment of these pathologies. We must never lose sight of the fact that the ultimate aim of infertile women undergoing any type of treatment is to take home a baby. Until this is achieved, the patients may be thankful for having their asymptomatic endometriosis resected but will remain dissatisfied and consider the treatment a failure should they not have a baby at the end. It will be interesting to know how many women in this cohort had a live birth after surgery.

Krithiga Ilangavan, M.R.C.O.G.
Kingston Hospital NHS Trust
Kingston Upon Thames, Surrey, United Kingdom

Emmanuel Kalu, M.R.C.O.G.
Assisted Conception Unit, Queen Mary’s Hospital
London, United Kingdom

November 12, 2009

doi:10.1016/j.fertnstert.2009.11.027

REFERENCES


Endometriosis: is laparoscopy justified without previous ultrasonogram and magnetic resonance imaging (MRI)?

To the Editor:

In the article by Meuleman et al. (1) I appreciated the new understandings brought by the investigators and the unexpected demonstration that pelvic pain was not explained by the existence of endometriotic lesions in 46% of cases in infertile women.

Nevertheless, I am surprised about the last sentence of their abstract, "Reproductive surgery is indicated in infertile women belonging to the study population . . . ." Nothing in the article supports this assertion, neither the statistical results nor the references. However, the following criticisms are more important:

1. Whereas so many details are credited to the expertise of the surgical team, nothing is mentioned about the ultrasonographer’s competence. Still d’Hooghe and Timmerman themselves had written that the results of ultrasonograms are dependent on the experience and interest of the ultrasonographer (2). The progress made in discovering nodular lesions of endometriosis and the abnormal position of pelvic organs due to adhesions, when the ultrasonographer is talented, cannot be ignored.

2. Magnetic resonance imaging is never mentioned. Even if the team does not have access to the necessary equipment, the information contributed by this technique is so well recognized (3) that it should have been mentioned, as the indications for surgery with its possible side effects are not the same if the lesions discovered necessitate it or if they might just be improved by surgery.

3. More surprisingly, the existence or absence of patients with adenomyosis associated with endometriosis was never mentioned in work from a team that has written a remarkable article on adenomyosis and infertility (2). It is possible that the diagnosis of adenomyosis being difficult for the ultrasonographer and, as no MRI had been used, the investigators decided not to raise the question, but this deficiency seriously affects the conclusions of the work as the internal adenomyotic lesions are not accessible to laparoscopic surgery! Nevertheless, because hysteroscopy was a mandatory part of the investigations, it is difficult to understand that a possible role of adenomyotic lesions has never been at least hypothesized.

Bearing in mind all of these uncertainties, it appears that the conclusions in the article are at least too abrupt, as the investigators insist on the advantages of surgery, which is today subject of discussion because its dangers have been hidden for such a long time and because the progress of MRI and ultrasonography are now well established, in parallel with the satisfactory results of assisted reproductive technology (ART). In the August 2009 issue of Fertility and Sterility, Chapron et al. (4) have written, “When the clinical examination (questioning and pelvic exam) suggests deep infiltrating endometriosis we feel that the first additional investigation should be transvaginal ultrasonography. In this context, the discovery of an ovarian endometrioma at transvaginal ultrasonography should prompt the practitioner to search for severe lesions (intestinal and/or ureteral involvement) rather than programming surgery immediately.”

It will be a pleasure if the authors’ reply shows that my criticisms were unjustifiably excessive.

Jean Belaisch, M.D.
Department of Gynaecology and Obstetrics, Saint Vincent de Paul Hospital, Paris, France
November 12, 2009
doi:10.1016/j.fertnstert.2009.11.026

REFERENCES

LETTER TO THE EDITOR

Reply of the Authors:

We thank colleagues Belaisch, Ilangoavanan, and Kalu for their interest in our work (1).

Our conclusion that reproductive surgery is indicated in infertile women with regular menstrual cycles whose male partners have normal sperm quality is justified. First, significant pelvic (including endometriosis), tubal or uterine pathology was observed in two-thirds of our patients and can be interpreted as significant comorbidity and justification for surgery according to the National Collaboration Centre for Women’s and Children’s Health guidelines (2). Second, a completely normal hysteroscopy and laparoscopy test was only observed in one-third of our patients (1), but in this “normal” group diagnostic hysteroscopy and laparoscopy can still be clinically justified to confirm the diagnosis of unexplained infertility, as a normal hysterosalpingography does not exclude significant pelvic pathology (3).

Although much progress has been made in the ultrasound diagnosis of endometriosis with respect to ovarian endometriotic cysts and nodular lesions in the rectovaginal area, and both experience and interest of the ultrasonographer are important in the diagnosis of adenomyosis (4), ultrasound is not reliable in the diagnosis or exclusion of pelvic peritoneal endometriosis found in women with minimal-to-mild endometriosis (5). Furthermore, some endometriotic nodules are situated higher in the rectosigmoidal area, which is not routinely accessible by transvaginal ultrasound. Finally, the retrospective nature of our study and the variable interval between preoperative ultrasound and surgery may have diluted the diagnostic value of ultrasound in this study. This aspect will be taken care of in our ongoing prospective cohort study.

We disagree with Dr. Belaisch that hysteroscopy is useful for the diagnosis of adenomyosis (no published data supporting this statement) or that magnetic resonance imaging (MRI) is needed for the diagnosis of adenomyosis, as several studies have shown that ultrasound diagnosis of adenomyosis is as reliable as MRI diagnosis (4–6). Adenomyosis was not a relevant issue in our study for the following reasons: [1] the relationship between adenomyosis and infertility is not properly quantified; and [2] adenomyosis cannot be treated by surgery or by medication in women who want to become pregnant. Therefore, in our study, adenomyosis was not a factor of importance in deciding for or against surgery.

Clearly, MRI is not a first-line investigation in this study population of infertile women whose husbands have normal sperm (5). The MRI or other imaging techniques, like intravenous pyelogram or bowel contrast radiography, are indicated and used in our center when more extensive endometriosis with impact on bowel, bladder, or ureter is suspected based on clinical examination and ultrasound imaging (5, 7). Furthermore, based on randomized controlled trials, excisional endometriosis surgery has been proven to improve fertility in women with minimal-to-mild disease and to reduce pain in women with mild-to-moderate endometriosis (5, 7), justifying surgery in this population. It is important to emphasize that about 50% of subfertile women with endometriosis also had pain, and that treatment of subfertility and pain is important in this group. The use of assisted reproductive technology (ART) (8) cannot be considered as a first-line infertility treatment of endometriosis (5). The possible risks of laparoscopic endometriosis surgery need to be acknowledged, but can be considered to be minimal when this surgery is done by experienced reproductive gynecological surgeons, in the context of a multidisciplinary center of excellence for endometriosis (9). Indeed, the integration of endometriosis care in such centers may be the only way to prevent overtreatment of women with endometriosis by assisted reproduction, potentially driven by the industrialization of assisted reproduction worldwide, and a useful way to embed endometriosis surgery in a larger context of reproductive medicine (9). Overall, the goal of infertility treatment in women with endometriosis should be to first surgically remove endometriosis and surgically treat associated pelvic pathology, and then to decide on expectant management, controlled ovarian hyperstimulation (COH) with or without IUI or ART (8), based on the woman’s age, tubal condition after surgery, and duration of infertility. This strategy is currently evaluated in a prospective outcome study.

Christel Meuleman, M.D.*
Carla Tomassetti, M.D.*
Dirk Timmerman, M.D., Ph.D.*
Thomas D’Hooghe, M.D., Ph.D.*

* Department of Obstetrics and Gynecology, Leuven University Fertility Centre, Leuven, Belgium

November 12, 2009


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Tijdschrift voor Geneeskunde, 66, nr. 11, 2010, Pagina’s 558-564
**Endometriose: uiteindelijke diagnose en therapie**

C. Van Turnhout, C. Meuleman, T. D’Hooghe

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**Samenvatting**

Endometriose is een ziekte die wordt aangetroffen bij vrouwen in de reproductieve leeftijd en die zich kenmerkt door de aanwezigheid van endometriale cellen buiten de baarmoederholte. Dit veroorzaakt een chronisch inflammatorisch proces waarbij de symptomen kunnen variëren van absoluut geen last tot een sterke menstruele of chronische pijn met fysieke, mentale en sociale impact. Verschillende onderzoeken kunnen worden aangewend voor het opsporen van endometriose maar de laparoscopie blijft de standaard. Andere beeldvormende onderzoeken kunnen nuttig zijn in de preoperatieve inschatting van de uitgebreidheid van de ziekte. De chirurgische behandeling van endometriose bestaat uit de excisie van endometrioseletsels en vergroeiingen, alsook uit het herstel van de reproductieve anatomie. In afwachting van een heelkundige ingreep kunnen hormonale en niet-hormonale medicamenten worden aangewend om pijnsymptomen te onderdrukken.

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**Inleiding**

Endometriose is een ziekte die zich op verschillende manieren kan uiten en een impact kan uitoefenen op verschillende organen. De diagnostische en therapeutische aanpak verschilt dan ook van patiënt tot patiënt. In dit artikel wordt een samenvatting gegeven van de verschillende onderzoeken en behandelingen van endometriose die mogelijk zijn, gebaseerd op de ESHRE guideline for the diagnosis and treatment of endometriosis. Deze richtlijnen worden jaarlijks door de Special Interest Group for endometriosis and endometrium aangepast volgens de nieuwste wetenschappelijke gegevens en zijn terug te vinden op de website van de European Society for Human Reproduction and Embryology (http://guidelines.endometriosis.org/).

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**Diagnose**

Verschillende onderzoeken kunnen worden aangewend voor het opsporen van endometriose maar de laparoscopie blijft de standaard. Andere beeldvormende onderzoeken kunnen nuttig zijn in het preoperatief inschatten van de uitgebreidheid van de ziekte.

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**Echografie**

Echografie heeft geen nut voor het opsporen van peritoneale endometriose. Het is wel een nuttig onderzoek voor het opsporen en opvolgen van ovariale endometriomen. Echografie is een uitstekend diagnostisch middel om een onderscheid te maken tussen de verschillende typen ovariale cysten. Ernstige endometrioseuitslag in het rectovaginale septum of in de vesico-uteriene plooi kunnen echografisch worden gevisualiseerd. Het is mogelijk aan te tonen wat de mobiliteit van de organen is en of het bestaan van een „frozen pelvis”.

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**MRI**

In vergelijking met laparoscopie zijn er momenteel onvoldoende argumenten om te stellen dat MRI een nuttige diagnostische test is om endometriose aan te tonen of uit te sluiten. De techniek wordt wel aangewend voor het diagnosticeren van endometriose op atypische localisaties zoals het diafragma, de pleura of de spieren.

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**Bloedtesten**

Het CA-125-gehalte is vaak gestegen tengevolge van endometriose, maar kan niet worden aangewend als een diagnostisch instrument om het effect van therapie of recidieven op te volgen gelet op het aspecifieke karakter van deze parameter.
**Intraveneuze pyleografie (IVP) en radiografie van het colon**

Deze onderzoeken zijn nuttig voor het in kaart brengen van de uitgebreidheid van endometriose. Met IVP kan de impact van endometriose op de ureters en secundaire de nieren aangetoond worden en zo kan besloten worden of preoperatieve stenting van de ureters nodig is. Radiografie van het colon geeft dan weer de impact van endometriose op de darm weer zonder dat preoperatief ingeschat kan worden of darmchirurgie nodig kan zijn. Dit onderzoek wordt uitgevoerd wanneer er klachten zijn van dyschezie of menstrueel anaal bloedverlies, of indien een nodulus wordt gevonden bij klinisch onderzoek en/of vastgesteld bij transvaginale echografie. Tekenen van hydronerfrose of darmocclusie zijn belangrijke argumenten voor een dringende chirurgische interventie.

**Laparoscopie**

Laparoscopie wordt beschouwd als het standaardonderzoek voor het diagnosticeren van endometriose, maar het herkennen van deze ziekte als dusdanig is afhankelijk van de ervaring van de chirurg. Belangrijk om te weten is dat geïsoleerde ovariale endometriose slechts bij 1% van de patiënten voorkomt; bij de overige is er steeds pelvine en/of intestinale endometriose aanwezig (4). De diagnose wordt best niet alleen door uitgebreide inspectie van de pelviene en abdominale caviteit gesteld, maar ook door palpatie van darmen, blaas, ovaria, eileiders, douglasholte, brede band, fossae ovaricae en para-rectale ruimten met een stomp instrument. Door de aanwezigheid van endometriose endometriale inplanten te induceren of pro liferatie van endometriale inplanten te stimuleren. De ectopische inplanten reageren in een bepaalde mate op steroïde hormonen net als het eutopisch endometrium. Hormonale behandeling is dan ook succesvol bij de behandeling van ovariale endometriose. Het is bekend dat oestrogenen de groei van endometriale inplanten bevorderen, terwijl progestaglandines de activatie van endogene opioïde en serotonerge mechanismen kunnen onderdrukken. In geval van chronische inname is maagbezuiveringsmiddel en NSAID-gebruik periovulatoire menstruatie. Eenmaal de menstruatie is er geen correlatie is tussen het aangetroffen stadium en de pijn- ervaring bij de patiënt (6, 7), en dat dit classificatiesysteem subjectief is en dus onderhevig aan inter- en intra-observervariabiliteit (8, 9). De classificatiesystemen kunnen wel bijdragen tot de prognose en behandeling van infertiliteit (6, 7).

**Beadeling van endometriose**

Aangezien de meeste vrouwen met endometriose actieve of passieve kinderwens hebben, is een aanpak waarbij de reproductive functie behouden wordt wenselijk. De minst invasieve en de goedkoopste aanpak die effectief is en het minste risico’s met zich meebrengt op lange termijn, moet dan ook worden verkregen. Hierbij is het belangrijk de patiënt te betrekken in het kiezen van de verschillende behandelingsopties. Symptomatische endometriosepatienten met pijn kunnen worden behandeld met pijnstellers, hormonen of een chirurgische ingreep. De keuze van behandeling wordt bepaald door de positie van de vrouwen met pijn soms actieve kinderwens hebben en problemen van subfertiliteit. Daarenboven is endometriose vaak een chronische ziekte zodat eliminatie ervan door chirurgische of medicamenteuze behandeling vaak slechts een tijdelijke verbetering brengt. Daarom moet de focus liggen op het verwijderen van de laesies, het behandelen van de pijn en de subfertiliteit en het voorkomen van heroptreden van de ziekte.

**Pijnmedicatie**

**Niet-steroid anti-inflammatoire middelen (NSAID’s)**

In het geval van bevestigde endometriose, worden bij voorkeur NSAID’s voorgeschreven als pijnstellers aangezien het gaat om een inflammatoire proces. Vooral dysmenorroeklachten verbeteren hiermee (10). Deze pijnstillers hebben niet enkel een effect door centrale remming van de prostaglandinesynthese maar ook door de activatie van endogene opioïde en serotonenergenicismen. In geval van chronische inname is maagbeschermering aanbevolen en NSAID-gebruik periovulatoire dient te worden vermeden bij patiënten met actieve kinderwens omdat prostaaglandinen betrokken zijn bij de ruptuur van follikels (11).**

**Hormonale behandeling**

Het is bekend dat oestrogenen de groei van endometriose stimuleren. De ektopye inplanten reageren in zekere mate op steroïde hormonen net als het eutopisch endometrium. Hormonale therapie is dan ook ontworpen om de oestrogeensynthese te verminderen en zo de stimulatie en bloeding te onderbreken.
Progestagenen

Progestagenen hebben een antiproliferatief effect door eerst een initiële decidualisatie te veroorzaken gevolgd door atrofie. Ze worden beschouwd als een eersteklassebehandeling omdat ze even efficiënt zijn als gonadotrofinerevijzelend hormoon (GnRH)-analogen in het reduceren van de AFS-score en de pijn, maar goedkoper zijn en minder bijwerkingen hebben (12). Tot dusver zijn er geen evidente aanwijzingen om één specifiek progestagen te verkiezen boven een ander. Bijwerkingen van progestagenen zijn misselijkheid, vochtretentie, gewichtstoename en doorbraakbloedingen door de hypo-oestrogene status. Deze doorbraakbloedingen kunnen worden behandeld door het toedienen van oestrogeneren gedurende 7 dagen. Bij 1% van de patiënten worden tevens depressies en andere gemoedswisselingen vastgesteld.

Het levensgestrestevenzettinge spiraalpijpje geeft een belangrijke vermindering van de dysmenorroe. Progestagenen, de pelvijen pijn en de dyspareunie en gaat gepaard met een hoge graad van tevredenheid bij de patiënt (13, 14). Bovendien werd een belangrijke volumeafname van rectovaginale noduli gezien (15). Ook bij toediening van de 3-maandelijkse injectie van medroxyprogesteronaacetaat wordt een effectieve pijnvermindering waargenomen (16). Over het etonogestrelimplantaat zijn nog maar weinig gegevens beschikbaar.

Gecombineerde orale anticonceptiva (OAC)

Elke contraceptive pil die 30-35 μg ethinylestradiol bevat, kan continu worden ingenomen om zo amenorroe te bekomen. Dit geeft een symptomatische verbetering van de dysmenorroe en de pelvijen pijn bij 60-95% van de patiënten (17). Of cyclische inname ook effectief is voor het behandelen van pijnklachten bij endometriosepatienten dient nog verder te worden onderzocht. De vermindering van de hoeveelheid menstrueel bloedverlies dat vaak optreedt bij vrouwen tijdens cyclisch gebruik van OAC’s, kan voordeel zijn voor vrouwen met hevige en langere menses. Menorragieën zijn immers een gekende risicofactor voor het ontwikkelen van endometriose (18). Oestrogeneren kunnen de proliferaatie van endometriose echter stimuleren en daarom is verder onderzoek nodig om na te gaan of cyclische inname van OAC’s de bescherming kan bieden tegen het ontwikkelen of heroptreden van endometriose.

Danazol

Dit middel onderdrukt de gonadotrofinesecreties uit de hypofyse en remt zo de secretie van geslachthormonen af. Danazol verhoogt ook de metabole klaring van de hypofyse en remt zo de secretie van geslachtshormonen. Dit middel onderdrukt de gonadotrofinesecreties uit het hypofyse. Danazol verhoogt ook de metabole klaring van de hypofyse en remt zo de secretie van geslachtshormonen.

Gewoonlijk wordt gestart met tweemaal daags 200 mg. De dosis kan worden verhoogd wanneer er nog geen amenorroe is of de pijnklachten onvoldoende onder controle zijn (19). Dit product heeft door zijn androgene en hypo-oestrogene effect echter veel bijwerkingen zoals gewichtstoename, vochtretentie, acne, vette huid, hirsutisme, atrофische vaginitis, warmteopwellingen, verminderd libido, misselijkheid, spierkrampen en emotionele instabiliteit. Bovendien kan een onomkeerbare verlaging van de stem optreden.

Gonadotrofine afgevend hormoon (GnRH)-agonisten


Ook hier worden vanwege de hypo-oestrogene status vaak bijwerkingen gezien zoals warmteopwellingen, vaginale droogte, libidooverlies en reductie van de botdensiteit.

Zo de behandeling wordt beperkt tot 6 maanden, wordt na 12 maanden een herstel van het dikteverlies gezien (20). Bij langere behandeling is het niet zeker of de botkwaliteit zich nog volledig zal herstellen. De bijwerkingen kunnen worden versterkt door het associëren van een „add-back”-therapie. Hierbij wordt dage-lijks hormonale substitutietherapie of tibolon toegediend (21).

Chirurgische behandeling

Chirurgische verwijdering van de endometrioseleukomen tijdens de laparoscopie blijft de beste behandeling (6, 22-24). Het doel van de chirurgie is het verwijderen van alle zichtbare peritoneale endometrioseleukomen, ovariale endometriosecysten, diepe rectovaginale noduli en geassocieerde adhesies om zo de normale anatomie te herstellen. In de meeste gevallen kan dit alles via laparoscopische ingrepen worden gedaan (21).

Er zijn tot dusver weinig prospectieve studies met een follow-up op lange termijn die aantonen wat het effect is van chirurgie op de pijn. Bij milde en matige endometriose is aanbevolen dat het chirurgisch verwijderen van endometriose superieur is aan een afwachtend
beleid op gebied van pijn, levenskwaliteit en verbetering van de fertiliteit (23). Bovendien gaat cystectomie ook gepaard met de verwijdering van endometrioom. Tijdens een tweede ingreep kan dan een cystectomie plaatsvinden. Als dusdanig wordt getracht zo weinig mogelijk gezond ovariaal weefsel te beschadigen om zo een optimale folliculaire reserve en fertiliteit te garanderen.

Om deze chirurgische beschadiging van ovaal weefsel te voorkomen, is voorgesteld om cystectomie volledig te vermijden en enkel nog lagenstriktie en coagulatie van de cystewand uit te voeren (38). Er is echter aangetoond dat de pijnklachten en de fertiliteit na cystectomie meer verbeterden dan na lagenstriktie en coagulatie (39,40). Bovendien gaat cystectomie ook gepaard met een lager recidiefrisco (41).

**Adhesiolyse**

Endometriosegerelateerde adhesies maken deel uit van de geïnflammaerde fibrose en dienen dus te verwijderen. Er zijn tot nog toe geen aanwijzingen dat het achterlaten van vacht of medicamenten in de peritoneale caviteit het ontwikkelen van postoperatieve adhesies vermindert.

**Diepe rectovaginale en rectosigmoidale noduli**

Diepe endometriose is gewoonlijk multifocaal en het doel is deze in één procedure volledig te verwijderen. Deze behandeling is complex en dient best te gebeuren in een centrum waar een multidisciplinaire aanpak mogelijk is. Door een team bestaande uit gynaecologen, abdominaal chirurgen en urologen. Deze radicale chirurgie kan bestaan uit het verwijderen van de uiterste vaginale wand, uit discoidale excisie of segmentale
darmresectie gevolgd door „end-to-end” reaanastomose bij invasive darmendometriose, uit partiele blaaresarctie en ureterolyse met eventuele resectie, reaanastomose en reimplantatie van de ureters bij invasive blaasendometriose, terwijl de uterus en de ovaria meestal bewaard blijven.

Het chirurgisch verwijderen van rectovaginale en rectosigmoidale endometriose is technisch moeilijk en kan gepaard gaan met zware verwikkelingen (bv. darmperforatie) die resulteren in peritonitis (42). Daarom is het aangewezen dat preoperatief een restenarm diert wordt gevolgd en darmvoorbereiding wordt toegepast zodat overhechting of resectie van de darm peroperatief mogelijk is. De segmentale sigmoïderesectie of anterioressectie kan laparoscopisch of via laparotomie gebeuren (43). Bij appendiculaire endometriose wordt best een appendectomie uitgevoerd. Preoperatieve diagnosestelling door middel van radiografie van het colon in geval van klachten of afwijkingen bij klinisch onderzoek, is dus ten zeerste aangezien resultert in optimale counseling en voorbereiding van de patiënt en organisatie van het multidisciplinaire team kunnen plaatsvinden.

Indien perireterale endometrioselaesies worden vermoed, wordt preoperatieve stenting van de ureters aanbevolen. De ureteren spelen tevens een belangrijke rol bij het primair herstellen van de blaas na excisie van de endometrioselaesies. Bij intrinsieke ureterale endometrióse laesies of significante obstructie kan segmentale excisie met end-to-endanastomose of reimplantatie noodzakelijk zijn.

Een laatste belangrijke component van het multidisciplinaire team is de pijnkliniek omdat hier, in afwachting van de chirurgische ingreep, pijnklachten kunnen behandeld worden en omdat niet alle patiënten na de operatie pijnvrij zijn.

Adnexectomie en hysterectomie
Deze radicale procedure is slechts geïndiceerd bij ernstige gevallen. Voor patiënten met adenomyose kan hysterectomie de enige behandeling zijn als hormonale therapie geen verbetering brengt. Adenomyose is een speciale vorm van endometriose waarbij endometriumcellen diffuus in het myometrium van de baarmoeder worden aangetroffen wat vaak gepaard gaat met ernstige dysmenorrhoe en menstruatieproblemen.

Wanneer een hysterectomie uitgevoerd wordt, kan best een totale en geen subtotale verwijdering van de baarmoeder gebeuren omdat ook in de cervix en de uterosa- crale ligamenten endometriose kan worden aangetroffen.

Besluit
Endometriose is een ziekte die zich kenmerkt door ectopisch gelegen endometriale cellen. De gouden standaard voor diagnostiek blijft de laparoscopie. Echografie, radiografie van het colon en intraveneuze pyelografie zijn nuttig voor het stellen van de diagnose en het bepalen van de uitgebreidheid van de ziekte wat van belang kan zijn voor de preoperatieve voorbereiding en de organisatie van de interventie.

Wanneer op basis van de klinische bevindingen vermoed wordt dat endometriose de oorzaak is van dysmenorróe en/of koorts dan is de diagnostiek en verduidelijking van de ziekte noodzakelijk. Het multidisciplinaire team van de interventie is zodanig opgesteld dat de interventie een succesvol koers kan nemen als de oorzaak van dysmenorróe en koorts de endometriose blijkt te zijn.

Postoperatief kan terug ovariale suppressie worden opgestart, niet zozeer om de pijn nog verder te reduceren maar om recidief uit te sluiten.

Mededeling
Geen belangenconflict en geen financiële ondersteuning gemeld.

Abstract
Endometriosis: final diagnosis and treatment
Endometriosis is a disease observed in women in the reproductive age when endometrial-like tissue is present outside the uterine cavity. This induces a chronic, inflammatory reaction. The symptoms of the disease can vary from absent to mild or strong pain during the menstruation or provoking chronic abdominal pain with impact on the general physical, mental and social well being.
Different investigations may be used to diagnose endometriosis but the golden standard remains a laparoscopy. Pelvic ultrasound, bowel barium enema and intravenous pyelography may help to assess the extent of the disease before surgery so that correct counseling and preparation of the patient for a multidisciplinary surgical intervention may take place.

Symptomatic patients can be treated with analgesia, hormonal or surgical therapy. As regards pain medication, NSAIDs are preferred. The combined oral contraceptives, the progestagens or the GnRH agonists or antagonists are equally effective in pain reduction, as the choice of the treatment applied should be guided by the various side effects and the cost price.

The goals of a surgical treatment of endometriosis include to excise all visible lesions, remove all adhesions and restore the reproductive anatomy as good as possible. During the postoperative period hormonal treatment is given to delay the pain recurrence.

Literatuur

2.4. Outcome after Multidisciplinary CO₂ Laser Laparoscopic Excision of Deep Infiltrating Colorectal Endometriosis

Christel Meuleman, M.D., André D’Hoore, M.D., Ph.D., Ben Van Cleynenbreugel, M.D., Thomas D’Hooghe, M.D., Ph.D.

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Letter to the Editor

Christel Meuleman, M.D., André D’Hoore, M.D., Ph.D., Ban Van Cleynenbreugel, M.D., Thomas D’Hooghe, M.D., Ph.D.

Journal of Minimal Invasive Gynecology, accepted for publication
Outcome after multidisciplinary CO₂ laser laparoscopic excision of deep infiltrating colorectal endometriosis

Dr Christel Meuleman MD has been trained in reproductive medicine and reproductive surgery at the University Hospital Leuven, Belgium. As Clinical Head she coordinates the program Endometriosis and Fertility Surgery at the Leuven University Fertility Centre of the department of Obstetrics and Gynecology of the University Hospital Leuven. At present she is completing a PhD on quality control in the surgical diagnosis and treatment of endometriosis.

Dr Christel Meuleman

Christel Meuleman¹, André D’Hoore², Ben Van Cleymenbreugel³, Nele Beksa, Thomas D’Hooghe¹,⁵
¹Leuven University Fertility Centre, Department of Obstetrics and Gynecology; ²Department of Abdominal Surgery; ³Department of Urology, University Hospital Leuven; ⁴Biomedical Science, University of Leuven, Belgium
⁵Correspondence: e-mail: thomas.dhooghe@uz.kuleuven.ac.be

Abstract

The aim of this retrospective cohort study was to evaluate clinical outcome after multidisciplinary laparoscopic excision of deep endometriosis. Patients (n = 56) were asked to complete questionnaires regarding quality of life (QOL), pain, fertility and sexuality to compare their status before and after surgery, and their medical files were analysed. Statistical analysis was performed with life table analysis, paired Wilcoxon and McNemar tests. Gynaecological pain, QOL and sexual activity improved significantly (P < 0.001; P < 0.0001 to P = 0.008 and P < 0.0001 to P = 0.0003 respectively) during a median follow-up 29 months after surgery. Post operative complications occurred in 11% but were directly related to surgery in only 5%. The cumulative recurrence rate of endometriosis was 2 and 7% at 1 and 4 years after surgery respectively. Cumulative pregnancy rate was 31 and 70% at 1 and 4 years after surgery respectively. In conclusion, multidisciplinary CO₂ laser laparoscopic excision of deep endometriosis with colorectal extension improves pain, QOL and sexuality with high fertility and low complication and recurrence rates.

Keywords: colorectal endometriosis, deep infiltrating endometriosis, dysmenorrhoea, dyspareunia, quality of life

Introduction

Endometriosis is a gynaecological disorder defined by the presence of endometrial glands and stroma outside the uterus, primarily affecting women during their reproductive years and associated with pelvic pain and infertility. Deep infiltrating endometriosis has been defined as endometriosis infiltrating deeper than 5-6 mm beyond the peritoneum (Koninckx and Martin, 1994; Vercellini et al., 2004) and is strongly associated with pelvic pain (Fauconnier et al., 2002; Koninckx et al., 1991; Porpora et al., 1999; Fauconnier and Chapron, 2005) and probably also with infertility (D’Hooghe et al., 2003; Darai et al., 2005; Vercellini et al., 2006). Deep endometriosis can be found in rectovaginal septum, uterosacral ligaments, bowel, ureters and bladder (Vercellini et al., 2004), and may result in complete obliteration of the cul-de-sac, representing a surgical challenge (Redwine and Wright, 2001). Many clinicians are convinced that deep infiltrating endometriosis is best treated by surgical excision (Garry, 2004) because of the relative ineffectiveness of medical therapy (Olive, 2003; Donnez et al., 2004). There is a positive correlation between the extent of endometriosis resection and the degree of post-operative improvement (Chapron et al., 2004). During reproductive age, radical excision of endometriosis combined with pelvic reconstruction appears to be the best option. This approach requires expertise, available in specialist centres (Redwine et al., 2001; Emmanuel and Davis, 2005; Perry, 2005) with multidisciplinary surgical collaboration in cases of complete obliteration of the cul-de-sac or the vesicouterine fold (Perry, 2005).
At the Leuven University Fertility Centre (LUF) of the University Hospital Leuven, Belgium, a tertiary referral centre for endometriosis, deep infiltrating endometriosis is treated by means of radical but fertility-sparing laparoscopic excision with CO2 laser in a multidisciplinary setting. The gynaecologist (CM), trained in endoscopic surgery for the restoration of fertility is backed up by a colorectal surgeon (AD) and a urologist (BVC), both also adept at laparoscopy. The aim of the present study was to evaluate the complication rate, cumulative recurrence and cumulative fertility rate, pain, quality of life and sexual satisfaction after multidisciplinary fertility-sparing radical CO2 laser laparoscopic excision of deep infiltrating endometriosis.

Materials and methods

The protocol of this retrospective cohort study (NCT00249834, ClinicalTrials.gov) was approved by the Ethical Committee of the University Hospital Leuven, Belgium.

Patients

All women (n = 56) who had undergone CO2 laser laparoscopic radical excision of deep infiltrating endometriosis with active involvement of a colorectal surgeon and/or urologist were selected retrospectively from the list of all patients (n > 2000) operated on at the Leuven University Fertility Centre between September 1996 and July 2004.

Pre-operative exploration

Before surgery, based on the medical history of the patient, 37 women underwent a bimanual vaginal examination and a speculum examination and 31 women underwent a vaginal ultrasound performed by a gynaecologist with special skills in pelvic ultrasound. An intravenous pyelogram (n = 38) and a bowel barium enema with double contrast (n = 33) were performed in order to map the involvement of the ureters, the bladder and the bowel in the endometriosis process.

Pre-operative bowel preparation

All patients were asked to follow a low-residue diet during 5 days before surgery. A Fleet Phospho-Soda (Wolfs, Belgium) (2 × 45 ml) was administered the day before operation, followed by 2 l of water without effervescence.

Operative procedure in three steps

Endometriosis was scored and staged according to the revised American Society for Reproductive Medicine (formerly American Fertility Society) classification of endometriosis system (rAFS; American Society for Reproductive Medicine, 1997). When peri-ureteral endometriosis was present, double J stents were placed into the ureters by the urologist (BVC) enabling ureterolysis by CO2 ‘micro’-dissection without accidental or unnoticed transection of the ureter.

Radical excision of endometriosis by the gynaecologist, using a CO2 laser (Lumenis Inc., USA: Compact 40C CO2 laser) in the 15 W Super Pulse mode, included resection of endometriotic adhesions and endometriotic cysts, wide excision of diseased peritoneum and radical nodulectomy. To perform a radical nodulectomy, an incision was made in healthy peritoneum surrounding the diseased peritoneum, ‘peeling’ off the affected peritoneum with restoration of normal anatomy. During this procedure, the mucosa of bladder and/or bowel is possibly ‘peeled off’ the mucosa. This procedure was monitored visually and by touching the indurations with the rinsing/aspiration probe. Perforation of the vagina due to segmental resection of the posterior wall was laparoscopically sutured by the gynaecologist.

Subsequently, the urologist (BVC) evaluated ureters and bladder. An injury of the ureter or a bladder perforation due to segmental resection for bladder endometriosis was laparoscopically sutured by the urologist. The double J stents remained in place for 6 weeks to 3 months in the following cases: extensive coagulation around the ureter, lesion of the ureter with or without suture, or transection of the ureter with suture.

Finally, the colorectal surgeon (AD) evaluated the integrity of the rectosigmoid colon and took the final decision to either suture the bowel wall (minor seromuscular injury: reinforcing suture) or to resect the bowel segment (with primary anastomosis) that had been involved in the endometriotic nodule and previously cleaned from all visible and palpable endometriosis by the gynaecologist. The treatment of bowel endometriosis depended on the type of the lesion and its extension, and was performed laparoscopically, following the basic rules of bowel surgery. Bowel perforation was the only indication for intravenous administration of broad spectrum antibiotics during 5 days. To perform a resection of the sigmoid, an anterior resection or a colon pouch, the rectosigmoid colon was mobilized. The mesentery was incised and the superior rectal artery was isolated, ligated and divided. The part of the rectum or sigmoid colon to be removed was identified. The proximal sigmoid was then mobilized to ensure a tension free anastomosis after resection of the diseased part. The distal rectum was transected using endoscopic stapling devices (Autosuture; Tyco Healthcare, USA) and the proximal bowel was retrieved through a small (<3 cm), muscle-splitting incision in the left lower quadrant for removal of the specimen and insertion of the anvil for the circular stapled anastomosis (Ethicon; Johnson and Johnson, USA). A purse-string suture was applied and the bowel was anastomosed with a standard trans-anal double-staple technique. A colonic J Pouch intervention was performed in cases of low colorectal or coloanum anus, in order to minimize the occurrence of transient post-operative digestive symptoms resulting from insufficient reservoir capacity of the rectum (Remzi et al., 2005; Dubernard et al., 2006). Post-operatively, as soon as bowel activity was noticed, progressive re-alimentation was given. The low-residue diet was continued until 4 weeks after the intervention, followed by stepwise introduction of a normal diet. Endometriosis involving the appendix, the caecum or the small bowel was also treated by the colorectal surgeon.

Care was taken not to resect the main branches of the pelvic autonomic nerves (Maas et al., 1999), as they are the pathway for the neurogenic control of rectal, bladder and sexual arousal ( lubrication and swelling of the vagina) (Landi et al., 2006). Using a CO2 laser at low power density, a meticulous
dissection of the endometriosis, without scarifying too much normal tissue, was performed. The dissection of the bowel, after ‘peeling-off’ diseased peritoneum and nodular endometriosis, was conducted only outside the mesorectum (as close to the bowel as possible), aiming to preserve the sympathetic fibres of the upper mesorectum (the superior hypogastric plexus, upper hypogastric nerves and lumbar sympathetic trunk), the sympathetic fibres of the lower mesorectum (lower hypogastric nerves and proximal part of the inferior hypogastric plexus), the pelvic splanchnic nerves and the cranial and middle part of the inferior hypogastric plexus in the lower mesorectal planes and the caudal part of the inferior hypogastric plexus (Landi et al., 2006). Only fibres of the resected segment of the bowel were cut, minimizing denervation. However, if minor nerve branches were impacted in an endometriotic/ fibrotic nodule, they were sacrificed using the technique of ‘radical excision of diseased tissue’ to avoid leaving behind endometriotic tissue.

All 56 procedures were performed by laparoscopy, without a single conversion to laparotomy, and no protective ileostomy was needed in this group of patients. A histological examination was performed on all resected tissue specimens, and endometriosis was confirmed by the presence of endometrial glands and stroma.

**Post-operative protocol of the Leuven University Fertility Centre**

When post-operative contraception was desired, a low dose oral contraceptive or a levonorgestrel-releasing intruterine device (Vercellini et al., 2005) was prescribed to minimize menstruation. Patients were asked to take the oral contraceptive continuously until breakthrough bleeding (Vercellini et al., 2003). After a pill-free period of 7 days, the oral contraceptive was restarted continuously until the next breakthrough bleeding.

When patients wanted to become pregnant, the fertility work-up was completed. In women younger than 36–38 years with a regular ovulatory cycle, normal tubal function and a male partner with normal sperm analysis, spontaneous conception was proposed during 6 months to 1 year. In case of normal tubal function but ovulatory dysfunction or mild male infertility, ovarian stimulation with low dose gonadotrophins combined with intrauterine insemination (IUI) was performed during three cycles (Spiessens et al., 2003). If this treatment was not successful and in all cases of compromised oocyte retrieval and transport capacity and/or advanced female age (>36–38 years), IVF was proposed.

### Questionnaires

All 56 multidisciplinary operated patients were asked to complete the Oxford Endometriosis Quality of Life questionnaire (Jones et al., 2001), a sexual activity questionnaire (Thirlaway et al., 1996) and visual analogue scales (VAS) for dysmenorrhoea, chronic pelvic pain and deep dyspareunia, to compare their status before surgery and at the time of the evaluation (January 2005).

### Statistical analysis

The cumulative recurrence rate and the cumulative pregnancy rate were calculated using life table analysis (D’Hooghe et al., 2006) up until the closure of the study (January 2005). The answers to the questionnaires were statistically analysed using paired Wilcoxon tests and paired McNemar tests. Statistical significance was reached at a P-value <0.05.

### Results

#### Response rate

The response rate to the questionnaires was 84% (47/56). Patients not responding to the questionnaires (9/56, 16%) were contacted by phone by an independent investigator (NB) and were asked about post-operative complications, surgical re-interventions, and fertility.

#### Patient characteristics and presenting symptoms of the study population

Table 1 summarizes the clinical data of the study population. Most patients (42/56, 75%) had received gynaecological surgery (58 laparoscopies and 12 laparotomies) before referral to the centre.

#### Intraoperative findings and surgical procedures

Table 2 summarizes the surgical procedures performed on the study patients. Nearly all patients (53/56 or 95%) had endometriosis rAFS stage III (n = 2) or endometriosis rAFS stage II (n = 1).

#### Table 1. Characteristics and presenting symptoms of study patients (n = 56).

<table>
<thead>
<tr>
<th>Characteristic/symptom</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age in years (range)</td>
<td>32 (24–42)</td>
</tr>
<tr>
<td>Median body mass index (range)</td>
<td>22 (17–31)</td>
</tr>
<tr>
<td>Primary infertility</td>
<td>38 (68)</td>
</tr>
<tr>
<td>Secondary infertility</td>
<td>11 (20)</td>
</tr>
<tr>
<td>Chronic pelvic pain</td>
<td>42 (75)</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>47 (84)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>34 (61)</td>
</tr>
<tr>
<td>Constipation/diarrhoea</td>
<td>29 (52)</td>
</tr>
<tr>
<td>Dyschezia</td>
<td>28 (50)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>15 (27)</td>
</tr>
<tr>
<td>Irregular cycle</td>
<td>17 (30)</td>
</tr>
<tr>
<td>Previous medical treatment</td>
<td>29 (52)</td>
</tr>
<tr>
<td>Previous surgical treatment</td>
<td>42 (75)</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise stated.
Urological interventions were carried out in 8/56 patients (14%). Bladder sutures were performed after either segmental bladder resection (n = 4) or resection of a non-perforating vesico–uterine endometriosis nodule (reinforcing suture, n = 1). Ureter transection was not performed or observed. Bowel resection was performed in most patients (50/56 or 89%). The six patients without bowel resection had bladder wall suture after resection of nodular bladder endometriosis (n = 3), reinforcing sutures on the right ureter (n = 1), or appendectomy due to endometriosis infiltration in the appendix (n = 2), in combination with reinforcing sutures on the wall of the rectosigmoid colon.

**Histology**

Detailed histological analysis is summarized in Table 3. Microscopic endometriosis was confirmed in all resected endometriosis specimens (endometriotic adhesions, peritoneal endometriosis, ovarian cystic endometriosis, deep nodules) and was observed in 86% (42/49) of colon specimens. There was no correlation between the presence of dyschezia before surgery and the depth of infiltration in the wall of the resected colon specimen. Patients with and without dyschezia demonstrated the same distribution of depth of infiltration in the wall of the resected bowel specimen.

**Duration of multidisciplinary intervention**

The median (range) duration of operation for the gynaecologist, the urologist and the abdominal surgeon was 224 (60–415), 18 (5–45) and 144 (20–300) min respectively. The median total operation time required for the multidisciplinary radical resection of deep infiltrating endometriosis was 7 h and 16 min (180–780 min).

**Post-operative complications**

Post-operative complications occurred in six patients (6/56, 11%), but were related to intra-abdominal surgery in only three cases (3/56, 5%). A subsequent laparoscopy was needed for two of these three patients to perform laparoscopic suturing of an anastomosis leak and sealing of a bleeding vessel respectively. The third patient, suffering from pelvic pain and fever 3 days after the intervention, was successfully treated with intravenous antibiotics. The other three cases developed a lower leg compartment syndrome immediately after the multidisciplinary intervention, two cases involving the left leg and one involving both legs. This problem, probably a consequence of the long lasting lithotomic position, was treated by fasciotomy the same day.

**Recurrence**

In case of recurrent or persistent pain, a new laparoscopy was performed to rule out recurrent disease. At the end of the study, five re-interventions had been performed. In four cases, recurrent endometriosis presented as an ovarian endometriotic cyst (n = 2), peritoneal endometriosis (n = 1), or a hydrosalpinx with the presence of microscopic endometriosis in the tubal wall. In the other case, only pelvic adhesions were observed without clinical or histological endometriosis. According to life table analysis, the cumulative re-intervention rate was 9, 17 and 23% at 1, 2 and 4 years respectively. The cumulative recurrence rate of endometriosis, proved by histological examination, was 2 and 7% at 1 and 4 years respectively.

**Fertility outcome after surgery**

Most patients (59%, 33/56) wanted to become pregnant after surgery. At the end of the study, 48% (16/33) of these patients had conceived, either spontaneously (n = 7, 44%) or after treatment (n = 9, 56%) including ovarian stimulation and IUI (n = 1) or IVF (n = 8). Nearly all spontaneous (67) and four out of eight IVF pregnancies occurred during the first year after surgery. The 15 patients who were not pregnant at the end of the study were all being treated with IUI or IVF. Two patients who had already conceived after the multidisciplinary surgery (one spontaneous pregnancy and one IVF pregnancy).
tried to become pregnant once more, both by means of IVF. Using life table analysis, the cumulative pregnancy rate was 31, 49, 55 and 70%, after 1, 2, 3 and 4 years respectively. The cumulative pregnancy rate at 40 months was comparable after spontaneous conception (65%) and after IUI or IVF (75%).

Effect of surgery on pain, general satisfaction and quality of life

The median follow-up period after multidisciplinary CO2 laser laparoscopic radical (but fertility-sparing) excision of deep infiltrating endometriosis with colorectal extension was 29 months (range 6–76 months).

The post-operative VAS scores for chronic pelvic pain, dysmenorrhoea and deep dyspareunia were significantly lower than the pre-operative scores ($P < 0.001$; Table 4). Significant improvement of chronic pelvic pain, dysmenorrhoea, and deep dyspareunia was observed in 93 (43/46), 100 (37/37) and 90% (37/41) of patients respectively.

Complete satisfaction was obtained in the majority of patients (86%; 49/57). General health ($P < 0.0001$), emotional wellbeing ($P < 0.001$; self-image: $P = 0.0007$) were significantly improved post-operatively when compared with the situation before the intervention. Fear and depression related to anxiety for infertility diminished significantly after surgery ($P = 0.0008$).

Sexual function improved significantly following surgery with respect to pleasure ($P < 0.0001$), amelioration of discomfort ($P < 0.0001$), and amelioration of the frequency of sexual intercourse $P = 0.0003$.

Discussion

The present study has demonstrated that multidisciplinary CO2 laser laparoscopic radical (but fertility-sparing) excision of deep infiltrating endometriosis with colorectal extension is followed by significant improvement of pain, quality of life and sexual activity.

The main limitation of the study is its retrospective nature, as assessment of pre-operative pain after surgery can be influenced by recall bias. In spite of this limitation, the results confirm that excision surgery for endometriosis results in reduced pain and improved quality of life (Abbott et al., 2003, 2004). Furthermore, the study confirms the positive clinical outcome after complete surgical excision of deep infiltrating endometriosis with segmental bowel resection observed in prospective studies (Thomassin et al., 2004; Darai et al., 2005; Dubernard et al., 2006). An advantage of this study is that the median duration of follow-up of the patients was longer than in these prospective studies (Thomassin, 2004; Darai et al., 2005; Dubernard et al., 2006) and represents the only retrospective follow-up study after laparoscopy.

Table 3. Detailed histological analysis (when available) of colon specimens resected in study.

<table>
<thead>
<tr>
<th>Histological analysis</th>
<th>All available specimens</th>
<th>Dyschesia (28 patients, 27 bowel resection specimens)</th>
<th>No dyschesia (28 patients, 22 bowel resection specimens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopic endometriosis</td>
<td>86 (42/49)</td>
<td>81 (22)</td>
<td>91 (20)</td>
</tr>
<tr>
<td>Serosal infiltration</td>
<td>85 (40/47)</td>
<td>74 (20)</td>
<td>91 (20)</td>
</tr>
<tr>
<td>Muscular infiltration</td>
<td>72 (34/47)</td>
<td>63 (17)</td>
<td>77 (17)</td>
</tr>
<tr>
<td>Submucosal infiltration</td>
<td>26 (12/47)</td>
<td>26 (7)</td>
<td>23 (5)</td>
</tr>
<tr>
<td>Mucosal infiltration</td>
<td>0 (0/49)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are % (n).

Table 4. Comparison of pre- and post-operative visual analogue scales pain symptom scores in 47 study patients who responded the questionnaires.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pre-operative score</th>
<th>Post-operative score</th>
<th>$P$-value$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pelvic pain</td>
<td>5 (0–10)</td>
<td>0.3 (0–10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>9 (0–10)</td>
<td>3 (0–10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>5 (0–10)</td>
<td>1 (0–10)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are median (range).

$^a$Wilcoxon test
A CO2 laser was used for excision of endometriosis (Nezhat and Nezhat, 1992; Sutton, 1993) because of its ‘non-touch’ characteristics, allowing continuous visualization of the section plane between healthy and diseased tissue and its precise cutting characteristics (Koninckx et al., 1996). A low power density mode of 15 W Super Pulse was used to minimize thermal damage to surrounding tissues and vital structures. The value of laser laparoscopy in the treatment of endometriosis-associated pain has been demonstrated in a prospective, randomized, double blind controlled trial (Sutton et al., 1994, 1997).

The results of the present study support the hypothesis that bowel resection anastomosis is superior to discoid excision in the treatment of deep bowel endometriosis (Redwine et al., 1991, 1996; Bailey et al., 1994; Redwine and Wright, 2001; Varol et al., 2003; Ford et al., 2004; Thomassin, 2004; Darai et al., 2003; Jatana et al., 2005; Dubernard et al., 2006; Lyons et al., 2006). This positive association between the extent of endometriosis resection and the degree of post-operative improvement, observed in the present study and in another report (Chapron et al., 2004), supports a ‘dose-effect’ relationship and the value of segmental resection (Chapron et al., 2004). Moreover, the high prevalence of persistent microscopic endometriosis in 86% of the colon specimens resected in this study prompts one to postulate that resection anastomosis leads to less recurrence of bowel endometriosis than discoid excision.

This hypothesis is supported by several observations. Firstly, full thickness discoid excision of true bowel endometriosis (peritoneal implants beyond the muscular layer) is associated with incomplete resection (persistent disease) in at least 40% of patients, regardless of a laparoscopic or laparotomic approach (Benagiano et al., 2005). Secondly, multifocal involvement (defined as the presence of endometriotic lesions within 2 cm from the main lesion), and multicentric involvement (defined as the presence of endometriotic lesions beyond 2 cm from the main lesion) can be observed in up to 62 and 38% of surgical en-bloc specimens respectively (Kavallari et al., 2003). Thirdly, the cumulative endometriosis recurrence rate of 7% within 48 months observed in the present study was lower than the cumulative endometriosis recurrence rate of 34% within 36 months reported in women (n = 83) after surgery for colorectal endometriosis (Fedele et al., 2004). In that study (Fedele et al., 2004), the risk for recurrence was lower in the subgroup (n = 30) who received a segmental bowel resection anastomosis by laparotomy than in patients treated with a more conservative approach.

The rate of complications (5%) directly caused by surgery was low in the present study when compared with published complication rates (2.4–15%) after similar surgery for endometriosis with colorectal extension (Dupreet et al., 2002; Darai et al., 2005; Dubernard et al., 2006, Ribeiro et al., 2006). In these studies, major post-operative complications included anastomosis leak, rectovaginal fistula and pelvic abscesses causing life threatening pelvi-peritonitis. In contrast, not a single case of late bowel perforation, major pelvi-peritonitis, rectovaginal fistula or temporary colostomy was observed in this series. Furthermore, no conversion to laparotomy was needed. So far, only one other group has reported a similar approach (Ribeiro et al., 2006) whereas most other investigators used a complete laparotomy approach or reported a laparoscopy to laparotomy conversion rate between 11 and 24% in a similar patient population (Dupreet et al., 2002; Thomassin et al., 2004; Darai et al., 2005; Dubernard et al., 2006).

It is postulated that low morbidity after radical resection of deep infiltrating endometriosis is the result of a multidisciplinary team approach, as has been proposed by other investigators using a laparotomy (Bailey et al., 1994) or laparoscopy (Varol et al., 2003) approach. Indeed, most gynaecologists are not properly trained in bowel surgery or in surgery of ureters and bladder. Furthermore, colorectal surgeons and urologists have little or no understanding of the ubiquitous nature of endometriosis. As a team, it is possible to exchange surgical skills and anatomical knowledge, and to develop the expertise necessary to carry out radical but nevertheless safe surgery (Perry, 2005) with optimal results. A team approach also has medico-legal advantages. If complications occur, it can be argued that optimal quality was provided based on the combined surgical skills of three surgeons from three different surgical disciplines, each trained in endoscopy surgery, with joined knowledge of the retroperitoneal pelvic anatomy concerning nerves and blood vessels, and treatment of bowel and uretero-vesical lesions according to protocols generally accepted in abdominal surgery and urology.

In the present study the cumulative pregnancy rate at 40 months was about 60%, and comparable to that for spontaneous conception (55%) and for conception after medically assisted procreation (IUI/IVF) (75%), suggesting that an individualized approach concerning infertility management following surgery is justified. It is impossible to compare this study’s fertility data with published reports, since life table analysis was not used by other investigators.

In a study of 204 women with severe endometriosis (RAFS stage IV) but without documented rectovaginal or colorectal involvement, treated by laparoscopy, the cumulative probability of pregnancy within 3 years from surgery was 44% (Vercellini et al., 2006). In a case control study, the same authors (Vercellini et al., 2006) questioned the relationship between rectovaginal endometriosis and infertility, since the cumulative pregnancy rate after 2 years in women with rectovaginal endometriosis was similar in those who had received laparotomic resection of rectovaginal endometriosis (n = 44, 50%) and those who chose expectant management (n = 61, 47%). Whereas this hypothesis may be relevant for cases of rectovaginal endometriosis without other pelvic endometriosis, it is not applicable to the present study patients with deep infiltrating colorectal or rectovaginal endometriosis associated with extensive endometriosis in other pelvic locations. Furthermore, the authors (Vercellini et al., 2006) also admitted that their study only allowed the conclusion that laparotomy does not appear to improve fertility in patients with isolated deep infiltrating endometriosis. A properly designed randomized trial is the only way to address this important question. In the meantime, surgical treatment of endometriosis-associated infertility is recommended clinical practice according to guidelines of evidence-based reproductive medicine (D’Hooghe et al., 2003, Kennedy et al., 2005). It is recommended that women with advanced endometriosis are treated in recognized referral centres for endometriosis (Kennedy et al., 2005; D’Hooghe and Hummershoj, 2006).

In conclusion, multidisciplinary CO2 laser laparoscopic radical excision of deep infiltrating endometriosis, performed with the aim of preserving fertility, is effective in improving pain scores, quality of life and sexual satisfaction, with a low complication rate, a low cumulative recurrence rate and a high cumulative pregnancy rate.
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Presented at the IX World Congress on Endometriosis, organized by the World Endometriosis Society, Maastricht, The Netherlands, 15 September 2005

Declaration: The authors report no financial or commercial conflicts of interest.

Received 6 February 2008; refereed 4 March 2008; accepted 28 August 2008.
Dear Editor,

In this letter, we want to address the incorrect presentation of our paper (Meuleman et al., 2009) in an opinion paper of your journal (Koninckx et al., 2010), in line with editorial recommendations to react if “an author has erred in giving data from previous works” (Corson, 2010).

First criticism: “Title concluded that “multidisciplinary excision of deep endometriosis improves pain, QOL, and sexuality with high fertility rates and low complication and recurrence rates”” (Koninckx et al., 2010). This is incorrect: the title of our paper is neutral: “Outcome after multidisciplinary CO₂ laser laparoscopic excision of deep infiltrating colorectal endometriosis”.

Second criticism: “Abstract concluded that “multidisciplinary excision of deep endometriosis improves pain, QOL, and sexuality with high fertility rates and low complication and recurrence rates”. There were no data to support the conclusion “improves” because there was no control group.” (Koninckx et al., 2010). Our paper (Meuleman et al., 2009) represents a nonrandomized quantitative uncontrolled before - after study, an acceptable design to study quality improvement (Fan et al., 2010). Controlled before-after study designs are infrequently used because of difficult in finding a suitable control group (Fan et al., 2010). As we stated in Discussion (Meuleman et al., 2009), retrospective design can be influenced by recall bias, since the magnitude of benefit can be overestimated in uncontrolled before-after studies (Fan et al., 2010).

Third criticism: “The data described only bowel resections” (Koninckx et al, 2010). This is incorrect. All patients received a radical excision of DIE including radical nodulectomy, as
written in Results (Meuleman et al., 2009) (Section Histology, Page 285, lines 1 - 3: “Microscopic endometriosis … deep nodules”) and at 3 different places in Materials and Methods (Meuleman et al., 2009) [Section Patients: Page 283, lines 1 - 3: “All women…urologist”; Section Operative Procedure, paragraph 3, lines 1 - 8 (page 283): “Radical excision…normal anatomy”; Section Operative Procedure, paragraph 5, lines 1 - 7 (page 283): “Finally…gynaecologist”].

Fourth criticism: “The low recurrence rate of 7% was based on 9 repeat laparoscopies only, in which endometriosis was found in just 4 cases” (Koninckx et al, 2010). This calculation was actually based on information from all 56 patients based on returned questionnaires (n = 46) and phone calls (n = 9), as specified (Results, Section Response Rate, lines 1 - 5, page 284). We state in Results, Section Recurrence, that “At the end of the study, 5 reinterventions had been performed. In 4 cases, recurrent endometriosis presented…. The cumulative recurrence rate of histologically proven endometriosis was 2% and 7% at 1 and 4 years respectively.”. This was calculated using life table analysis to correct for duration of follow-up per patient (Materials and Methods) (Meuleman et al., 2009). The cumulative endometriosis recurrence rate of 7 % within 4 years was identical to the total endometriosis recurrence rate in all 56 patients (n = 4/56 = 7%) (Meuleman et al., 2009).

Fifth criticism: “No endometriotic nodule was observed in 7 women, or a nodule outside the muscularis in 6 women, nor a mean operating time of 7 hours, both the highest figures ever reported” (Koninckx et al, 2010). As mentioned in our response to criticism 3, nodules were excised radically in all patients and all contained histological endometriosis. Our low incidence of postoperative bowel complications (n = 3/56 or 5%), when compared to other groups (Discussion section, paragraph 6) (Meuleman et al., 2009), supports our practice to allow the abdominal surgeon to decide to either suture the bowel wall or to do bowel resection anastomosis. The absence of microscopic endometriosis in 7 resected colon specimens, and the absence of muscular infiltration in the resected colon specimen of 6 women is a reflection of the fact that the bowel nodule (containing histologically proven endometriosis) had been completely excised by the gynecological surgeon before bowel resection. The decision of the bowel surgeon to remove the bowel in these 6 cases was based on limited integrity of the bowel wall after
radical nodulectomy, not restorable by bowel suture, primarily in order to prevent postoperative bowel complications and not because of the residual presence of macroscopic or microscopic endometriosis on/in the bowel wall, in line with approaches advocated by other groups (De Nardi et al., 2009; Dousset et al., 2010; Keckstein and Wiesinger, 2000; Possover et al., 2000; Seracchioli et al., 2007;). Comparison of operation time between our study (Meuleman et al., 2009) and other studies is hard, since the start (patient entry in OR, induction of anesthesia, introduction Verress needle, start of actual surgery) or end (end of actual surgery, end of abdominal/vaginal closure, end of anesthesia, patient exit from OR) of the surgical intervention has not been defined in similar studies (Meuleman et al., 2011). In our study (Meuleman et al., 2009), operation time was calculated from the induction until the end of anesthesia, whereas other studies may have calculated only the actual duration of surgery. The duration of our surgery (Meuleman et al., 2009) was not exceptionally long, as 6 studies included in our systematic review (Meuleman et al., 2011) reported a mean/median duration of surgery of at least 300 minutes (Daraï et al., 2007; Lyons et al., 2006; Meuleman et al., 2009; Minelli et al., 2009; Pereira et al., 2009; Ruffo et al, 2010). Furthermore, we studied (Meuleman et al., 2009) a highly selected (< 3% of all laparoscopies between 1996 - 2004) group of patients with mostly (75%) recurrent DIE with colorectal extension. Additionally, the long duration of surgery has to be balanced against the low rate of complications, reinterventions and recurrences and the high rate of pain relief, improvement of QOL, and fertility, that were recently confirmed in our prospective study (Meuleman et al., submitted) carried out according to clearly defined terms, definitions and outcome variables proposed before (Meuleman et al., 2011).
References


2.5. Case Report: Lower Limb Compartment Syndrome (LLCS) as a Complication of Laparoscopic Laser Surgery for Severe Endometriosis
Carla Tomassetti, M.D., Christel Meuleman, M.D., Bernard Vanacker, M.D., Ph.D., Thomas D’Hooghe, M.D., Ph.D.
Fertility and Sterility, Volume 92, Issue 6, December 2009, Pages e9- e12
CASE REPORT

Lower limb compartment syndrome as a complication of laparoscopic laser surgery for severe endometriosis

Carla Tomassetti, M.D.,* Christel Meuleman, M.D.,* Bernard Vanacker, M.D., Ph.D.,* and Thomas D’Hooghe, M.D., Ph.D.*

* Department of Obstetrics and Gynaecology, Leuven University Fertility Centre, University Hospitals Leuven, Leuven, Belgium; and * Department of Anesthesiology, University Hospitals Leuven, Leuven, Belgium

Objective: To report a case of lower limb compartment syndrome (LLCS) during long duration laparoscopic interventions for resection of extensive endometriosis, and evaluate the efficiency of a novel patient positioning method to reduce its prevalence.

Design: Case report and observational study.

Setting: University Hospitals, Belgium.

Patient(s): Thirty-year-old woman undergoing a long duration laparoscopic intervention for resection of stage IV pelvic endometriosis.

Intervention(s): Laparoscopic intervention for resection of stage IV pelvic endometriosis.

Main Outcome Measure(s): The occurrence of LLCS after laparoscopic surgery for extensive endometriosis, in this case, and the prevention of subsequent LLCS after the application of a novel patient positioning method including the following steps: maximal avoidance of the lithotomy position, patient positioning in a modified supine position, mobilization of the legs of the patient in between different surgical phases, and application of intermittent compression stockings.

Result(s): The prevalence of lower limb compartment syndrome has been reduced to 0 since the application of the new patient positioning method.

Conclusion(s): Lower limb compartment syndrome can be prevented in patients undergoing long duration multidisciplinary laparoscopic resection of extensive endometriosis by a novel sequential positioning method of patients before and during surgery. (Fertil Steril 2009;92:2038.e9–e12. ©2009 by American Society for Reproductive Medicine.)

Key Words: Laparoscopic surgery, endometriosis, compartment syndrome, postoperative complication, prevention
serum levels of creatine kinase, suggesting rhabdomyolysis. The clinical diagnosis of bilateral LLCS was made. Anterior, posterior, and lateral compartment pressures in the right lower leg were raised, respectively, 34, 98, and 52 mmHg. Compartment pressures in the left lower leg were normal, so this leg was treated conservatively. During subsequent four-compartment fasciotomy of the right lower leg, macroscopic muscle necrosis was not observed. Eighteen months after fasciotomy, the patient underwent a surgical elongation of the Achilles tendon and cosmetic correction of hypertrophic scar tissue at the initial fasciotomy incision. Subsequent recovery of motor function was satisfactory.

**DISCUSSION**

**Lower Limb (Well Leg) Compartment Syndrome**

Compartment syndrome is a condition in which increased pressure within a limited space compromises the blood circulation and the normal function of tissues within this space. At the lower limb, for example, four compartments can be identified, each enclosed by unyielding osteofascial tissue and containing muscular, neural, and vascular structures (3, 4).

In 1872, Von Volkmann described the features and long-term effects of (forearm) compartment syndrome leading to an ischemic contracture (5). About 100 years later, LLCS, as a result of a long duration lithotomy position, was first reported by Leff and Shapiro (6). Over the last 30 years, several reports on LLCS have been published in the field of urology (4, 7), gastroenterology (8–11), and gynecologic surgery (2, 13).

General etiologic factors for LLCS include increased compartmental content, decreased compartmental volume, and external pressure. The key factor appears to be the change of pressure in the microcirculation of the compartmental tissues. Reduction in the arterial–venous gradient and the ischemia–reperfusion syndrome are seen as complementary hypotheses to explain the increase of compartmental pressure. Along with the increase of tissue pressure, capillary blood flow is decreased, followed by reduced tissue oxygen pressure, resulting in metabolic tissue deficit causing ischemia and necrosis. The latter provoke additional oedema, and lead to a vicious circle of increasing tissue pressure (14).

As different tissue types have different sensitivity to oxygen depletion, first sensory nerves, then motor nerves, muscle, and finally bone, are permanently damaged (15). A variety of intraoperative events, including hypotension, fluid deficit, vasoconstricting drugs, vascular occlusion because of extreme flexion and increased intraabdominal pressure, peripheral elevation, compressive bandages, or points of pressure (increased risk in obese patients), can lead to a reduction of perfusion pressure that may cause ischemia (11).

**Preventive Measures at the Leuven University Fertility Centre for Laparoscopic Multidisciplinary Radical Resection of Endometriosis**

Gynecologic laparoscopic surgery has historically been performed with the patient in the lithotomy and Trendelenburg positions to facilitate access to the deep pelvis. This type of patient positioning is associated with an increased risk of developing LLCS, as illustrated by the existing literature and our three cases. To prevent the development of LLCS in our patients receiving laparoscopic surgery for endometriosis, we have adopted a series of preventive measures starting in our center since January 2004. Both installation methods are described.

**Situation during the time period 1996–2003 (before January 2004)**

Cases of severe endometriosis with colorectal involvement were operated by a multidisciplinary team (2). The median total general anesthesia time required for the multidisciplinary laparoscopic radical resection of deep infiltrating endometriosis with colorectal involvement was 436 minutes (180–780 minutes). The patient was installed in the lithotomy position for approximately 40 minutes, for placement of ureteral double J stents (18 minutes, range: 5–45 minutes) and for performing a diagnostic hysteroscopy with endometrial biopsy. Then the operation field was again disinfected and covered in new sterile drapes for main surgery, including laser laparoscopy for resection of endometriosis by the gynecologist (mean duration 224 minutes, range: 60–415 minutes) and laparoscopic bowel surgery by the colorectal surgeon of the team (mean duration 144 minutes, range: 20–300 minutes). During the whole length of the procedure, the patient thus remained in the lithotomy position. During this period of time, the prevalence of LLCS was 0.8% (3/371) laparoscopic resections of endometriosis (2000–2003). No cases of deep vein thrombosis occurred. It is important to mention that none of the three patients with LLCS started a medicolegal case after the complication had occurred.

**Prevention policy of LLCS at the Leuven University Fertility Centre since January 2004**

In view of the occurrence of LLCS after laparoscopic surgery in prolonged lithotomy position (Lloyd-Davies) as described in our three cases and in the literature, and in view of the pathophysiologic mechanisms, the following specific preventive measures have been applied at the Leuven University Fertility Centre since January 2004 to keep the risk of LLCS as minimal as possible.

1. Avoidance of the lithotomy position where possible: the first important goal is to avoid as much as possible the classical lithotomy position (Lloyd-Davies) by repositioning the patient when the surgical technique does not require lithotomy (16). Since January 2004, the lithotomy position is only used for three surgical phases of the multidisciplinary laparoscopic interventions that require full and easy access to the vulvar/perineal region: cystoscopic placement of ureteral stents, diagnostic/operative hysteroscopy, and bowel surgery including primary resection anastomosis (standard transanal circular double-staple technique). During the main part of the surgery, namely, the CO2 laser laparoscopic resection of endometriosis, the patient is positioned in a modified supine position.
2. Modified supine position: since 2004, a modified supine position is used during laparoscopic resection of endometriosis integrating two previously described techniques (8, 11) in a novel approach. In the first modified lithotomy position, the patient’s calves are placed slightly below the level of the right atrium (which minimizes the degree of elevation once the patient is in the Trendelenburg) but the calves are still supported by stirrups (11). In the second modified lithotomy position (8) the classical supine position is used during laparoscopic advanced surgery with a lateral approach by the surgeon. However, this approach has the disadvantage that it reduces surgical access to the deep pelvis. Therefore, in Leuven we have combined these two methods into a new method, as illustrated in Figure 1, which we would like to refer to as the Leuven Endometriosis Surgery (LES) position. After the patient is placed in a supine position, the stirrups (Maquetmatic, Maquet, Rastatt, Germany) are applied to support the full length of the leg. Abduction of both legs is possible, allowing enough access to the perineal region to manipulate a transvaginally placed instrument. Abduction of the legs is possible, allowing enough access to the perineal region to manipulate a transvaginally placed instrument. Moreover, the application of ICS during laparoscopy may result in lower CP, regardless of the position of the patient’s legs (supine vs. lithotomy) and recommend the application of ICS. In view of these data, and as the only evidence against the use of ICS came from case reports where other contributing factors could not be excluded as a cause of LLCS, we decided to use ICS.

3. Mobilization of the legs of the patient in between surgical phases: the lithotomy position is applied during the first phase (hysteroscopy and cystoscopy) and the third phase (bowel surgery) of the intervention, whereas the modified supine position is applied during the second phase (laparoscopic excision of endometriosis) of the intervention. Obviously, the legs of the patient are mobilized in between these three phases, which has a positive effect on local blood circulation.

4. Application of intermittent compression stockings: intermittent compression stockings (ICS) (Sequential Compression Sleeves (Tyco Healthcare Group LP, Mansfield, MA, USA) are used on both legs in combination with TED (antithrombosis) stockings. The use of this externally applied antithrombosis device is somewhat controversial. According to several case reports (13, 17, 18) there is a possible association between the use of these stockings and the presence of LLCS when patients are in the lithotomy position. Some investigators (17, 18) recommend that sequential compression stockings should not be used on patients in a prolonged lithotomy position because venous and lymphatic drainage is facilitated anyway because of the elevation of the lower legs. However, other investigators (19) observed that external compression by ICS resulted in lower CP, regardless of the position of the patient’s legs (supine vs. lithotomy) and recommend the application of ICS. In view of these data, and as the only evidence against the use of ICS came from case reports where other contributing factors could not be excluded as a cause of LLCS, we decided to use ICS.

5. Finally, all patients were installed on a moldable bean bag, and their upper body was covered by a forced-air warming device (Bair Hugger, Arizant, Eden Prairie, MN, USA).

Using this approach, not a single case of LLCS has been observed in the 425 patients (2004–2006) who have received a laparoscopic resection of endometriosis, even though the mean duration of surgery has not decreased during this time, because increased experience of the surgical team was matched by increasing severity of endometriosis affecting the pelvic, bowel, and ureter structures in operated patients.

In conclusion, gynecologic surgeons should be aware that LLCS is a rare but important complication of surgery performed in the prolonged lithotomy position. The prevalence of LLCS in our patients who were operated for extensive endometriosis affecting pelvis, bladder/ureter, and bowel by a multidisciplinary team was 0.8% (3/371) up to January 2004. Appropriate measures are needed to prevent LLCS, and a high level of suspicion is warranted in all patients with postoperative pain in the lower limbs, to allow early diagnosis and treatment of LLCS. Moreover, early diagnosis of LLCS is only possible if the patient is completely woken up at the end of the intervention. In our center, we have reduced the prevalence of LLCS to 0 (0/425) using a new method to
prevent LLCS in all our patients operated during long-lasting multidisciplinary laparoscopy resections of deep infiltrating endometriosis involving bladder, ureters, and bowel. This method is based on the avoidance of the lithotomy position when possible, the preference for a modified supine position labeled as the LES position, the mobilization of the limbs between surgical phases, and the application of intermittent compression stockings.

REFERENCES


Fertility and Sterility®
2.6. Clinical Outcome after CO₂ Laser Laparoscopic Radical Excision of Endometriosis with Colorectal Wall Invasion combined with Laparoscopic Segmental Bowel Resection and Reanastomosis

Christel Meuleman, M.D., Carla Tomassetti, M.D., André D’Hoore, M.D., Ph.D., An Buyens, M.D., Ben Van Cleynenbreugel, M.D., Steffen Fieuws, Ph.D., Freddy Penninckx, M.D., Ph.D., Ignace Vergote, M.D., Ph.D., Thomas D’Hooghe, M.D., Ph.D.

Human Reproduction, under review
Abstract

**Background:** Clinical outcome assessment of CO$_2$ laser laparoscopic radical excision combined with laparoscopic segmental bowel resection and reanastomosis for endometriosis with colorectal wall invasion.

**Methods:** Retrospective cohort study of a consecutive group of patients treated between September 2004 and September 2006 ($n = 45$) in a tertiary academic referral centre for reproductive medicine. By the use of questionnaires, QOL, pain, sexuality and fertility was assessed. Postoperative complications were recorded, and Life Table analysis was used for calculation of pregnancy rates and endometriosis recurrence.

**Results:** Between September 2004 en September 2006, 45 patients underwent extensive surgery with colorectal resection and reanastomosis. No immediate major postoperative complications requiring surgical re-intervention were recorded. 67% (30/45) of the patients responded to the questionnaires. At a median follow-up period of 27 months (range 16 – 40 months), gynaecological pain, sexual function and QOL have improved significantly. Although 5 patients (11%) had a reintervention for various reasons, in only 2 of them (4%) recurrent endometriosis was histologically proven, resulting in a cumulative endometriosis recurrence rate of 2.2% and 4.4% after 1 year and 3 years respectively. Thirteen out of 28 patients who wanted to become pregnant immediately after the intervention, conceived during the follow-up period. One of them delivered twice, whereas another patient had a miscarriage. These 14 pregnancies were achieved spontaneously ($n = 9$) or after IVF ($n = 5$). The cumulative pregnancy rate was 47% after 3 years.

**Conclusion:** Pain, sexual function and QOL improved significantly, and were associated with a good fertility rate and a low complication and recurrence rate after CO$_2$ laser laparoscopic radical excision of endometriosis with colorectal wall invasion combined with laparoscopic segmental bowel resection and reanastomosis.
Introduction

Endometriosis is defined as functioning ectopic endometrial tissue and affects 10% of women of child bearing age (D’Hooghe et al., 2003; Eskenazi and Warner, 1997; Wheeler, 1989). The main symptoms of endometriosis are pain and infertility (Burns and Schenken, 1999). As many as 60% of infertile women are afflicted with endometriosis (D’Hooghe et al., 2003; Eskenazi and Warner, 1997; Strathy et al., 1982). DIE is characterized by the invasion of anatomical structures and organs deeper than 5 – 6 mm beyond the peritoneum (Koninckx and Martin, 1994; Vercellini et al., 2004) and affects about 20-35% of the women with endometriosis (Chapron et al., 2001). DIE mainly involves the uterosacral ligaments, followed by the rectosigmoid colon, the vagina and the bladder (Jenkins et al., 1986). Intestinal involvement is frequent and has been estimated to occur in 3 – 37% of cases (Collin and Russell, 1990; Coronado et al., 1990; Graham and Mazier, 1988). The rectum and rectosigmoid junction together account for 70% to 93% of all intestinal endometriotic sites (Bailey et al., 1994; Coronado et al., 1990). In addition to the rectosigmoid junction, the most common intestinal sites are the appendix (2 - 18%), the distal ileum (2 - 16%) and the caecum (< 2%) (Zwas and Lyon, 1991). The term “bowel endometriosis” is used when endometrial-like glands and stroma infiltrate the bowel wall reaching at least the subserous fat tissue or adjacent to the neurovascular branches (subserous plexus) (Remorgida et al., 2007). As initially suggested by Chapron et al. (Chapron et al., 2003) endometriotic foci located on the bowel serosa should be considered peritoneal and not bowel endometriosis (Remorgida et al., 2007). Bowel endometriosis can cause severe symptoms which may affect QOL, such as bowel cramping, abdominal bloating, diarrhoea, constipation, dyschesia and cyclical rectal bleeding (Garry et al., 2000; Redwine and Wright, 2001). Previous investigators have shown that complete removal of deep pelvic endometriosis improves QOL and potentially fertility, but may be associated with a high risk of postoperative complications (Abbott et al., 2003; Adamson, 1997; Coronado et al., 1990; Hughes et al., 1993; Redwine and Wright, 2001). It is commonly accepted that DIE, which involves intestines and/or bladder and ureters, is a challenging condition that requires the skills of an experienced team led by a gynaecological reproductive surgeon working together with a colorectal surgeon and an urologist (Kennedy et al., 2005). However, there is still debate to which extent gynaecologists can be trained to perform bowel resection at the same level of colorectal surgeons (Pereira et al., 2009).
At the LUFc of the University Hospital Leuven, advanced endometriosis with colorectal invasion and/or invasion of the bladder and ureters is treated laparoscopically by a multidisciplinary team (Meuleman et al., 2009). The gynaecologist (C.M.), trained in reproductive (endoscopic) surgery, defined as surgery performed to diagnose, conserve, correct and/or improve reproductive function (Zegers-Hochschild et al., 2009), performs a radical excision of endometriosis with a CO₂ laser. Laser surgery is an accepted method of reproductive surgery for patients with endometriosis, as demonstrated by several groups worldwide (Donnez, 1987; Koninckx et al., 1991; Nezhat et al., 1986; Nisolle and Donnez, 1990; Sutton, 1989), with minimal thermal damage to the surrounding tissue when compared to electro-surgery (Mage and Bruhat, 1983; Tulandi, 1986). Furthermore, the no-touch technique allows clear visibility of section planes between healthy tissue and diseased tissue surrounded by fibrosis, which is an advantage during surgery for bowel endometriosis.

After radical excision of all macroscopically visible diseased tissue by the gynaecologist a colorectal surgeon (A.D.) and an urologist (B.V.C.) evaluate the integrity of the wall of the intestines and the urological system respectively. If necessary, as judged by the colorectal surgeon, a colorectal resection and reanastomosis is performed. Following conditions will indicate resection and reanastomosis: large direct full-thickness trauma to the colorectal wall, extensive lesion to the bowel wall musculature, and extensive lateral dissection compromising the colorectal wall vascularity and/or innervation (Chapron et al., 2001; Garry et al., 2000; Meuleman et al., 2009; Meuleman et al., 2011; Ruffo et al., 2010). The aim is to treat bowel endometriosis with the lowest complication rate possible by leaving the decision about the integrity of the bowel wall and the restoration of this integrity to a colorectal surgeon adept at laparoscopy and with sufficient knowledge of endometriosis. Discoid resection followed by bowel suture plays a limited role in our centre, is reserved for smaller transmural lesions of the wall of the rectum (but not the sigmoid) and is not discussed in this paper. This approach is built on the work from pioneers in laparoscopic surgery for the treatment of deeply infiltrative endometriosis with bowel resection and reanastomosis or discoid resection (Landi et al., 2008; Lewis and Nezhat, 2007; Nezhat et al., 1991; Nezhat et al., 1992; Nezhat et al., 1993; Possover et al., 2000; Redwine and Sharpe, 1991; Redwine, 1992; Redwine et al., 1996; Sharpe and Redwine, 1992; Varol et al., 2000; Varol et al., 2003). In our approach, the multidisciplinary
approach is central, i.e. the colorectal surgeon decides which type of bowel surgery (resection and reanastomosis or suturing/reinforcement sutures) is needed in which cases, and carries out this surgery in an effort to minimize postoperative complications that would impair future fertility.

In a first pilot study (Meuleman et al., 2009), performed between 1996 and 2004, feasibility and safety of the above described multidisciplinary approach was shown in 56 patients, as well as improved QOL, pain, sexual function, high pregnancy rate and low postoperative complications and recurrence rate. The current study was executed as a validation of these previously good results, focusing on a selected subgroup of women with DIE with colorectal wall invasion who underwent multidisciplinary CO₂ laser laparoscopic radical excision and segmental bowel resection and reanastomosis. QOL, pain, sexual function, pregnancy rate, postoperative complications and recurrence rate are assessed in patients operated between September 2004 and September 2006. This subgroup was chosen because it is important to report clinical outcome after segmental bowel resection and reanastomosis, since this technique possibly increases the risk of complications when compared to discoid excision (Fanfani et al., 2010; Landi et al., 2008; Mohr et al., 2005; Ret Davalos et al., 2007; Roman et al., 2010). Also, very few long term follow-up data are available regarding QOL, cumulative pregnancy rate or cumulative recurrence rate after this type of surgery according to a recently published systematic review on this topic (Meuleman et al., 2011).

Material and Methods

The protocol of this retrospective cohort study (ClinicalTrials.gov ID: NCT00462176) was approved by the Ethical Committee of the University Hospital Leuven, Belgium.

Patient selection

Data were retrieved retrospectively from a prospectively maintained electronic database. All women (n = 45) who had undergone a bowel resection and reanastomosis at the end of a CO₂ laser laparoscopic radical excision of endometriosis between September 2004 and September 2006 were selected. During that time period, a total number of 427 patients underwent surgery via laparoscopy at the LUFe (of whom 238/427 or 56% in one day surgery). 60% (n = 258/427)
of these patients had a laparoscopic excision of endometriosis of any rAFS stage, and 33% (n = 40/427) underwent surgery for DIE in hospitalization setting. The study group thus accounts for 10.5% (n = 45/427) of all performed procedures, and for 32% (n = 45/140) of procedures performed for treatment of DIE. The study group also clearly excludes women with peritoneal or deep endometriosis which can be peeled off or excised from the bowel with the CO₂ laser without any major consequences for the integrity of the bowel wall.

**Preoperative procedure**

All patients were treated according to a standardized clinical protocol, in line with the clinical standard operating procedures that are in place at the LUFc following ISO 9001-2000 certification in 2004 (Meuleman et al., 2009).

Briefly, during a first consultation at the LUFc, a medical history is taken and a clinical examination is performed followed by a transvaginal ultrasound performed by an appropriately skilled gynaecologist. In absence of previous surgery demonstrating endometriosis lesions on the rectosigmoid level or above, an additional barium enema and intravenous pyelogram is performed to assess to which extent the wall of the bowel, the bladder and/or the ureters are involved by the surrounding endometriosis in patients with a clinical picture suggestive for deeply infiltrative disease, based on medical history, surgical history, abdominal and vaginal examination, and expert gynaecological ultrasound. This information is necessary to organize the operation program, as a multidisciplinary intervention requires the presence of colleagues of different disciplines.

During a second consultation, the expected extent of the intervention is explained to the patient based on the results of the above mentioned investigations. All patients are informed about the collaboration of the reproductive surgeon with a colorectal surgeon and an urologist. Patients with documented colorectal wall involvement are preoperatively informed of the possibility of segmental resection and reanastomosis. In case a low resection and reanastomosis seems necessary, the possibility of colonic pouch reconstruction with optional temporary protective ileostoma is discussed with the patient.
Although there are no data to promote hormonal treatment prior to surgery to improve the success of surgery (Kennedy et al., 2005; Muzii et al., 1996), patients received GnRH–analogue treatment 3 months prior to surgery, as in our experience surgery is facilitated in a “dry” pelvis minimally affected by inflammation and/or hyper vascularisation.

**Preoperative bowel preparation**
All 45 patients had full mechanical bowel preparation using Fleet Phospho-Soda® (Wolfs, Belgium) (2 x 45 ml) the day before surgery.

**Operative procedure**
Our multidisciplinary 3-step operative procedure for patients with extensive DIE with colorectal extension has been described in detail previously (Meuleman et al., 2009).

After the induction of anaesthesia, Double J stents are placed routinely by the urologist (B.V.C) for patients who will eventually undergo bowel resection and reanastomosis for deeply infiltrative endometriosis because at least one of the following conditions is encountered during this surgery: ovarian fossa surgery in case of endometriomas larger than 4 cm, ureteral surgery in case of peri-ureteral endometriosis with or without displacement, narrowing or stenosis of the ureters, and extensive endometriosis/frozen pelvis (at least one previous pelvic surgery for endometriosis in most cases) where ureters serve as reference points in the pelvis.

This stenting allows ureterolysis by CO₂ ‘micro’-dissection without accidental or unnoticed trans-section of the ureter. Since ureterolysis was performed in 91% (41/45) of cases in this study, we preferred to place Double J stents instead of other ureteral stents or catheters as a one step procedure to limit the number of ureteral manipulations that may harm the internal ureteral wall. A Double J stent can always be removed when no ureterolysis has been performed (less than 10% of cases in our study), but has to remain in place for 6 weeks to 3 months to prevent stricture formation or urine leakage after ureterolysis involving extensive coagulation around the ureter, lesion of the ureter with or without suture, or trans-section of the ureter with suture. Single J stents have to be removed at the end of the intervention and eventually replaced by double J stents in the above mentioned cases, which increases the number of ureteral manipulations.
Patients are installed in a modified supine position as described previously (Tomassetti et al., 2009).

After induction of pneumo-peritoneum at a maximum of 15 mmHg, a 12 mm operative laparoscope is introduced through the umbilicus. Three supplementary 5 mm trocars are placed supra-pubically (n = 1) and left (n = 1) and right (n = 1) at approximately two fingers medially from the spina ischiadica anterior superior, respectively.

All visible endometriosis is excised with a CO₂ laser (Lumenis Inc, USA: Compact 40W CO₂ laser) at a power density of 15 Watt Super pulse. The laser is used at such a low power for the following reasons: minimal thermal damage of the surrounding tissue (minimal risk of adhesion formation); possibility to work at the border of healthy and diseased tissue (intact dissection possible enabling “peeling off” the diseased tissue); avoidance of complications (leakage of ureters/bladder/bowel). Normal anatomic relationships and normal function of the pelvic organs are restored as much as possible in principle by excision of all by endometriosis infiltrated peritoneum. If perforation of the vaginal fold occurs, it is laparoscopically sutured by the reproductive surgeon (C.M.). The presence of endometriosis is scored and staged according to the rAFS classification system of the ASRM (rAFS, 1997).

After excision of all endometriotic lesions by the reproductive surgeon (C.M.), the urologist (B.V.C.) evaluates the ureters and the bladder. In case of extensive vesico-uterine de-peritonealisation, the bladder is filled with blue dye. If the blue colour is visible through the bladder wall (seromuscular injury), the urologist (B.V.C.) places reinforcement sutures on the bladder wall laparoscopically. A perforation of the bladder or a ureter injury are also sutured laparoscopically by the urologist (B.V.C.).

Subsequently, the colorectal surgeon (A.D.) evaluates the integrity of the rectosigmoid colon and takes the final decision, in mutual agreement with the reproductive surgeon (C.M.), to resect the involved segment with primary reanastomosis in the studied group. The decision of bowel resection and reanastomosis is taken in the following conditions: large direct full-thickness trauma to the colorectal wall too extensive to be sutured without impact on the functionality of
the bowel, extensive lesion to the bowel wall musculature in the absence of full-thickness damage but with impact on functionality, and extensive lateral dissection compromising the colorectal wall vascularity and/or innervation.

In all cases, bowel resection is performed laparoscopically. Different types of bowel resection are performed dependent on the type, location and extension of the lesion (see results section). The dissection of the bowel, after excision of nodular endometriosis, is conducted merely inside the mesorectum (as close to the bowel as possible) aiming to preserve the sympathetic fibers of the upper mesorectum (the superior hypogastric plexus, upper hypogastric nerves and lumbo-sacral sympathetic trunk), the sympathetic fibers of the lower mesorectum (lower hypogastric nerves and proximal part of the inferior hypogastric plexus), the pelvic splanchnic nerves and the cranial and middle part of the inferior hypogastric plexus in the lower mesorectal planes and the caudal part of the inferior hypogastric plexus (Landi et al., 2006). Only fibres of the resected segment of the bowel are cut, minimizing denervation. However, if nerve branches are impacted in an endometriotic/fibrotic nodule, they are sacrificed due to the technique of ‘radical excision of diseased tissue’ to avoid as much as possible leaving behind endometriotic tissue.

A histological examination is performed on all resected tissue specimens.

**Postoperative procedure**

Postoperatively, re-alimentation is started after restoration of bowel transit (flatus).

Postoperative appointments are arranged: with the urologist (B.V.C.) between three weeks and three months after the intervention to remove the double-J stents, with the colorectal surgeon (A.D.) six weeks after surgery, and with the reproductive surgeon (C.M.) eight weeks postoperatively. The reproductive surgeon (C.M.) evaluates the pain complaints and discusses postoperative contraception or fertility.

When postoperative contraception is desired, a low dose oral contraceptive or a levonorgestrel-releasing intrauterine device (Vercellini et al., 2005) is prescribed to minimize menstruation.
Patients are asked to take the oral contraceptive continuously till break-through bleeding and then to stop for seven days (Vercellini et al., 2003).

In women younger than 36 – 38 years with a regular ovulatory cycle, normal tubal function and a male partner with a normal sperm analysis, spontaneous conception is proposed during 6 months to one year. In case of normal tubal function but ovulatory dysfunction or mild male factor infertility, controlled ovarian stimulation with low dose gonadotrophins combined with intrauterine insemination is performed during 3 cycles. If this treatment is not successful, IVF is proposed. In all cases of compromised ovum pick-up and transport capacity and/or major sperm problems and/or advanced female age (> 36 - 38 years), IVF is proposed after the patient has recovered from the intervention.

**Questionnaires**

All 45 patients who had undergone a bowel resection and reanastomosis were asked to complete the Oxford Endometriosis QOL questionnaire (Jones et al., 2001), a sexual activity questionnaire (Thirlaway et al., 1996), visual analogue scales (VAS) for dysmenorrhoe, chronic pelvic pain and deep dyspareunia, and to answer questions about medication and fertility, in order to compare their status before surgery and at the moment of the evaluation (December 2007), as described before (Meuleman et al., 2009).

**Statistical analysis**

Paired Wilcoxon tests are used to compare scores before and after surgery. A correction for multiple testing is applied using a step-down Bonferroni procedure. P-values are two-sided and considered significant if smaller than 0.05. Analyses have been performed using the statistical package SAS (version 9.1). The cumulative pregnancy rate and the cumulative recurrence rate were calculated using Life Table analysis.
Results

Results were obtained from both patient questionnaires (QOL scores, sexual satisfaction scores, the 3 VAS pain scores, pregnancy rates), patient phone calls for those patients who had not returned the questionnaires (pregnancy rates and recurrences) and medical chart reviews (patient characteristics, presenting symptoms, pre-, per- and postoperative care, histology, complication rate, recurrence rate, reintervention rate and pregnancy rate).

Questionnaire Response rate

The response rate to the questionnaires was 67% (n = 30/45). Patients not responding to the questionnaires (n = 15/45, 33%) were contacted by phone by an independent investigator (A.B.) who was not part of the clinical team and were asked about postoperative complications, surgical re-interventions, and fertility. Lack of interest and/or lack of time were cited as the reason for not completing the questionnaires, but all patients agreed to answer by phone the above mentioned questions and these answers were also entered into our database and analyzed.

Patient characteristics with respect to reproductive wishes and previous surgery (Table I)

The median age of the patients was 30 years (range 18 - 42 years). Most patients (n = 40/45 or 89%) were operated because of pain in combination with a wish to become pregnant. This wish to become pregnant was present as either active infertility [62%, n = 28/45, primary infertility (n = 23) and secondary infertility (n = 5)], or as a wish to become pregnant some time in the future or at least to keep this option open (27%, n = 12/45, including 11 women who were childless and 1 who had been pregnant before). Only 5 patients (n = 5/45, 11%) were operated because of pain only, although at least 3 of these patients would have wished to have (more) children but were not able because of other reasons (no more funding for IVF treatment, hereditary congenital anomaly, age).

Of the 45 patients, 32 patients (with in their history 22 diagnostic laparoscopies, 15 operative laparoscopies, 1 laparotomy) were referred to our centre because of extensive endometriosis and 13 patients (with in their history 6 diagnostic laparoscopies, 11 operative laparoscopies, 3 laparotomies) came on their own initiative.
Most patients (n = 39/45, 87%) had already undergone surgery for endometriosis performed by another gynaecologist before undergoing a multidisciplinary radical resection of endometriosis in our centre. Previous surgery for endometriosis in these patients consisted of in total 28 diagnostic laparoscopies, 26 operative laparoscopies and 4 laparotomies. Only 6 patients had undergone no previous surgery, but had dyshesia and confirmed trans-mural invasion of the colorectal wall as demonstrated by bowel barium enema (n = 5/6) or CAT scan (n = 1/6).

**Presenting pain symptoms (Table I)**

Pain symptoms retrieved from the medical files included chronic pelvic pain (26/45, 58%), dysmenorrhoe (44/45, 98%), deep dyspareunia (27/45, 60%), and dysuria (13/45, 29%). Symptoms regarding abnormal bowel function were present in all patients: constipation/diarrhea (26/45, 58%), dyshesia (40/45, 89%), and cyclical rectal bleeding (7/45, 15%). This information was fully in line with the information provided by the 30 patients who returned the questionnaires.

**Preoperative tests**

According to the preoperative report of a vaginal examination, available in the clinical file of 34/45 patients, a nodule was felt in the fornix posterior in 29/34 patients. The 5 patients with a ‘negative’ vaginal examination included 1 obese patient (BMI 37) in whom the clinical value of vaginal examination was limited, and 4 patients with other evidence of bowel endometriosis: 1 patient with intramural bowel invasion according to bowel barium enema, 1 patient with a bowel nodule left after a previous operative laparoscopy by another gynaecologist, 1 patient with significant bowel involvement during 2 previous operative laparoscopies, and 1 patient with a frozen pelvis according to a previous laparotomy.

A gynaecological trans vaginal ultrasound, performed by a gynaecologist with special skills in pelvic ultrasound, was abnormal in 35/37 cases, showing either an endometriotic nodule in the fornix posterior (n = 22/37 or 60%), and/or a frozen pelvis (n = 21/37 or 57%), and/or echo dense ovarian cysts compatible with endometriosis (n = 16/37 or 43%, 7 bilateral and 9 unilateral), i.e. adnexal masses with ground glass echogenicity of the cyst fluid, one to four locules, without papillations and with detectable blood flow (Van et al., 2010). The 2 patients without either endometriotic nodules, ovarian endometriomas or frozen pelvis on pelvic ultrasound,
demonstrated mural invasion of the sigmoid and rectosigmoid respectively on bowel barium enema with double contrast.

A bowel barium enema with double contrast, performed in 40/45 patients, clearly demonstrated mural invasion of the bowel wall in 35/40 (88%) patients, at the level of the sigmoid colon (n = 11), recto-sigmoid junction (n = 21), and upper rectum (n = 3). The 5/40 patients with normal findings as protocolled on X-ray, all had their bowel barium enema performed in a peripheral hospital. These radiographies were deemed to be of insufficient quality to conclude on endometriotic bowel involvement according to the surgeons in our centre, but still these patients were predicted to have significant bowel involvement according to their previous history: 1 patient with 3 previous operative laparoscopies and surgically documented bowel nodule, 2 patients with a previous operative laparoscopy demonstrating significant bowel endometriosis, 1 patient with previous laparotomy showing frozen pelvis and bowel nodule, and 1 patient with a clinical nodule in the fornix posterior combined with a pelvic mass behind the uterus compatible with bowel endometriosis. Only 5/45 patients had not undergone a preoperative bowel barium enema: in 4 patients previous diagnostic laparoscopy revealed the presence of bowel wall involvement, and in 1 patient a CT-scan was conclusive. These findings were confirmed during final curative surgery.

In 41 of the 45 patients also an intravenous pyelogram (IVP) (n = 41) was performed. IVP was abnormal in 14/41 (34%) patients, including ureter dislocation (n = 14), diminished expansion of the pelvic segment (n = 10), left-sided hydro-uretero-nephrosis (n = 1) and unilateral ureteral stenosis (n = 1).

**Intra-operative staging of endometriosis and surgical procedures (Table II)**

Except for one patient with rAFS stage III (score: 30), all patients had endometriosis rAFS stage IV (n = 44/45) with a mean score of 85 ± 24 (range 30 - 126).

At the start of the operation, Double J stents were placed bilaterally (n = 42) or unilaterally (n = 1) into the ureters by the urologist (B.V.C.) in 43 out of 45 patients. At surgery bladder
suturaing was necessary in 3 patients and left ureter suturing in 1 patient, all performed by the urologist (B.V.C.).

The reproductive surgeon (CM) performed a complete resection of all macroscopically visible endometriosis tissue present in the pelvis. Endometriotic nodules present on the rectum and rectosigmoid were removed by excision with the aim to preserve bowel wall integrity (n = 26) or by excision with perforation of the bowel wall (n = 19). Furthermore, the reproductive surgeon performed 19 cystectomies for ovarian endometriotic cysts (7 left ovary, 8 right ovary, 4 bilateral), one ovariectomy because the left adnexa was deformed by the endometriosis to a fibrotic mass, 17 salpingectomies (14 left, 2 right and 1 bilateral) and 3 salpingostomies on the right tube.

The colorectal surgeon (A.D.) performed a bowel resection because suturing of the bowel wall was judged to be unsafe after bowel perforation following excision of endometriotic nodules (n = 19) or the bowel wall was judged to be too deeply damaged or weakened over a relatively large surface area (n = 26) after excision of bowel endometriotic nodules without opening the bowel wall. In these cases, bowel resection and reanastomosis was preferred over bowel suture in order to prevent postoperative bowel perforation (short term) and narrowing (long term).

A sigmoid resection (end-to-end reanastomosis) was performed in 5 patients, a recto-sigmoid resection (end-to-end reanastomosis) in 37 patients. A colonic J-pouch was performed in 3 other patients with low rectal endometriotic nodules in order to promote the recovery of the rectal reservoir function, since an end-to-end reanastomosis at such a low rectal level would compromise this function during at least six months to one year after the operation.

Only one patient had a temporary covering ileostoma for prevention of rectovaginal fistula, which was closed at 3 months after surgery. The colorectal surgeon also performed 4 appendectomies.
Duration of multidisciplinary intervention with bowel resection

The median total operating time was 420 min (range 240 - 600 min). The median duration of operation for the urologist was 10 minutes (range 0 - 90 min), mostly limited to the placement of ureteral Double J stents. The median duration of the CO\textsubscript{2} laser operative laparoscopy for endometriosis was 240 min (range 80 - 390 min) and of the colorectal surgery 120 min (range 50 - 300 min).

Postoperative complications

Average duration of hospital stay was 7 days (range 4 - 15 days). Postoperative complications within 6 weeks after the intervention occurred in 2 patients (n = 2/45, 4.4%) but did not require a surgical reintervention.

The first patient had normal plasma concentrations of C-reactive protein and white blood cells at her discharge from the hospital 8 days after the operation but needed readmission to the hospital 6 weeks after surgery due to Pelvic Inflammatory Disease (PID). This patient was treated with broad spectrum intravenous antibiotics, and one year after the multidisciplinary surgery, she needed laparoscopic salpingectomy as a hydrosalpinx developed.

The second patient developed an atonic neurogenic urinary bladder necessitating intermittent urethral catheterisation during the first 10 weeks after the operation. Subsequently, the patient went to the toilet to urinate every 2 hours and managed well without a need for catheterization, with a limited but acceptable degree of stress incontinence. Nine months after the operation, this patient became pregnant spontaneously and the baby was delivered by caesarean section.

Histology

Endometrial glands and stroma were found in all resected endometriosis tissues removed from the pelvis and from the bowel, illustrating that all 45 patients had histologically confirmed bowel endometriosis.

The length (median 13 cm, range 8 - 22 cm) of the resected bowel specimens was available in 43/45 cases.
Histological examination of the bowel resection specimens demonstrated remaining (microscopic) endometriotic foci (endometrial glands and stroma) in 91% (n = 41/45), located in the subserosal area in 6% (n = 3/45, subserosal invasion till the muscularis), in the muscularis area in 53% (n = 24/45) and in the submucosal area in 31% (n = 14/45). Intramucosal or transmucosal remaining (microscopic) endometriotic foci were not observed.

The 4 bowel specimens without remaining (microscopic) endometriotic foci, were marked by a large perforation after excision of an endometriotic nodule (histologically positive for endometriosis) with endometriotic extension to the bowel muscularis area (n = 2) or to the bowel submucosal area (n = 2). In these 4 cases, in fact full thickness discoid excision was performed by the reproductive surgeon (C.M.) but the large defect left after this excision was judged by the colorectal surgeon (A.D.) to be too extensive to be treated with a bowel suture and so resection and reanastomosis was performed of the bowel segment involved in the endometriotic process.

Positive section margins were diagnosed in 22% (n = 10/45) of the resected specimens. Only one of these 10 patients developed a rapid recurrence (Case 1 in the section “Reintervention and Recurrence”).

In 2 patients, lymph nodes that were incidentally resected during the bowel resection procedure, were histologically positive for endometriosis.

**Pain, general satisfaction and QOL after surgery**

Assessment was performed at a median follow up of 27 months (range 16 - 40 months).

Significant postoperative improvement was observed for the VAS scores related to chronic pelvic pain, dysmenorrhea and deep dyspareunia (p-value < 0.0001) (Table III).

Statistical analysis of the QOL questionnaires showed a significant improvement in both general health and quality of professional life (p < 0.0001), pain (p < 0.0001), and emotional wellbeing (p < 0.0001), and a significant reduction in perceived lack of control (p < 0.0001), and need of social support (p < 0.0001).
The sexual activity questionnaire showed a significant postoperative improvement of sexual pleasure ($p = 0.009$) and frequency of sexual activity ($p = 0.003$), and a significant reduction of discomfort during sexual intercourse ($p = 0.026$).

**Fertility outcome after surgery**

Fertility outcome after surgery was assessed in 28 patients who actively wanted to become pregnant after surgery and who had either primary infertility ($n = 23/28, 82\%$) or secondary infertility ($n = 5/28, 18\%$). Thirteen out of 28 patients became pregnant (pregnancy rate of 46\%) during a median follow-up period of 27 months (range 16 - 40 months) after surgery, resulting in a cumulative pregnancy rate (Life Table analysis) of 7\%, 29\% and 47\% after 1 year, 2 years and 3 years, respectively. One patient was pregnant twice, and one patient had a miscarriage. Pregnancy occurred spontaneously ($n = 8$) or after IVF ($n = 5$) in patients with either primary ($n = 10/13$) or secondary ($n = 3/13$) infertility.

**Reintervention and recurrence**

Recurrent/persistent complaints suggestive for endometriosis indicated a new laparoscopy in 5 out of 45 patients (11\%). This results in a cumulative reintervention rate (Life Table analysis) of 4.4\%, 6.6\% and 11\% after one, two and three years respectively. Histologically proven recurrence of endometriosis occurred only in 2 patients, resulting in a total recurrence rate of 4\% ($n = 2/45$) and a cumulative endometriosis recurrence rate of 2.2\% and 4.4\% after one, and three years respectively. These 5 patients are briefly reviewed in the following paragraphs.

In one patient laparoscopic salpingectomy was performed after 11 months for the development of a hydrosalpinx after PID (cfr. Section Postoperative Complications), but no recurrence of endometriosis was found.

Another patient underwent a hysterectomy after 17 months because of persisting pain and vaginal bleeding unresponsive to hormonal therapy, but at repeat surgery no macroscopic visible nor histologically proven endometriosis was present.
In a third patient a pseudo-peritoneal cyst with pain symptoms warranted a second look laparoscopy after 31 months for adhesiolysis; no evidence of recurrent endometriosis was present.

The first patient with recurrent disease underwent a re-laparoscopy at 14 months for recurrent pain. At first surgery, an anterior resection was performed but the distal resection margin was positive. At re-surgery, a small nodule at the stapler line was the only site of recurrence, and a re-resection was performed.

A second patient developed an endometriotic ovarian cyst which was diagnosed at a screening ultrasound before an IVF cycle at 32 months of follow-up. At re-surgery minor postoperative adhesions were resected and a cystectomy at the left ovary was performed. Histological examination confirmed the presence of an endometriotic ovarian cyst.

**Discussion**

Our data demonstrate favourable clinical outcome after laparoscopic CO₂ laser radical excision of DIE with colorectal wall invasion with segmental bowel resection anastomosis in “difficult to treat” patients who had mostly (39/45 or 87%) received at least one previous intervention for the same pathology.

Indeed, our results demonstrate a better outcome when compared with those reported in our systematic review of clinical outcome after bowel resection and reanastomosis for bowel endometriosis (Meuleman et al., 2011) or another recent review paper (Darai et al., 2007) or a recently published large case series (Ruffo et al., 2010) with respect to conversion to laparotomy [0% versus 7/8% (Darai et al., 2007)], complications requiring surgical intervention [0% versus 4.5% (Meuleman et al., 2011), 6.5% (Darai et al., 2007) or 8.3% (Ruffo et al., 2010)], pregnancy rate [46% versus 39% (Meuleman et al., 2011) or 44.6% (Darai et al., 2007)], and endometriosis recurrence rate [4% versus 6% (Meuleman et al., 2011)]. Furthermore, it was not our goal to compare different methods with respect to their effect on bowel integrity. In fact, such a
comparison is impossible according to the current status of the literature, as we demonstrated in our systematic review (Meuleman et al., 2011).

The current study adds novel and relevant data since it reports clearly defined outcome variables (complications, pain, fertility, QOL, recurrence) in a well characterized group of patients after laparoscopic intervention by a multidisciplinary surgical team without conversion to laparotomy when compared to the current literature in this field (Meuleman et al., 2011). Furthermore, we used patient-based VAS to assess the major pain complaints [used in less than 20% of studies (Meuleman et al., 2011)] with a follow up period of more than 24 months [reported in less than 50% of studies (Meuleman et al., 2011)]. According to current consensus (Vincent et al., 2010), a patient-based 11-point Numerical Rating Score, in which the pre-operative and post-operative symptoms are given by the patient, allows a better evaluation of the postoperative pain situation as well as the evaluation of de novo pain symptoms possibly associated with a specific type of surgery, when compared to the rating of symptom prevalence and severity by others (physicians, nurses) who may be biased themselves or may introduce bias among patients. Additionally, we also reported data on the QOL after treatment for extensive DIE with colorectal extension [reported in only 10% of studies (Meuleman et al., 2011)], fertility outcome data (reported in less than 40% of studies (Meuleman et al., 2011) covered in our review) using life table analysis [used before only in our pilot study (Meuleman et al., 2009) and in 2 other studies (Coronado et al., 1990; Stepniewska et al., 2009)] and recurrence data [reported in less than 45% of studies (Meuleman et al., 2011) covered in our review] using life table analysis [used before only in our pilot study (Meuleman et al., 2009)].

Our data confirm the favourable clinical outcome data reported in our previously published pilot study including all patients (n = 56) who had undergone CO₂ laser laparoscopic radical excision of DIE with active involvement of colorectal surgeon and/or urologist selected retrospectively from the list of all patients (n = more than 2000) operated at the LUFc between 1996 and 2004 (Meuleman et al., 2009). In the current study, we only included the most complex cases of patients who received a bowel resection and reanastomosis, representing only 10.5% (n = 45/427) of all performed procedures, and only 32% (n = 45/140) of procedures performed for treatment of Deeply Infiltrative Endometriosis, between 2004 and 2006. After 2004, patients with more
extensive endometriosis were referred to our centre compared to cases referred during the previous period (1996 - 2004) described in the pilot study. Firstly, the percentage of women with previous endometriosis surgery was higher in the current study (n = 39/45, 87%) than in the previous pilot study (n = 42/56, 75%), reflecting a referral shift towards more complicated cases to our unit. Secondly, the 50 patients with bowel resection and reanastomosis described in the pilot study were collected during nearly 8 years (September 1996 - July 2004), whereas it only took us only 2 years (September 2004 - September 2006) to collect about the same number (n = 45) for the current study. It is normal that the number of charts reviewed for the current study (n = 427, September 2004 - September 2006, 2 years) was 4 times smaller than the number reviewed for the pilot study (n = 2000, September 1996 – July 2004, about 8 years) since the time period covered in the current study was also 4 times smaller than in the pilot study (Meuleman et al., 2009). The questionnaire response rate was not significantly lower in the current study (67%) than in the pilot study (87%, p = 0.05). Similarly, the pilot study (Meuleman et al., 2009) and the current study were statistically comparable with respect to duration of follow-up (29 and 27 months, respectively), pregnancy rate (48% and 46%), cumulative pregnancy rate after 3 years (55% and 47%, respectively), spontaneous pregnancy rate (44% and 62%), and the pregnancy rate after IVF (50% and 39%).

The clinical profile of the patients included in our study challenges the current dichotomized concept that symptomatic patients with endometriosis have either pain or infertility, and supports our hypothesis that the majority of women of reproductive age (15 - 45 years) with pain (more than 90% in our study) also have uncompleted reproductive status, i.e. a desire to still have a child in the future. We propose that the reproductive status and wishes of patients should be reported in a more refined way in outcome studies after endometriosis surgery using the following 3 categories: patients with infertility, defined as a time to pregnancy longer than 12 months according to WHO criteria (Zegers-Hochschild et al., 2009), patients who want to become pregnant in the immediate future and who are not (yet) infertile, patients who still want to become pregnant at some time in the future but who have postponed their pregnancy wish for a variety of reasons (no partner, too much pain, social reasons, etc.). For each of these categories, it would be useful to indicate if the patient already has at least one child (yes/no). Furthermore, some patients who did not even consider pregnancy before surgery, may change their mind.
following improved QOL and sexual functioning after successful surgery. In view of their fertility desire, it is important that reproductive surgery (surgery aimed at the diagnosis, maintenance, correction and preservation of reproductive function (Zegers-Hochschild et al., 2009) is available to these patients and is associated with the lowest possible rate of complications that will impair tubo-ovarian function. In women with advanced endometriosis, radical excision combined with pelvic reconstruction appears to be the best option to preserve reproductive function but requires expertise, available in specialist centres (Emmanuel and Davis, 2005; Perry, 2005; Redwine and Wright, 2001) with multidisciplinary surgical collaboration in cases of complete obliteration of the cul-de-sac or the vesico-uterine fold (Perry, 2005).

A certain degree of flexibility is important in the organization of multidisciplinary surgery, as it was not possible to predict trans-mural bowel involvement of endometriosis in 20% (n = 9/45) of our patients, even after thorough preoperative imaging. At surgery, 9 patients had a frozen pelvis and required laparoscopic bowel resection and reanastomosis after excision of bowel and pelvic endometriosis because the bowel wall was deemed to be too weakened/damaged by the colorectal surgeon. This observation illustrates the need for careful preoperative planning of multidisciplinary surgery for endometriosis to ensure that the colorectal surgeon and urologist are either present or stand-by in case they are needed.

Expertise can lead to a reduced laparoscopy-laparotomy conversion rate, in most series varying between 11 and 29% (Darai et al., 2005; Dubernard et al., 2006; Duepree, et al., 2002; Thomassin et al., 2004). In our study, conversion to laparotomy was not needed. So far, only one other group has reported a similar approach (Ribeiro et al., 2006). A close bowel resection will maximize the chance for a nerve-sparing resection and decrease the risk for autonomic nerve damage and related dysfunction. Evidently, endometriosis does not require the same degree of bowel dissection as surgery used in oncologic procedures (Remorgida et al., 2007).

Our postoperative major complication rate (4.4%) was relatively low when compared to the prevalence of published major complication rates (2.4-15% including anastomosis leak, rectovaginal fistula and pelvic abscesses causing life threatening pelvi-peritonitis) after similar surgery for endometriosis with colorectal involvement (Darai et al., 2005; Dubernard et al., 2006;
Duepree et al., 2002; Ribeiro et al., 2006). We hypothesize that our low complication rate is the consequence of careful preoperative staging of the invasiveness of pelvic endometriosis into the bowel and the bladder/ureter, of careful planning of the surgery as mentioned above, and of an excellent multidisciplinary collaboration built up since 1996. In our study, we did not observe any rectovaginal fistulae, anastomosis leak or pelvic abscess. One patient developed a PID postoperatively despite routine antibiotic prophylaxis (Darai et al., 2007), but it is not proven that the PID was due to the intervention because of the relatively long lapse of time (6 weeks) between the intervention and the first symptoms of PID. It is unclear if the development of an atonic neurogenic urinary bladder in one patient – initially necessitating intermittent urethral catheterisation – could have been avoided. Although our surgical technique was designed to spare the pelvic autonomic nerves as much as possible, as recommended before (Dubernard et al., 2008), it is not always possible to avoid the pelvic autonomic nerves when they are surrounded by an extensive fibrotic endometriosis nodule. We hypothesize that nerve fibres innervating the bladder had been transected during the removal of the endometriotic nodule and/or the colo-anal J-Pouch performed for an extensive rectal ampulla perforation. However, other groups (Dubernard et al., 2008) have described a much higher prevalence (19 - 42%) of postoperative bladder dysfunction after surgery for posterior DIE.

The significant improvement of pelvic pain and QOL after surgery is in line with results from other studies (Darai et al., 2005; Dubernard et al., 2006; Thomassin et al., 2004), as reviewed before (Meuleman et al., 2011). A limitation of our study is its retrospective design, especially with respect to possible bias in the assessment of pre-operative pain. A strength of our study is the long follow-up period (more than 2 years) and the fact that patient-based VAS scoring was used to assess pain, which has been reported in only a few studies (Bracale et al., 2009; Darai et al., 2005; Darai et al., 2007; De Nardi et al., 2009; Dubernard et al., 2006; Meuleman et al., 2009; Meuleman et al., 2011). Furthermore, the improved QOL observed within 27 months after bowel resection and reanastomosis in our study confirms and extends observation from 2 prospective studies (Lyons et al., 2006; Thomassin et al., 2004) in a total of 34 patients, with a median follow-up time of only 12 and 15 months, respectively.
Invasive endometriosis surgery with bowel resection and reanastomosis has a positive effect on fertility, as we observed a total pregnancy rate of 46% and a cumulative pregnancy rate of about 50% within 3 years, with spontaneous conception in the majority (n = 8/13) of our patients. Remarkably, life table analysis has been used in only 4 out of 21 studies reporting fertility outcome after surgery for endometriosis with colorectal extension as reviewed recently (Coronado et al., 1990; Ferrero et al., 2009; Meuleman et al., 2009; Meuleman et al., 2011; Stepniewska et al., 2009). This is surprising in view of the fact that it is generally accepted for more than 20 years (Olive, 1986) that life table analysis is the best way to calculate fertility outcome while controlling for the duration of follow-up and drop-out rate for each patient.

Our results are in line with those from 2 recent studies (Bianchi et al., 2009; Stepniewska et al., 2009). In a retrospective cohort study of women with bowel endometriosis (Stepniewska et al., 2009), the monthly fecundity rate was significantly higher after segmental bowel resection and reanastomosis than after endometriosis bowel nodule excision without bowel resection and reanastomosis. In a prospective cohort study (Bianchi et al., 2009) of 179 symptomatic infertile women with ultra-sonographic signs of DIE, IVF pregnancy rates were 2.45 times higher after extensive laparoscopic excision of DIE when compared to expectant management (no surgery).

The low cumulative endometriosis recurrence rate (4.4%) within 3 years can be explained by a high surgical experience of surgeons adept at total laparoscopic peeling of the pelvis and the establishment of a multidisciplinary surgical team aiming at radical resection of endometriosis. It is likely that bowel resection and reanastomosis leaves behind less microscopic disease (Remorgida et al., 2005; Roman et al., 2009), possibly resulting in lower recurrence rates (Meuleman et al., 2011; Stepniewska et al., 2009) when compared to simple resection of a fibrotic bowel nodule, because bowel endometriosis, rather than having the shape of a plaque, may follow the enteric nervous system (Anaf et al., 2004), may spread laterally to the point of serosal invasion (Remorgida et al., 2005), and has a multifocal and multicentric nature (Kavallaris et al., 2003; Keckstein and Wiesinger, 2005; Redwine and Wright, 2001; Remorgida et al., 2007). On the other hand, even where rectal segmental resection is performed, endometriotic foci may be found on and outside the limits of the digestive resection, as we (Meuleman et al., 2009) and others (Roman et al., 2009) have shown.
It is not necessary to systematically perform a bowel resection in all patients with extensive endometriosis with colorectal involvement: the patients included in our study do only represent 32% of all patients with deeply infiltrative bowel endometriosis operated during the same time interval. The other 68% received radical resection of all macroscopically visible endometriosis without bowel resection and reanastomosis. Based on the data reported in this paper and in our pilot study (Meuleman et al., 2009), in our systematic review (Meuleman et al., 2011) and together with other groups (Chapron et al., 2001; Garry et al., 2000; Ruffo et al., 2010) we believe that an experienced colorectal surgeon has the necessary background and training to decide whether “bowel wall damage” after radical resection of pelvic and bowel endometriosis should be treated by reinforcement sutures, suturing of a perforation (after disc resection) or a resection and reanastomosis of the bowel segment involved in endometriosis, in order to restore optimal function of the bowel with the lowest chance of postoperative problems.

In conclusion, pain, sexual function and QOL improve significantly, and are associated with a good fertility rate and a low complication and recurrence rate after CO2 laser laparoscopic radical excision of endometriosis with colorectal wall invasion combined with laparoscopic segmental bowel resection and reanastomosis.

**Funding**

This research was supported by the Clinical Research Fund of the University Hospitals Leuven, Belgium.
Reference List


Table I: Characteristics and presenting symptoms of study patients (n = 45).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years; median (range)]</td>
<td>30 (18-42)</td>
</tr>
<tr>
<td>Pain only (n, %)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Pregnancy wish impossible to fulfill (n)</td>
<td>3</td>
</tr>
<tr>
<td>No further pregnancy wish (n)</td>
<td>2</td>
</tr>
<tr>
<td>Pain + pregnancy wish (n, %)</td>
<td>40 (89%)</td>
</tr>
<tr>
<td>Active pregnancy wish (n)</td>
<td>28</td>
</tr>
<tr>
<td>Primary (n)</td>
<td>23</td>
</tr>
<tr>
<td>Secondary (n)</td>
<td>5</td>
</tr>
<tr>
<td>Passive pregnancy wish (n)</td>
<td>12</td>
</tr>
<tr>
<td>Primary (n)</td>
<td>11</td>
</tr>
<tr>
<td>Secondary (n)</td>
<td>2</td>
</tr>
<tr>
<td>Chronic pelvic pain (n, %)</td>
<td>26 (58%)</td>
</tr>
<tr>
<td>Dysmenorrhea (n, %)</td>
<td>44 (98%)</td>
</tr>
<tr>
<td>Dyspareunia (n, %)</td>
<td>27 (60%)</td>
</tr>
<tr>
<td>Constipation/diarrhea (n, %)</td>
<td>26 (58%)</td>
</tr>
<tr>
<td>Dyschesia (n, %)</td>
<td>40 (89%)</td>
</tr>
<tr>
<td>Cyclical rectal bleeding</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Dysuria (n, %)</td>
<td>13 (29%)</td>
</tr>
<tr>
<td>Previous surgical treatment (n, %)</td>
<td>39 (87%)</td>
</tr>
</tbody>
</table>
Table II: Surgical procedures performed during multidisciplinary resection of endometriosis in study patients (n = 45).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Percentage</th>
<th>Left</th>
<th>Right</th>
<th>Bilateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureter stent</td>
<td>96% (n = 43/45)</td>
<td>0</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Ureter suture</td>
<td>2% (n = 1/45)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bladder suture</td>
<td>7% (n = 3/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>11% (n = 5/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectosigmoid resection</td>
<td>82% (n = 37/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon pouch</td>
<td>7% (n = 3/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendectomy</td>
<td>9% (n = 4/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>0% (n = 0/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protective ileostoma (temporarily)</td>
<td>2% (n = 1/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystectomy</td>
<td>42% (n = 19/45)</td>
<td>7</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>2% (n = 1/45)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Salpingectomy</td>
<td>38% (n = 17/45)</td>
<td>14</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Salpingostomy</td>
<td>7% (n = 3/45)</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Resection fornix posterior</td>
<td>16% (n = 7/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureterolysis</td>
<td>91% (n = 41/45)</td>
<td>4</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>Adhesiolysis</td>
<td>100% (n = 45/45)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table III: Comparison of pre- (n = 29) and post-operative (n = 30) VAS pain symptom scores (paired Wilcoxon test) in patients undergoing laparoscopic segmental bowel resection and reanastomosis performed at the end of a CO₂ laser laparoscopic radical excision of endometriosis with colorectal wall invasion.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pre-operative score (median, range)</th>
<th>Post-operative score (median, range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pelvic pain</td>
<td>61 (0 - 100)</td>
<td>2 (0 - 43)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>92 (0 - 100)</td>
<td>13,50 (0 - 70)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>28 (0 - 95)</td>
<td>1 (0 - 63)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
2.7. Systematic Review: Surgical Treatment of Deeply Infiltrating Endometriosis with Colorectal Involvement.
Christel Meuleman, M.D., Carla Tomassetti, M.D., André D’Hoore, M.D., Ph.D., Ben Van Cleynenbreugel, M.D., Freddy Penninckx, M.D., Ph.D., Ignace Vergote, M.D., Ph.D., T. D’Hooghe, M.D., Ph.D.
Human Reproduction Update. 2011, Published online January 13, doi: 10.1093

Letter to the Editor
Why we need international agreement on terms and definitions to assess clinical outcome after endometriosis surgery
Christel Meuleman, M.D., André D’Hoore, M.D., Ph.D., Ben Van Cleynenbreugel, M.D., Carla Tomassetti, M.D., Thomas D’Hooghe, M.D., Ph.D.
Hum Reproduction, accepted for publication
Surgical treatment of deeply infiltrating endometriosis with colorectal involvement

Christel Meuleman¹, Carla Tomassetti¹, André D’Hoore³, Ben Van Cleynenbreugel³, Freddy Penninckx², Ignace Vergote¹, and Thomas D’Hooghe¹,*

¹Leuven University Fertility Centre, Department of Obstetrics and Gynecology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium ²Department of Abdominal Surgery, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium ³Department of Urology, University Hospital Leuven, Herestraat 49, 3000 Leuven, Belgium

*Correspondence address. Fax: +32-16-34-43-68; E-mail: thomas.dhooghe@uz.kuleuven.ac.be

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BACKGROUND: Treatment of colorectal endometriosis is difficult and challenging. We reviewed the clinical outcome of surgical treatment of deeply infiltrating endometriosis (DIE) with colorectal involvement.

METHODS: Review was based upon a literature search using following search terms: (1) ‘surgery’ and ‘colorectal endometriosis’, (2) ‘bowel’ and ‘endometriosis’ and ‘surgery’. Inclusion criteria: clear explanation of surgical technique and follow-up data on at least one of the following items: complications, pain, quality of life (QOL), fertility and recurrence.

RESULTS: Most of the 49 studies included complications (94%) and pain (67%); few studies reported recurrence (41%), fertility (37%) and QOL (10%); only 29% reported (loss of) follow-up. Out of 3894 patients, 71% received bowel resection anastomosis, 10% received full-thickness disc excision and 17% were treated with superficial surgery. Comparison of clinical outcome between different surgical techniques was not possible. Post-operative complications were present in 0–3% of the patients. Although pain improvement was reported in most studies, pain evaluation was patient-based in 50% (Visual Analogue Scale in only 18%). While QOL was improved in most studies, prospective data were only available for 149 patients. Pregnancy rates were 23–57% with a cumulative pregnancy rate of 58–70% within 4 years. The overall endometriosis recurrence rate in studies (>2 years follow-up) was 5–25% with most of the studies reporting 10%. Owing to highly variable study design and data collection, a CONSORT-inspired checklist was developed for future studies.

CONCLUSIONS: Prospective studies reporting standardized and well-defined clinical outcome after surgical treatment of DIE with colorectal involvement with long-term follow-up are needed.

Key words: deeply infiltrating endometriosis / surgery / colorectal / bowel / outcome

Introduction

Endometriosis is a gynecologic disorder, characterized by the presence of ectopic endometrium outside the endometrial cavity. Endometriosis predominantly affects women of reproductive age and is associated with pelvic pain and infertility (Kennedy et al., 2005). The prevalence of endometriosis in the general female population has been estimated to be 10% (Vigné et al., 2004). The pathogenesis of endometriosis may be explained by ectopic implantation of endometrial cells following retrograde menstruation via the Fallopian tubes into the pelvis (Sampson, 1927). However, the precise etiology of endometriosis remains unknown.

Three clinical presentations of endometriosis have been described: peritoneal endometriosis, ovarian endometriosis (endometriomas) and deeply infiltrating endometriosis (DIE; Dornmez et al., 1992). In women with endometriosis, intestinal involvement is estimated to occur in 3.8–37% of the patients (Remorgida et al., 2007). Intestinal endometriosis usually affects the rectosigmoid colon and can be associated with symptoms such as diarrhea, dyschezia (defined as the difficulty in defecating, usually as a consequence of long continued voluntary suppression of the urge to defecate, wordnetweb.princeton.edu/perl/webwn), bowel cramping and pain on defecation (Sinaii et al., 2002).

DIE nodules extend more than 5 mm beneath the peritoneum and may involve the uterosacral ligaments, vagina, bowel, bladder or
Laparoscopic segmental excision of the rectum and other types of colorectal surgery, such as discoid excision and superficial shaving, have become increasingly popular but the most appropriate surgical approach for this difficult disease remains controversial. However, little is known about the impact of the different types of surgery in the treatment of DIE on complications, pain, the patients’ quality of life (QOL), recurrence rate and pregnancy rate or fertility. The aim of this literature review is therefore to evaluate the outcomes of the different surgical modalities for management of DIE with colorectal involvement based on the above-mentioned parameters.

Methods
This review is based upon a literature search in Pubmed using the following search terms: (1) ‘surgery’ and ‘colorectal endometriosis’, (2) ‘bowel’ and ‘endometriosis’ and ‘surgery’. The original search was performed on 03 June 2009 and was completed with studies published until 31 December 2009. To ensure the relevance of the publications retrieved, additional inclusion criteria were applied. To be included, the published studies had to be in English and had to contain a clear explanation of the surgical technique used as well as an adequate follow-up phase describing data on at least one of the following terms: post-operative complications, evaluation of pain (dysmenorrhea, dyspareunia, chronic non-menstrual pelvic pain) and QOL (preoperative versus post-operative), fertility (pregnancy rate) and recurrence rate. A flow diagram describing the selection of the papers is given in Fig. 1.

Anatomical considerations
Before describing the different options for surgical management and their outcome, it is essential to take into account the anatomical distribution and histological findings of intestinal endometriosis. Intestinal endometriosis can be found in many areas between small bowel and anal canal, but the main locations of intestinal endometriosis are the rectum and rectosigmoid junction. In a recent observational study, 426 patients presented with 172 intestinal DIE lesions. The rectum and rectosigmoid junction were involved in 65.7% of the cases, followed by the sigmoid colon (17.4%), caecum and ileocaecal junction (4.1%), appendix (6.4%), small bowel (4.7%) and omentum (1.7%) (Chapron et al., 2006).

An important characteristic that should be taken into account before deciding on the surgical strategy for intestinal endometriosis is its multifocality (defined as the presence of endometriotic lesions within a 2 cm area from the main lesion) and its multicentric involvement (defined as the presence of endometriotic lesions beyond 2 cm from the main lesion; Kavaliers et al., 2003). Multifocal and multicentric involvement was observed in 62 and 38% of surgical en bloc specimens, respectively (Kavaliers et al., 2003). This multifocal/multicentric involvement can possibly be explained by the observation that endometriosis infiltration of the large bowel wall occurs preferentially alongside the bowel nerves, even at a distance from the palpated lesion (Anaf et al., 2004). Additionally, fibrosis in the muscular layer does not always surround bowel endometriotic lesions (Remorgida et al., 2002). Moreover, in almost 70% of the cases, intestinal endometriosis lesions are associated with DIE in other locations, justifying specific associated surgical procedures for the uterosacral ligaments, vagina, bladder and/or ureter (Chapron et al., 2003b).

The depth of infiltration of endometriotic lesions into the bowel wall is another important variable to consider in the surgical treatment of choice. In this context, a distinction can be drawn between the presence of endometriotic lesions on the bowel serosa and endometriotic lesions infiltrating the muscularis. According to Chapron, lesions of the serosa without infiltration of the muscularis must not be considered as true intestinal...
endometriosis because these superficial lesions do not justify any specific bowel procedure from a surgical point of view (Chapron et al., 2003b). In practice, this superficial form of serosal bowel endometriosis may not be recognized, be ignored or be treated by surgical shaving, or eventually by full-thickness discoid excision if shaving resulted in significant bowel trauma.

Other relevant anatomical parameters include the effect of previous surgery on abdominopelvic anatomy, the existence and extension of associated pelvic adhesions and the distance between the intestinal lesion and the linea dentata.

**Surgical technique**

Several surgical procedures for endometriosis with bowel involvement have been described using a laparoscopic, a laparotomic, a transvaginal or a combined approach. Different options include shaving [defined as superficial peeling of bowel serosal and subserosal endometriosis (with diathermy or laser)], superficial excision (defined as selective excision of the bowel endometriosis lesion without opening of the bowel wall) full-thickness disc excision (defined as selective excision of the bowel endometriosis lesion with opening, followed by closure, of the bowel wall), or bowel resection anastomosis (defined as resection of a bowel segment affected by endometriosis followed by anastomosis). The choice of the operative technique depends on the extent and depth of bowel infiltration, and on the personal preferences and skills of the surgeon. However, when the intestinal tract is involved, a multidisciplinary approach has been proposed as mandatory (Meuleman et al., 2009a, b; Ruffo et al., 2009). Indeed, the concept is emerging that the best results, in terms of improvement of symptoms and QOL, are achieved by complete surgical excision of all endometriotic implants with a combined gynecological/general surgeon intervention (Garry et al., 2000; Chapron et al., 2001; Meuleman et al., 2009a, b; Ruffo et al., 2009).

**Outcome variables**

In this review, we have listed the number of patients in each study, the time of follow-up, the number of patients lost during follow-up, the number of previous therapeutic surgeries, the indication for surgery as well as histological data, post-operative complications, evaluation of pain (dysmenorrhea, dyspareunia, chronic non-menstrual pelvic pain), QOL (preoperative versus post-operative), fertility (pregnancy rate) and recurrence rate. At the level of histological data, we checked if the following parameters were reported: histological confirmation of endometriosis, degree of endometriosis in the bowel wall, median length of the resected colorectal segment, median of the largest diameter lesions and positive margins (resected bowel specimens that were positive for endometriosis in at least one resection margin).

Major complications were defined as rectovaginal fistulae, anastomotic leakage, pelvic abscesses and post-operative bleeding and their prevalence and clinical management were reviewed. The number and nature of concomitant surgical procedures was noted. Concomitant surgical procedures were defined as surgical procedures that were carried out during the same surgery when also bowel endometriosis was treated surgically.

Pain and QOL were evaluated at the level of methodology (which test was used, patient-reported versus physician-reported etc.) and content (preoperative versus post-operative comparison).

Fertility outcome was assessed as follows: number of patients with a history of infertility, number of patients wishing to conceive and who conceived, median time to conceive after surgery, mode of conception (spontaneous or artificial) and live birth rate, presence of life table analysis.
The endometriosis recurrence rate was reported as follows: number of patients with recurrence after surgery, median time to recurrence, and data on life table analysis. The level of evidence for recurrence of endometriosis was classified in five categories:

1. Symptom recurrence based on patient history, but no proof of recurrence by imaging and/or surgery.
2. Endometriosis recurrence based on non-invasive imaging [e.g. ultrasound, magnetic resonance imaging (MRI)] in patients with or without symptoms (pain, infertility).
3. Surgical reintervention without recurrence of endometriosis: in patients with recurrent symptoms, surgery without visual diagnosis of endometriosis, and with either normal pelvis or other abnormalities (e.g. adhesions).
4. Recurrence of visual endometriosis without histological proof: during laparoscopy endometriosis is visually observed but either not biopsied or biopsied without histologically proven endometriosis.
5. Recurrence of histologically proven endometriosis: during laparoscopy endometriosis is visually observed and confirmed histologically.

Suspicious recurrent endometriosis was present if the criteria for Categories 1 and 2 were met. Proven recurrent endometriosis was present if the criteria for Categories 4 and 5 were met. Additional surgery without evidence for endometriosis was present if the criteria for Category 3 were met.

Statistical analysis

Because of the different styles of reporting data throughout the reviewed papers as well as the heterogeneity of the mixed study group (including studies performing different surgical techniques for the treatment of DIE), no statistical comparisons were made on any of the outcome variables. All data provided are therefore treated in a descriptive manner.

Results

Overview

The process of literature identification and selection is shown in Fig. 1. From the electronic search, 639 original publications were reviewed (93 articles using ‘surgery’ and ‘colorectal endometriosis’ and 599 articles using ‘bowel’ and ‘endometriosis’ and ‘surgery’ as keywords; 53 articles were found in both categories). After screening the titles and/or abstracts, 124 articles were retrieved. Additionally, by checking the publications, two additional cross-references were included. Finally, after investigation of the full manuscripts, 49 articles were included. Preoperative assessment of colorectal involvement by imaging techniques

Supplementary data, Table SI shows that preoperative assessment of colorectal involvement was not recorded in 37% (18/49) studies, or was limited to gynecological ultrasonography (transrectal, vaginal or abdominal) in 4% (2/49) of the studies. In more than half of the studies (59%; 29/49 studies) preoperative assessment of colorectal involvement was recorded by bowel barium enema (26%; 13/49 studies), computerized tomography-scan (31%; 15/49 studies) and/or MRI (28%; 14/49 studies) was documented. Preoperative assessment of possible bladder/ureter involvement by i.v. pyelography or by ultrasonography of kidneys and bladder was recorded in only 10% (5/49) of studies.

Level of invasion of endometriosis in resected bowel specimens

In the bowel resection endometriosis studies reporting transmural invasion, 99.2% of the cases (1067/1076 patients) were histologically...
Table I Surgical treatment of DIE with colorectal involvement.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bowel surgery done</th>
<th>n (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>n (%)&lt;sup&gt;b&lt;/sup&gt; previous therapeutic surgeries</th>
<th>Indication (%)</th>
<th>Histological confirmation n (%)</th>
<th>median or mean ± SD follow-up time (months)</th>
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<td>Abrao et al. (2005)</td>
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<td>Pain (100)</td>
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<td>31 (100)</td>
<td>26 ± 5.7</td>
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<td>Pain (69.6)</td>
<td>56 (100)</td>
<td>45 (6–90)</td>
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<td>30.0</td>
<td>Pain (100)</td>
<td>10 (100)</td>
<td>NR</td>
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<td>Bowel resection anastomosis</td>
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<td>0 (0)</td>
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<td>7 (100)</td>
<td>38.7 (1–84)</td>
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<td>70 (98.6)</td>
<td>24.4 ± 2.2</td>
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<td>18–36</td>
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<td>de Nardi et al. (2009)</td>
<td>Bowel resection anastomosis</td>
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<td>23 (100)</td>
<td>45.2 ± 18.0</td>
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<td>81.8</td>
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<td>NR</td>
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<td>24 (100)</td>
<td>12 (4–15)</td>
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<td>12</td>
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<td>Meireu et al. (2007)</td>
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<td>75.0</td>
<td>Pain and infertility (100)</td>
<td>56 (100)</td>
<td>29 (6–76)</td>
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<td>Minelli et al. (2009)</td>
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<td>39.2</td>
<td>Pain (100)</td>
<td>334 (100)</td>
<td>19.6 (6–48)</td>
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<td>Pereira et al. (2009)</td>
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<td>NR</td>
<td>Pain and infertility (100)</td>
<td>168 (100)</td>
<td>37 ± 23</td>
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<td>NR</td>
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<td>34 (100)</td>
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Continued
Table I Continued

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<th>Reference</th>
<th>Bowel surgery done</th>
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<th>n (%)b previous therapeutic surgeries</th>
<th>Indication (%)</th>
<th>Histological confirmation n (%)</th>
<th>median or mean ± SD follow-up time (months)</th>
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<td>Seracchioli et al. (2007)</td>
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<td>22 (100)</td>
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<td>Stepniewska et al. (2009)</td>
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<td>Urbach et al. (1998)</td>
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<td>6 (100)</td>
<td>4 (66.6)</td>
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<tr>
<td>Total</td>
<td>Bowel resection anastomosis</td>
<td>2039 (100)</td>
<td>948/1607 (59.0)</td>
<td>Pain (75.2)</td>
<td>Pain and infertility (24.8)</td>
<td>1067 (99.2)</td>
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Mixed procedures

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<th>Indication (%)</th>
<th>Histological confirmation n (%)</th>
<th>median or mean ± SD follow-up time (months)</th>
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<td>Bailey et al. (1994)</td>
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<td>123 (94.6)</td>
<td>76 (58.5)</td>
<td>Pain (100)</td>
<td>NR</td>
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<td>Full-thickness disc excision</td>
<td>Bowel resection anastomosis</td>
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<td>76 (58.5)</td>
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<td>60 (16–184)</td>
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<td>68 (7–158)</td>
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<td>Shave</td>
<td>Bowel resection anastomosis</td>
<td>18 (8.9)</td>
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<td>Coronado et al. (1990)</td>
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<td>72 (93.5)</td>
<td>40 (51.9)</td>
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<td>77 (100)</td>
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<td>Indication (%)</td>
<td>Histological confirmation n (%)</td>
<td>median or mean ± SD follow-up time (months)</td>
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<tr>
<td>Maytham et al (2010)</td>
<td>Full-thickness disc excision</td>
<td>27 (50.0)</td>
<td></td>
<td>Pain (100)</td>
<td>101 (100)</td>
<td>24 (2–81) or 28.2 ± 19.6</td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel resection anastomosis</td>
<td>7 (13.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohr et al (2005)</td>
<td>Full-thickness disc excision</td>
<td>48 (25.7)</td>
<td></td>
<td>Pain and infertility (31.0)</td>
<td>101 (96.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel resection anastomosis</td>
<td>20 (37.0)</td>
<td></td>
<td>Pain (69.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redwine and Wright (2001)</td>
<td>Full-thickness disc excision</td>
<td>6 (7.1)</td>
<td></td>
<td>Pain (100)</td>
<td>101 (100)</td>
<td>50.9 ± 34.2</td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribeiro et al (2006)</td>
<td>Full-thickness disc excision</td>
<td>115 (92.0)</td>
<td></td>
<td>Pain (100)</td>
<td>125 (100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bowel resection anastomosis</td>
<td>3 (2.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slack et al (2007)</td>
<td>Full-thickness disc excision</td>
<td>8 (6.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varol et al (2003)</td>
<td>Full-thickness disc excision</td>
<td>85 (48.0)</td>
<td></td>
<td>Pain (79.1)</td>
<td>174 (98.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wills et al (2009)</td>
<td>Full-thickness disc excision</td>
<td>80 (45.2)</td>
<td></td>
<td>Infertility (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shave/superficial excision</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zanetti-Dällenbach et al (2008)</td>
<td>Full-thickness disc excision</td>
<td>47 (97.9)</td>
<td></td>
<td>Pain and infertility (100)</td>
<td>46 (95.8)</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Table I Continued

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bowel surgery done</th>
<th>n (%)</th>
<th>n (%)&lt;sup&gt;a&lt;/sup&gt; previous therapeutic surgeries</th>
<th>Indication (%)</th>
<th>Histological confirmation</th>
<th>n (%)</th>
<th>median or mean ± SD follow-up time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full-thickness disc excision</td>
<td>8</td>
<td>8</td>
<td>Pain and infertility</td>
<td>NR</td>
<td>5–18</td>
<td></td>
</tr>
</tbody>
</table>

Overview of the studies included in the review: bowel resection anastomosis studies; studies including mixed procedures; full-thickness disc excision studies. NR, Not Recorded;

Histological confirmation — histological confirmation of transmural invasion.

<sup>a</sup>Number of patients treated with this technique and percentage of patients treated reported in the paper.

<sup>b</sup>Number of patients who underwent previous surgery (for total percentage of patients, if previous surgery was not reported, studies were excluded).

confirmed compared with 83.2% of the reported cases (883/1061 patients) in the mixed surgical group (Table I). Although 31/49 studies reporting the outcome of surgery for endometriosis with colo-rectal extension included patients with histologically confirmed endometriosis, only 18 of these 31 studies contained specific histopathological data for bowel endometriosis, or included details on the bowel lesion diameters and length of the resected segment (Supplementary data, Table SII). The microscopic extent of bowel invasion by colorectal endometriosis in surgically excised bowel specimens was presented in 15 out of 18 studies evaluating either bowel resection anastomosis (11/14 studies) or a combination of bowel resection anastomosis and full-thickness disc excision (4/4 studies). As shown in Supplementary data, Table SII, the bowel serosa was reported to be involved in 94.5% of the patients undergoing bowel resection anasto-
mosis (121/128). In the same category of studies, endometriotic lesions were reported to be found in the muscularis propria in 95.1% of the cases (583/613). In 37.8% (74/196) and 6.4% (17/265) of the cases, the submucosa and the mucosa, respectively, were reported to be involved. Exclusive involvement of the bowel serosa was not observed, probably because these cases are not clini-
cally labeled as ‘bowel endometriosis’, as discussed in the Methods section (Anatomical considerations).

Furthermore, the prevalence of resection specimens with margins that were histologically positive for endometriosis was only reported in 33% (6/18) of the studies. After bowel resection anastomosis, margins positive for endometriosis were observed in 25/127 patients (19.7%; Supplementary data, Table SIII). In case of bowel resection anasto-
mosis, the median length of the resected colorectal segment ranged between 0.92 and 21 cm, while the median largest diameter of the col-
orectal endometriosis lesions varied between 2.9 and 4.1 cm.

Surgical complications

The large majority of studies (94%; 46/49) included complication rates. Major complications, as defined in the Methods section, varied between 0% (especially in the smaller studies with a low number of patients) and 42.9% (Supplementary data, Table SIII). In the bowel resection anastomosis group, 55 (2.7%) rectovaginal fistu-
lae, 30 (1.5%) anastomotic leakages and 7 (0.3%) abscesses were reported in a total of 2036 patients. In the mixed surgical group, 12 (0.7%) rectovaginal fistulae, 12 (0.7%) anastomotic leakages and 6 (0.3%) abscesses were reported for 1799 patients. The rectovaginal fistulae were treated with colostomy/loop ileostomy, Hartmann surgery or resuturing (Supplementary data, Table SII). Information on the time of occurrence of the rectovaginal fistulae (early or late) was only reported in one study (Slack et al., 2007).

In the studies included in this review, post-operative bleedings were reported as (1) a drop in hemoglobin requiring blood transfusion without surgical intervention (Urbach et al., 1998; Ford et al., 2004; Keckstein and Wiesinger, 2005; Mohr et al., 2005; Ferrero et al., 2009; Juhasz-Boss et al., 2010; Maytham et al., 2010; Minelli et al., 2009), or (2) a drop in hemoglobin requiring surgical reintervention (Flessch et al., 2005; Ruffo et al., 2009). Post-operative bleeding occurred rarely with a prevalence of 3.1% (63/2036) in the bowel resection anastomosis group and 0.3% (6/1799) in the mixed group. However, it should be noted that, in the bowel resection anasto-
mosis group, the majority of the post-operative bleedings (36/63) were reported in one study (Minelli et al., 2009).

Additionally, in approximately half of the studies (14/29 bowel resection anastomosis studies and 10/17 in the mixed study group), the number and nature of the concomitant procedures were reported, as shown in Supplementary data, Table SIII.

Outcome on pain

The majority of the included studies (67%; 33/49) contained data on pain outcome (Supplementary data, Table SIV), but <50% of the studies reporting the outcome on pain [48% (16/33)] had a median or mean follow-up period of more than 24 months (11 studies with bowel resection anastomosis and 5 mixed studies). The other studies...
(52%, 17/33) had a mean/median follow-up period <24 months. Supplementary data, Table SV illustrates that most of the studies reporting pain outcome showed an improvement in pain, gynecological and digestive symptoms after surgery for colorectal endometriosis.

However, there is a lack of consistency in the way of measuring and reporting symptomatic efficacy between different series. Some authors report in terms of overall improvement of pain (Bailey et al., 1994; Nezhat et al., 1994; Jerby et al., 1999; Possover et al., 2000; Kavalidis et al., 2003; Vard et al., 2003; Ford et al., 2004; Abrav et al., 2005; Campagnacci et al., 2005; Coronado et al., 1995; Mohr et al., 2005; Jain et al., 2006; Boni et al., 2007; Stall et al., 2007; Ghezzi et al., 2008; Bracale et al., 2009; Maytham et al., 2010; Minelli et al., 2009; Pereira et al., 2009), while others focus on the intensity of specific symptoms before and after surgery (Redwine and Wright, 2001; Chopin et al., 2005; Flesch et al., 2005; Landi et al., 2006; Langebrakke et al., 2006; Lyons et al., 2006; Brouwer and Woods, 2007; Darai et al., 2007; Seracchioli et al., 2007; de Nardi et al., 2009; Meuleman et al., 2009a). To evaluate pain symptom outcome, a variety of methods of measurement have been applied, ranging from non-specified methods (33%, 11/33) to interviews in person or by telephone and unspecifed questionnaires to a qualitative and/or semi-quantitative visual analogue symptom scale (VAS, Supplementary data, Table SV). In <50% of the studies reporting outcome on pain [42% (14/33)], the pain evaluation was reported to be patient-based (Redwine and Wright, 2001; Ford et al., 2004; Chopin et al., 2005; Flesch et al., 2005; Landi et al., 2006; Brouwer and Woods, 2007; Darai et al., 2007; Bracale et al., 2009; Juhasz-Boss et al., 2010; Maytham et al., 2010; Minelli et al., 2009; Pereira et al., 2009; Meuleman et al., 2009a). In only 18% (6/33) of the studies, a patient-based VAS was used to assess the major pain complaints, including dysmenorrhea, chronic pelvic pain and dyspareunia, to compare the patient’s status before surgery and at the time of the post-operative evaluation (Ford et al., 2004; Flesch et al., 2005; Lyons et al., 2006; Brouwer and Woods, 2007; Bracale et al., 2009; Meuleman et al., 2009a).

Outcome on QOL

Another important outcome measurement, related to the outcome on pain, is the impact of surgery for colorectal endometriosis on the QOL. Several validated questionnaires exist for the evaluation of the QOL (e.g. EHP-30, SF-36, EQ-5HD). However, only 10% (5/49) of the studies selected in this paper (Supplementary data, Table SV) reported data on the QOL after treatment for extensive DIE with colorectal extension (Ford et al., 2004; Keckstein and Wiesinger, 2005; Lyons et al., 2006; Maytham et al., 2010; Meuleman et al., 2009a). In three of these studies, only bowel resection anastomosis was applied, whereas mixed surgical techniques were used in two studies (Supplementary data, Table SV). Only two prospective studies (Keckstein and Wiesinger, 2005; Lyons et al., 2006) reported the QOL in a total of 149 patients, with a median follow-up time of <2 years. Overall, most studies observed a significant improvement in QOL after surgery.

Post-operative pregnancy rate

In only 37% (18/49) studies (11 bowel resection anastomosis studies, six mixed studies and one full-thickness disc excision study), fertility outcome was reported after surgery for advanced endometriosis with colorectal extension, with pregnancy rates varying between 23.5 and 57.1% (Tables II and III). In the study of Lyons et al. (2006), a pregnancy rate of 100% was reported but the sample size of this study was very small (three women wishing to conceive). About half of the pregnancies occurred after spontaneous conception whereas the other half occurred after medically assisted conception (Supplementary data, Table SVI). In the studies under review, 39 spontaneous pregnancies and 6 artificial pregnancies were reported in the bowel resection anastomosis studies compared with 24 spontaneous and 9 artificial pregnancies in the mixed study group.

In only three studies, life table analysis was used to calculate the cumulative pregnancy rate (Coronado et al., 1990; Stepniakowska et al., 2009; Meuleman et al., 2009a). In our retrospective study with 56 patients who underwent multidisciplinary laparoscopic excision of DIE with colorectal extension, an overall pregnancy rate of 48% was associated with a cumulative pregnancy rate of 31, 49, 55 and 70% after 1, 2, 3 and 4 years, respectively (Meuleman et al., 2009a). In another study (Coronado et al., 1990), a pregnancy rate of 39.4% was associated with a cumulative pregnancy rate of 38% at 18 months and 52% at 29 months. In another study (Ferreiro et al., 2009), a cumulative pregnancy rate of 57.6% was reported 50 months after laparoscopic colorectal resection, which was significantly higher than after laparotomic procedures (23.1%). Unfortunately, in most studies, the number of patients wishing to conceive prior to or after surgery is not clear; the distinction between active child wish, passive child wish, completed child wish and absent child wish is not made and likewise the mean period for conception following surgery and the spontaneous/assisted nature and outcome of the pregnancies are often not reported.

Recurrence of endometriosis

Recurrence of endometriosis was only reported in 43% (21/49) of the included studies. The studies reporting no or a very limited number of recurrences were performed with a short follow-up period (<2 years) and included a small sample size. Studies with a longer follow-up period (>2 years) generally showed a higher recurrence rate (Supplementary data, Table SVII). In general, the recurrence rate in studies with a follow-up period >2 years varied between 4.69 and 25%, with most of the studies reporting a recurrence rate of about 10% after surgery. Overall, the recurrence rate was 5.8% in the bowel resection anastomosis group compared with 17.6% in the mixed study group.

The recurrence of endometriosis was defined according to the level of evidence, as mentioned in the Methods section, into three categories: suspicious endometriosis recurrence, additional surgery without endometriosis evidence and visually and/or histologically proven endometriosis recurrence. As shown in Supplementary data, Table SVII, recurrence after bowel resection anastomosis (n = 44) included suspicious recurrence (n = 21, 48%), additional surgery without endometriosis evidence (n = 3, 7%) and proven endometriosis recurrence (n = 20, 45%). Recurrence reported after mixed surgical techniques (n = 138) included suspicious recurrence (n = 2, 1%), additional surgery without endometriosis evidence (n = 87, 63%) and proven endometriosis recurrence (n = 49, 35%). Overall, the proven endometriosis recurrence rate appeared to be lower in the resection anastomosis group (2.5%, 20/812) than in the mixed surgical group (5.7%, 49/865) (Supplementary data, Table SVII). Furthermore, the cumulative recurrence rate was reported only in one
study (Meuleman et al., 2009a) and was 2 and 7%, 1 and 4 years after surgery, respectively.

In only a few studies, the use of post-operative hormonal treatment was recorded (Verspyck et al., 1997; Urbach et al., 1998; Fleisch et al., 2005; Brouwer and Woods, 2007).

**Discussion**

**General**

Our review included 49 studies and a total of 3894 patients with advanced endometriosis and colorectal extension. Remarkably, a large majority of these patients has been treated by bowel resection anastomosis (n = 2832, 72.7%), and only a minority had been treated by full-thickness disc excision (n = 383, 9.8%), or shaving/superficial excision (n = 679, 17.4%). Data were reported in such a way that comparison of different surgical techniques was not possible. It was impossible to meaningfully analyze the mixed surgical group since outcome was very often not specified according to surgical technique used (bowel resection anastomosis, disc excision or another surgical technique). The group of patients with discoid excision only was described in only one study with limited outcome data.

**Table II** Fertility outcome after with surgical treatment of DIE with colorectal involvement: bowel resection anastomosis group.

<table>
<thead>
<tr>
<th>Reference</th>
<th>n (%) with infertility</th>
<th>n (%) wishing to conceive</th>
<th>n (%) conceived</th>
<th>Mean (SD) time interval between surgery and conception (months)</th>
<th>n live births/n women wishing to conceive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronado et al. (1990)</td>
<td>41/77 (53.2%)</td>
<td>33/41 (80.5%)</td>
<td>NR</td>
<td>NR</td>
<td>13/33 (39.4%) term</td>
</tr>
<tr>
<td>Ferrero et al. (2009)</td>
<td>5/46 (10.8%)</td>
<td>46/46 (100%)</td>
<td>3/5 (60%)</td>
<td>10.0 ± 5.3</td>
<td>3/5 (60%) fertile</td>
</tr>
<tr>
<td></td>
<td>20/46 (43.5%)</td>
<td>10/20 (50.0%)</td>
<td>1/13 (7.7%)</td>
<td>18.5 ± 13.4</td>
<td>8/20 (40%) unknown</td>
</tr>
<tr>
<td></td>
<td>21/46 (45.6%)</td>
<td>9/21 (42.9%)</td>
<td>NR</td>
<td>NR</td>
<td>8/21 (38.1%) infertile</td>
</tr>
<tr>
<td>Fleisch et al. (2005)</td>
<td>4/23 (17.4%)</td>
<td>17/23 (73.9%)</td>
<td>Overall 4/17 (23.5%)</td>
<td>NR</td>
<td>4/17 (23.5%) term</td>
</tr>
<tr>
<td>Ghezzi et al. (2008)</td>
<td>15/33 (45.5%)</td>
<td>13/15 (86.7%)</td>
<td>4/13 (30.8%)</td>
<td>NR</td>
<td>3/13 (23.1%) term 1/13 (7.7%) pregnancy ongoing</td>
</tr>
<tr>
<td>Juhasz-Boss et al. (2010)</td>
<td>3/6 (50%)</td>
<td>3/6 (50.0%)</td>
<td>1/3 (33.3%)</td>
<td>NR</td>
<td>1/3 (33.3%) term</td>
</tr>
<tr>
<td>Kavallaris et al. (2003)</td>
<td>38/50 (76%)</td>
<td>17/38 (44.7%)</td>
<td>8/17 (47%)</td>
<td>NR</td>
<td>4/17 (23.5%) healthy newborns 3/17 (17.6%) first trimester abortions 1/17 (5.9%) pregnant at time of interview</td>
</tr>
<tr>
<td>Keckstein and Wiesinger (2005)</td>
<td>NR</td>
<td>36/142 (25.3%)</td>
<td>18/36 (50.0)*</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lyons et al. (2006)</td>
<td>4/7 (57.1%)</td>
<td>3/7 (42.9%)</td>
<td>3/3 (100%)</td>
<td>NR</td>
<td>3/3 (100%) term</td>
</tr>
<tr>
<td>Meuleman et al. (2009a)</td>
<td>NR</td>
<td>33/56 (59%)</td>
<td>16/33 (48%)</td>
<td>6 spontaneous &lt; 1 year post-operative 4 IVF &lt; 1 year post-operative</td>
<td>NR</td>
</tr>
<tr>
<td>Minelli et al. (2009)</td>
<td>113/357 (31.6%)</td>
<td>NR</td>
<td>47/113 (41.6%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Possover et al. (2000)</td>
<td>15/34 (44.1%)</td>
<td>15/34 (44.1%)</td>
<td>8/15 (53.3%)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Stepnowska et al. (2009)</td>
<td>60/60 (100%)</td>
<td>48/60 (80.0%)</td>
<td>17/48 (35.4%)</td>
<td>696 days</td>
<td>1/48 (2.1%) miscarriage</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>339/693 (48.9%)</td>
<td>264/469 (56.3%)</td>
<td>135/344 (39.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Two women conceiving twice.
Remarkably, only one study (Meuleman et al., 2009a, b) included all relevant outcome variables: type of study (prospective/retrospective), number of patients, histopathological confirmation of DIE, follow-up time and procedure, surgical method applied, number of previous surgeries for endometriosis, indication for surgery (pain, fertility or both), complication rates, outcome data on pain, QOL, recurrence, fertility rate, number of patients lost during follow-up.

Histological confirmation

In the majority of the studies, histological confirmation of endometriosis with colorectal extension was obtained, and some studies, mainly in case of bowel resection anastomosis, contained additional histopathological details. At present, it is not known if endometriosis-positive histological margins on the resected bowel specimen, observed in six studies (Kavallaris et al., 2003; Anaf et al., 2004; Remorgida et al., 2005; Lyons et al., 2006; Zanetti-Dällenbach et al., 2008; Meuleman et al., 2009a), are associated with a higher recurrence rate after bowel resection anastomosis. Interestingly, in one of these six studies (Kavallaris et al., 2003), it was noted that a distance of 2 cm between the margin and the main lesion was not sufficient to obtain endometriosis-free margins in more than one-third of the patients. Furthermore, margins of the resected bowel specimens were still positive for endometriosis in six patients (19%) after bowel resection was performed in an area with a distance of at least 3 cm from the edges of the palpated lesion, free of any induration at manual palpation, and free of any serosal or muscular visible endometriosis implant (Anaf et al., 2004). It can be hypothesized that endometriotic lesions infiltrate the large bowel preferentially along the nerves, even at a distance from the palpated lesion (Anaf et al., 2004), and may spread laterally to the point of serosal invasion, possibly explaining the positive margins (Remorgida et al., 2005).

This ‘neural metastasis’ hypothesis also provides an explanation why full-thickness disc resection may result in an incomplete removal of bowel endometriosis. Indeed, evaluating histology in bowel specimens from 16 patients receiving a full-thickness disc resection first, followed by a bowel resection anastomosis during the same surgical procedure, showed that residual bowel endometriosis was still present in more than 40% of the bowel resection anastomosis specimens (Remorgida et al., 2005). Interestingly, it has also been reported that fibrosis in the muscular layer does not always surround bowel endometriotic lesions (Remorgida et al., 2005). Knowing that fibrosis is a main landmark during surgical resection, this explains why incomplete resection may occur.

Complications

Surgery for advanced endometriosis with colorectal extension can be associated with complications, such as rectovaginal fistulae.

### Table III Fertility outcome after with surgical treatment of DIE with colorectal involvement: mixed studies group.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>n (%) with infertility</th>
<th>n (%) wishing to conceive</th>
<th>n (%) conceived</th>
<th>Mean (SD) time interval between surgery and conception (months)</th>
<th>n live births/n women wishing to conceive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailey et al. (1994)</td>
<td>BRA</td>
<td>49</td>
<td>28/49 (57.1)</td>
<td>NR</td>
<td>28/28 (100) viable</td>
<td></td>
</tr>
<tr>
<td>Donnez et al. (1995)</td>
<td>FTDE</td>
<td>48/151 (31.8%)</td>
<td>25/48 (52.1)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerby et al. (1999)</td>
<td>BRA</td>
<td>7</td>
<td>3/7 (42.8)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mohr et al. (2005)</td>
<td>BRA</td>
<td>58/187 (31.0%)</td>
<td>23/58 (39.7)</td>
<td>NR</td>
<td>22/28 (78.6) full-term pregnancies*</td>
<td></td>
</tr>
<tr>
<td>Nezhat et al. (1994)</td>
<td>FTDE</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5/28 (17.9) miscarriages</td>
<td></td>
</tr>
<tr>
<td>Redwine and Wright (2001)</td>
<td>FTDE</td>
<td>NR</td>
<td>1/8 (12.5)</td>
<td>NR</td>
<td>5/12 (41.7) term pregnancies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shave</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>4/12 (33.3) spontaneous miscarriages</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td>28</td>
<td>12/28 (42.9)</td>
<td>NR</td>
<td>1/12 (8.3) ectopic gestation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FTDE</td>
<td></td>
<td></td>
<td>NR</td>
<td>2/12 (16.7) pregnant at time questionnaire</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SE</td>
<td></td>
<td></td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BRA, bowel resection anastomosis; FTDE, full-thickness discoid excision; SE, superficial excision.

*Three women conceiving twice, one woman conceiving three times.
anastomotic leakage, pelvic abscesses and post-operative bleeding. The prevalence of these complications was highly variable among studies. Although most of these complications are related to bowel surgery, it is important to realize that most of these patients also required additional surgery, such as uterosacral ligament resection, vaginal resection, ureterolysis and ovarian cystectomy, for endometriosis. Although it is not always reported, opening of the vagina at the time of the intestinal procedure is certainly a possible risk factor for these major complications. This plea for the introduction of a systematic protective colostomy in case of concomitant vaginal and rectal resection as already applied in some recent studies (Daria et al., 2005a; Zanetti-Dallenbach et al., 2008; Bracale et al., 2010; de Jong et al., 2009; Maytham et al., 2010). Additionally, extensive electrocoagulation can lead to necrosis of the posterior vaginal cuff with a higher risk for rectovaginal fistulae and abscesses (Dubernard et al., 2006). On the basis of our review, it is difficult to compare the complication rates associated with different types of surgery, since most of the published series are based on laparoscopic segmental colorectal resection whereas data on complications after full-thickness excision and superficial-thickness excision are very limited.

To avoid functional problems (urine retention, de novo dysuria, sexual dysfunction) related to pelvic denervation, different nerve-sparing techniques proven to be successful in the prevention of urinary, rectal and sexual dysfunction after radical surgery for pelvic malignancies, have been introduced in surgery for advanced endometriosis with colorectal extension (Maas et al., 1999; Possover et al., 2005; Landi et al., 2006). However, if minor nerve branches are impacted in an endometriotic/fibrotic nodule, they are sacrificed owing to the technique of ‘radical excision of diseased tissue’ to avoid leaving behind endometriotic tissue.

Considering the complexity and morbidity of these procedures, colorectal endometriosis is therefore best managed by a multidisciplinary approach, requiring at least a laparoscopically experienced gynecologist, a colorectal surgeon and an urologist (D’Hooghe and Hummelshoj, 2006). Precise pre-operative assessment of disease extent is necessary to select an appropriate treatment adapted to the individual case, as described previously (Abrao et al., 2007; Piketty et al., 2009; Meuleman et al., 2009a).

Quality of life

There is still a need to document prospectively the QOL after surgery for endometriosis with colorectal extension, as only 10% (5/49) of the studies (only 4% or 2/49 prospective) reported data on the QOL after surgical treatment for extensive endometriosis with colorectal extension, only three used standardized questionnaires; all of the studies showed a significant improvement in QOL after surgery. This observation is in contrast with the improvement in QOL documented after laparoscopic treatment of DIE without significant bowel surgery (Garry et al., 2000; Abbott et al., 2004; Fedele et al., 2004).

More and larger studies with a long-term follow-up using the same validated QOL questionnaires are required to allow comparison between the different surgical techniques used and to confirm the positive impact of colorectal resection on the QOL.

Fertility

The prevalence of endometriosis in infertile women is about 30% (D’Hooghe et al., 2003) and was about 50% in infertile women with normal ovulation and normospermic partners (Meuleman et al., 2009b). Improvement of fertility is often an important objective for women undergoing surgery for endometriosis. For mild endometriosis, laparoscopic surgery has been shown to improve fertility and pregnancy outcomes (Jacobson et al., 2002) and to have less negative impact on fertility than the laparotomy approach (Ferrero et al., 2009). However, it should be noted that patients undergoing laparoscopic or laparatomic treatment might not belong to the same group in daily practice. Although some studies suggest that complete removal of DIE potentially improves fertility (Chapron et al., 1999; Redwine and Wright, 2001; Abbott et al., 2003; Daria et al., 2005b), no RCTs or meta-analyses are available to answer the question of whether surgical excision of moderate to severe endometriosis enhances pregnancy rate. On the basis of three studies (Adamson et al., 1993; GuTEK et al., 1997; Osuga et al., 2002) there seems to be a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was reached in only one study (Osuga et al., 2002).

In our opinion, the fertility wish of patients with advanced endometriosis with colorectal extension is underestimated in the papers...
reviewed, revealing the indication infertility with or without pain in only 22–36% of all patients included in these papers. In our experience (Meuleman et al., 2009a, b), most patients have a combined problem of pain and unfulfilled or uncompleted child wish, which may be formulated by the patient either passively (wish for preservation/restoration of fertility during surgery, without well defined child wish at the time of surgery) or actively (well defined child wish in the near or distant future). Furthermore, it is important to realize that many women with pelvic endometriosis and colorectal extension have been told for many years that they will never become pregnant as a result of their disease. Additionally, before surgery these women are in pain, implying that their first concern is how to stop the pain, rather than a child wish. In these women, child wish may only emerge after a successful removal of the endometriosis and pain reduction.

Life table analysis was used to calculate the cumulative pregnancy rate in only 4 out of 18 (22%) studies reporting fertility outcome (Coronado et al., 1990; Stepnowska et al., 2009; Ferrero et al., 2009; Meuleman et al., 2009a). This is surprising in view of the fact that it has been generally accepted for more than 20 years (Olive, 1986) that life table analysis is the best way to calculate fertility outcome while controlling for the duration of follow-up and drop-out rate for each patient. Overall, this observation supports the need for prospective follow-up studies with sufficient duration of follow-up and complete follow-up of all operated patients.

Recurrence
The recurrence rate was remarkably low in view of the number of patients who had already undergone previous therapeutic surgery for endometriosis (Table I). When evaluating the recurrence rate of endometriosis, several factors must be taken into consideration. First, it is important to distinguish symptom recurrence and actual disease recurrence with a need for further medical or surgical therapy. Second, it is difficult to distinguish between residual and recurrent disease (McDonough et al., 2001). Many authors believe that incomplete excision of endometriosis is a major cause for clinical recurrence (Chopin et al., 2005; Vignali et al., 2005). If this is true, then visually and/or histologically proven recurrence of endometriosis recurrence must be lower after resection anastomosis than after disc excision or superficial excision, since resection anastomosis is associated with a more complete excision of bowel endometriosis, as discussed above. It is hard to prove this hypothesis in view of the absence of outcome studies reporting recurrence after disc excision, shaving or superficial excision except for one study published 15 years ago (Donnez et al., 1995). In previous studies, where only local excision or ablation was performed, the rate of recurrence varied between 3.7 and 74.7% (Kavalari et al., 2003). In this review both the total recurrence rate and the visually and/or histologically proven recurrence rate appeared to be lower in the bowel resection anastomosis group (5.8 and 2.5%, respectively) than in the mixed study group (17.6 and 5.7%, respectively). Interestingly, in a follow-up study of 83 women for over 12 months after conservative surgery for rectovaginal endometriosis (Fedele et al., 2004), the cumulative rates of pain recurrence, clinical or sonographic recurrence and new treatment were 28, 34, and 27%, respectively, and were lower in patients who underwent segmental bowel resection anastomosis.

More prospective follow-up studies with large sample sizes and clear definitions of endometriosis recurrence (using life table analysis to calculate the cumulative endometriosis recurrence rate) are needed to compare endometriosis recurrence between patient groups receiving different surgical techniques for the treatment of endometriosis with colorectal extension. If endometriosis recurrence rates are shown in the future to be comparable according to surgical technique, this does not necessarily mean that each of these techniques has similar value in each patient, but merely implies that the correct technique has been used for the correct indication (i.e. a more conservative approach for superficial serosal bowel endometriosis only, more radical approach for more invasive/multifocal/bowel involvement, taking into consideration bowel functionality after surgery).

Conclusion
Of the 49 studies included in this review, only one study (Meuleman et al., 2009a) reported data on all the outcome variables under review. Most studies documented the clinical outcome for surgical treatment of DIE with colorectal extension regarding post-operative complication rate (94%) and pain (67%). However, <50% of the studies included data with respect to the recurrence rate (41%), fertility outcome (37%) and QOL (10%). Additionally, these studies are often limited by a short-term follow-up period (1 or 2 years), making it difficult to estimate the actual pregnancy and recurrence rates. Furthermore, only a limited number of authors mention the number of patients that are lost during follow-up. However, a patient who is lost during follow-up is not necessarily cured, but has possibly turned to another gynecologist because of lack of satisfaction with the surgery received. As the fertility results in the different studies are encouraging, we can conclude that infertility or desire of pregnancy are not contra-indications for surgery. Finally, there is a lot of variability among studies regarding the exact indication of surgery, the exact surgical methods used, definitions of outcome variables etc. Indeed, there is a need for full documentation and standardization in clinical trials which evaluate endometriosis surgery with respect to indication, methodology, outcome variables and long-term follow-up. In the checklist in the next section we propose definitions to be used to record post-operative complications, document pelvic pain (dysmenorrhea, dyspareunia, chronic non-menstrual pelvic pain) and assess QOL, fertility (pregnancy rate) and recurrence rate after surgery for endometriosis. Hopefully, this checklist will help health professionals involved in the research into surgery for endometriosis to report unequivocally and completely in much needed prospective studies with large sample sizes and complete follow-up of all patients for a period of at least 2 years after surgery for DIE with colorectal extension.

Checklist
Supplementary data, Table SVIII shows a checklist based on the issues raised during this review and on the need to establish completeness and uniformity of the data collected during outcome studies evaluating the impact of surgery for DIE with colorectal extension. This checklist is similar to the CONSORT guidelines concerning randomized trials for non-pharmacological interventions (Boutron et al., 2008). The
checklist contains 32 items that should ideally be taken into account when designing a study for the surgical treatment of DIE and reporting the results of that study. More specifically, the checklist provides details on the description of participants, interventions, follow-up period, pain measurement, QOL measurement, and how to report data on histological confirmation, complications, additional interventions, fertility rate and recurrence rate.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

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References


Surgical outcomes for deeply infiltrating endometriosis


Letter to the Editor

Why we need international agreement on terms and definitions to assess clinical outcome after endometriosis surgery


Dear Editor,

We congratulate the authors of a prospective clinical outcome study after conservative surgery by the shaving technique for deep rectovaginal endometriotic (RVE) nodules (Donnez et al., 2010), but have some post publication peer review comments (Anderson et al., 1999).

Firstly, only one group worldwide has published outcome data after the shaving technique in 2 studies in the last 16 years (Donnez et al., 2010; Donnez et al., 1995). Other groups have reported clinical outcome after conservative surgery for deep RVE nodules, but always in cohorts mixed with patients treated with bowel resection anastomosis (mixed study groups, n = 16, Meuleman et al., 2011a), except for 1 paper describing outcome after discoid excision only (Nezhat et al., 1994). In contrast, twice as many papers (n = 32) have documented the outcome of bowel resection anastomosis (Meuleman et al., 2011a) and overall, the endometriosis recurrence rate was lower in the bowel resection anastomosis group (5.8%) than in the mixed study group (17.6%) (Meuleman et al., 2011a).

Secondly, the study (Donnez et al., 2010) included selected “good prognosis patients” without previous surgery for endometriosis, including cases with non-adherent type II lesions (easy to dissect) and excluding cases with bowel endometriosis in other or in multiple parts of the bowel system (rectosigmoid, sigmoid, small bowel, etc.) and any conclusions made need to take this into account. It is unclear how many cases with rectosigmoid endometriosis were diagnosed preoperatively, and how these cases were handled surgically.

Thirdly, in this prospective study (Donnez et al., 2010), a number of key variables were either not reported, not standardized, or not defined: no exact start and end dates of patient recruitment, no correction for the duration of follow-up per patient (no life table analysis), no documentation of follow-up (method, type of assessment during follow-up, N lost for follow-
up, etc.). Outcome assessment of pain or QOL was not patient based although validated and recommended methods exist (Vincent et al., 2010), have been applied Meuleman et al., 2009; Meuleman et al., 2011b, are recommended (Harvey and Warwick, 2010), also by the President of the World Endometriosis Foundation (Evers, 2010), and are essential to document possibly compromised sexual function after removal of the posterior vaginal fornix (Donnez et al., 2010). Complications or recurrences were not defined, even though recurrence of severe pelvic pain was high (20%) among non-conceiving patients in this good prognosis population (Donnez et al., 2010).

Fourthly, Table III (Donnez et al., 2010) includes only 11 selected papers, whereas 32 papers have documented clinical outcome after bowel resection anastomosis resulting in a visually and/or histologically proven recurrence rate of 2.5% only (Meuleman et al., 2011a).

Fifthly, our work (Meuleman et al., 2009) is not correctly discussed. We studied (Meuleman et al., 2009) clinical outcome in a highly selected (< 3% of all laparoscopies between 1996-2004) group of patients with mostly (75%) recurrent DIE with colorectal extension requiring radical nodulectomy and multidisciplinary surgery. The more severe clinical picture of our study population (Meuleman et al., 2009) compared to the “good prognosis” patients included in this study (Donnez et al., 2010) partially explains the longer duration of surgery. The duration of our surgery (Meuleman et al., 2009) was not exceptionally long, as 5 other studies reported a mean/median duration of surgery of at least 300 minutes (Lyons et al., 2006; Darai et al., 2007; Minelli et al., 2009; Pereira et al., 2009; Ruffo et al., 2010). Additionally, long duration of surgery has to be balanced against our low rate of complications, reinterventions and recurrences and high rate of pain relief, improvement of QOL, and fertility (Meuleman et al., 2009), confirmed prospectively (Meuleman et al., 2011b), according to terms and definitions proposed recently in a CONSORT based checklist (Meuleman et al., 2011a). Although the incidence of lower leg compartment syndrome was indeed 5% (3/56) in our series (Meuleman et al., 2009), subsequent measures have been successful to prevent this complication subsequently (Tomassetti et al., 2009). Furthermore, nerve sparing surgery is possible during colorectal segmental resection (Meuleman et al., 2009). Finally, the decision to do a bowel resection anastomosis does not need to be justified by the presence of mucosal infiltration in the resected specimens, but was based on limited integrity of the bowel wall after radical nodulectomy, not restorable by bowel suture, primarily in order to prevent postoperative bowel complications (Meuleman et al., 2009), and the same approach is
advocated by other groups (Keckstein and Wiesinger, 2005; Serrachioli et al., 2007; Dousset et al., 2010).

References


2.8. Two-Year Prospective Clinical Outcome Assessment after Radical Excision of Moderate-Severe Endometriosis with or without Bowel Resection and Reanastomosis

Christel Meuleman, M.D., Carla Tomassetti, M.D., André D’Hoore, M.D., Ph.D., Albert Wolthuis, M.D., Ben Van Cleynenbreugel, M.D., Annouschka Laenen, Ph.D., Freddy Penninckx, M.D., Ph.D., Ignace Vergote, M.D., Ph.D., Thomas D’Hooghe, M.D., Ph.D.

Human Reproduction, submitted for publication
Abstract

Background
To prospectively evaluate the outcome of a CO2 laser laparoscopic and radical but fertility sparing approach of moderate to severe endometriosis with or without bowel resection and reanastomosis in a multidisciplinary setting.

Methods
QOL, pain, postoperative complications, reintervention/recurrence rate and pregnancy rate were prospectively assessed in 203 patients with moderate (n = 67) or severe (n = 136) endometriosis operated at the LUFc between 1 September 2006 and 30 September 2008 (n = 435). A thorough evaluation of the electronic patient files yielded information regarding age at the moment of intervention, referred by whom, complaints at time of admittance, results of preoperative examinations, intervention and histological examination of biopsies and resection specimens as well as reintervention/recurrence and postoperative fertility. Patients were asked to complete the EHP30 questionnaire and visual analogue scales (VAS) for dysmenorrhea, chronic pelvic pain and deep dyspareunia, one month before and 6, 12, 18, 24 months after the intervention and to answer questions about postoperative complications, reintervention/recurrence and fertility.

Results
Overall, the major complication rate was 2%; a cumulative reintervention rate of 1, 7 and 10% after 1, 2 and 3 years, respectively and a cumulative endometriosis recurrence rate of 1, 6 and 8% after 1, 2 and 3 years, respectively were obtained. After surgery, average VAS scores en EHP30 were significantly better than prior to surgery, remaining stable for 24 months after surgery. The pregnancy rate was 51%. Of the 203 patients, 76 underwent bowel resection and reanastomosis (37%). No statistically significant differences were observed between the bowel and non-bowel resection group.

Conclusion
Radical but fertility sparing CO2 laser laparoscopic resection of moderate to severe endometriosis in a multidisciplinary setting resulted in a low complication rate, a low reintervention/recurrence rate and a high pregnancy rate. Moreover, this paper is a first attempt to report about surgical treatment of moderate to severe endometriosis following a CONSORT inspired checklist proposed in a recently published systematic review about surgical treatment of extensive (bowel) endometriosis.
Introduction

Endometriosis is a gynaecologic disorder defined by the presence of endometrial glands and stroma outside the uterus. It predominantly affects women of reproductive age and is associated with pelvic pain and fertility problems.

Three clinical presentations of endometriosis have been described (Donnez et al., 1995): peritoneal endometriosis, endometriomas and DIE. The ectopic endometrium can be limited to the superficial peritoneum in an otherwise normal pelvis (peritoneal endometriosis) but can also develop into ovarian endometriotic cysts (endometriomas), which can be located in the ovary (included endometrioma) or between ovary and ovarian fossa (invaginated endometrioma), often coexistent with adnexal adhesions. DIE is characterized by the invasion of anatomical structures and organs deeper than 5 mm beyond the peritoneum (Koninckx and Martin, 1994; Vercellini et al., 2003). It mainly involves the uterosacral ligaments, the rectosigmoid colon, the vagina and the bladder (Jenkins et al., 1986) and can cause a complete distortion of the pelvic anatomy.

Findings during clinical examination can be suggestive of endometriosis, but a normal clinical examination does not rule out endometriosis. The definitive diagnosis of endometriosis is made following laparoscopic inspection of the pelvis (Kennedy et al., 2005) and should ideally be confirmed by histological examination of the excised lesions. During laparoscopy or laparotomy, the degree of endometriosis is scored and staged according to the revised American Fertility Society (rAFS) classification system of the American Society of Reproductive Medicine (rAFS, 1997). The disease score from stage I to stage IV (minimal, mild, moderate, severe, respectively) increases with the degree of ovarian involvement and with the extent of adnexal and cul-de-sac adhesions.

Because of the relative ineffectiveness of medical therapy (Donnez et al., 2004; Olive, 2003), it is widely agreed that surgical management is the primary treatment for more severe forms of endometriosis, such as symptomatic DIE with colorectal involvement (Garry, 2004; Emmanuel and Davis, 2005). Intestinal involvement has been estimated to occur in approximately 3 to 37% of the DIE cases (Collin and Russell, 1990; Coronado et al., 1990; Graham and Mazier, 1988). The rectum and rectosigmoid junction together account for 70 to 93% of all intestinal endometriotic sites (Baily et al., 1994; Coronado et al., 1990), next to the
appendix (2 - 18%), the distal ileum (2 - 16%) and the caecum (< 2%) (Zwas and Lyon, 1991).

A positive correlation seems to exist between the extent of endometriosis resection and the degree of postoperative improvement (Chapron et al., 2004). However, the appropriate surgical approach for DIE with involvement of the bowel remains controversial. Little is known about the impact of the different types of surgery in the treatment of DIE on complications, pain, the patients’ QOL, recurrence rate and fertility. During reproductive age, radical intervention has been reported to improve QOL and potentially fertility, but it may be associated with a high risk of postoperative complications (Abott et al., 2003; Adamson, 1997; Coronado et al., 1990; Hughes et al., 1993; Redwine and Wright, 2001).

A radical approach requires expertise, available in specialist centres (Redwine and Wright, 2001; Emmanuel and Davis, 2005; Perry, 2005; Kennedy et al., 2005) with multidisciplinary surgical collaboration in cases of complete obliteration of the cul-de-sac or the vesico-uterine fold (Perry, 2005). Previously, we have reported the clinical outcome after multidisciplinary treatment of DIE and rAFS III and IV patients (with or without colorectal extension) (Meuleman et al., 2009; Meuleman et al., 2011a). However, the retrospective character of these and most other published studies is a limitation. Additionally, as we have previously shown, long-term follow-up data about complication rate, cumulative recurrence and cumulative pregnancy rate, pain and QOL after treatment of endometriosis are often missing (Meuleman et al., 2011b). However, all of these aspects are important factors to improve the quality of the data and to allow comparison of the different studies.

Therefore, the goal of this study was to provide a prospective clinical outcome assessment in order to evaluate the quality of care of the multidisciplinary surgical team developed at the LUFc over the past 15 years and to thoroughly and systematically report the complication rate, re-intervention/recurrence rate, pregnancy rate and the influence of the technique on QOL as well as on dysmenorrhea, deep dyspareunia and chronic pelvic pain. In reporting these data, we followed the checklist proposed in a recent systematic review about the surgical treatment of extensive (bowel) endometriosis (Meuleman et al., 2011b).
Material and Methods

Study design - Patient selection
The protocol of this prospective study (ClinicalTrials.gov ID: NCT00463398) was approved by the Ethical Committee of the University Hospital Leuven, Belgium. All women who underwent reproductive surgery between September 1, 2006 and September 30, 2008 at the LUFc had been asked to participate in this prospective follow-up study. For this paper, only the group of patients classified during intervention as moderate or severe endometriosis (rAFS III or IV, respectively) was selected.

Participating patients were asked to complete Visual Analogue Scales (VAS) about dysmenorrhea, chronic pelvic pain and deep dyspareunia and the Endometriosis Quality of Life questionnaire (EHP30; Jones et al., 2001) one month prior to and 6, 12, 18 and 24 months after the intervention. The EHP30 questionnaire consists of 30 core questions and 6 modules. Module A concerns the effect endometriosis has on the patient’s work, module B asks for the relationship with the patient’s child(ren), module C deals with the sexual relationship of the patient, module D is about the patient’s feelings on the medical profession, module E assesses the feelings of the patient about the treatment for endometriosis and finally, module F contains questions on the patient’s feelings around fertility difficulties.

Additionally, the postoperative questionnaire contained questions about postoperative complications, reintervention/recurrence and fertility/pregnancy. In order to ensure the completeness of the study database, the information about complications, reintervention/recurrence and fertility/pregnancy obtained from the postoperative questionnaires was compared with the information from the electronic patient files and calculated taking into account the last date of contact with the patient (database closed on 31 July, 2010). No inconsistency between the electronic patient files and the questionnaires was observed. Next to this, the following parameters obtained from the electronic patient files were thoroughly evaluated: age at the moment of intervention, referred by whom, complaints at time of admittance, results of preoperative examinations, intervention and histological examination of biopsies and resection specimens.
**Definitions**

*Chronic pelvic pain* (CPP) was defined as recurrent or constant pain in the lower abdominal region that had lasted for at least 6 months (Campbell and Collett, 1994). However, women who experience pain only around menstruation (dysmenorrhea or during sexual intercourse (dyspareunia) are usually excluded from this CPP diagnosis (Dick, 2004). *Dysmenorrhea* was defined as pain only around menstruation and the different degrees of dysmenorrhea were defined according to the definition of Andersch and Milsom (1982) (Grade 1: Menstruation is painful but seldom inhibits the woman’s normal activity; analgesics are seldom required; mild pain. Grade 2: Daily activity is affected; analgesics required and give sufficient relief so that absence from school/work is unusual; moderate pain. Grade 3: Activity clearly inhibited; poor effect of analgesics; vegetative symptoms [e.g. headache, fatigue, vomiting, and diarrhoea]; severe pain). *Deep dyspareunia* was defined as pelvic pain during sexual intercourse (Zondervan and Barlow, 2000).

An abnormal finding in the preoperative vaginal investigation was defined as the presence of an induration, nodule or adnexal mass. For the preoperative gynaecological transvaginal ultrasound test, the presence of an induration, nodule or endometrioma was considered as abnormal. Preoperative bowel barium enema findings were considered slightly abnormal in case of an external compression and abnormal if transmural or serosal invasion was observed. The result of the preoperative intravenous pyelogram was considered abnormal when stenosis or hydro-ureteronephrosis was observed and slightly abnormal if periureteral endometriosis or a medial/lateral dislocation was found.

The number and nature of concomitant surgical procedures was noted (Table I). *Concomitant surgical procedures* were defined as surgical procedures that were carried out by the reproductive surgeon during the main surgery for endometriosis.

*Distal tubal occlusion* was defined as a condition where the terminal part of the tube is totally blocked and the fimbriae are obscured (Brosens, 1989). Distal tubal occlusion can lead to the formation of a thin-walled or a thick-walled hydrosalpinx. A *thin-walled hydrosalpinx* was defined to be present if the fallopian tube was grossly distended by copious straw-coloured fluid which made it appear translucent). A *thick-walled hydrosalpinx* was defined to be present if it had a fibrous wall and had a smaller lumen with less fluid when compared to a thin-walled hydrosalpinx. (Brosens, 1989).
A resection and reanastomosis was defined as a resection of a bowel segment with restoration of bowel continuity by reanastomosis of the two bowel segments left after the resection of a bowel segment. A transmural lesion of bowel/ureter/bladder can be sutured to close the perforation. A lesion till the muscularis of bowel/bladder (not transmural) can be treated with ‘reinforcement sutures’, aiming at restoring the strength of the bowel/bladder wall to prevent rupture of the wall at distention.

The depth of infiltration of remaining (microscopic) endometriosis in the wall of the resected bowel specimen was evaluated (subserosa, musculosa, submucosal, mucosa).

Major complications were defined (Meuleman et al., 2011b) as rectovaginal fistulae, bowel leakage, pelvic abscesses and postoperative bleeding requiring a surgical approach within 42 days after surgery. Minor complications were defined as those that could be solved with a conservative approach.

Fertility outcome was assessed as follows (Meuleman et al., 2011b): number of patients with a history of infertility, number of patients wishing to conceive passively (wish for preservation/restoration of fertility during surgery, without well defined child wish at the time of surgery), number of patients wishing to conceive actively with a well defined child wish at the time of surgery, and number of patients wishing to conceive actively with a well defined child wish in the near future, and number of patients wishing to conceive actively with a well defined child wish in the distant future, median time to conceive after surgery, mode of conception (spontaneous or artificial) and live birth rate, presence of life table analysis.

The endometriosis recurrence rate was reported as follows (Meuleman et al., 2011b): number of patients with recurrence after surgery, median time to recurrence, and data on life table analysis. The level of evidence for recurrence of endometriosis was classified in 5 categories:

1. Symptom recurrence based on patient history, but no proof of recurrence by imaging and/or surgery.
2. Endometriosis recurrence based on non-invasive imaging [e.g. ultrasound, magnetic resonance imaging (MRI)] in patients with or without symptoms (pain, infertility).
3. Surgical reintervention without recurrence of endometriosis: in patients with recurrent symptoms, surgery without visual diagnosis of endometriosis, and with either normal pelvis or other abnormalities (e.g. adhesions).
4. Recurrence of visual endometriosis without histological proof: during laparoscopy endometriosis is visually observed but either not biopsied or biopsied without histologically proven endometriosis.

5. Recurrence of histologically proven endometriosis: during laparoscopy endometriosis is visually observed and confirmed histologically.

Suspicious recurrent endometriosis was present if the criteria for categories 1 and 2 were met. Proven recurrent endometriosis was present if the criteria for categories 4 and 5 were met. Additional surgery without evidence for endometriosis was present if the criteria for category 3 were met.

**Preoperative procedure**

The preoperative procedure applied in this prospective study has already been described in detail in two earlier published retrospective studies (Meuleman et al., 2009 and 2011a). All patients were treated following a standardized clinical protocol, in line with the clinical standard operating procedures that are in place at the LUFc following ISO 9001-2000 certification in 2004. During a first consultation at the LUFc, medical history was taken and a clinical examination was performed followed by a trans-vaginal ultrasound. In case of suspicion of extensive DIE, an additional barium enema and intravenous pyelogram were performed to assess the extent of invasion of the endometriosis. In a second consultation, the expected extent of the intervention was explained to the patient. Patients suspected of extensive endometriosis received GnRH–analogue treatment 3 months prior to surgery. All 203 patients had full mechanical bowel preparation using Fleet Phospho-Soda® (Wolfs, Belgium) (2 x 45 ml) the day before surgery.

**Operative procedure**

Our multidisciplinary 3-step operative procedure for patients with extensive DIE with colorectal extension has previously been described in detail (Meuleman et al., 2009 and 2011a). Briefly, in a first step, patients underwent temporary Double J ureteric stenting by the urologist (B.V.C.) in case of endometriomas exceeding 4 cm diameter, DIE invading the bladder wall or in the posterior compartment of the pelvis extending to the fossae (Meuleman et al., 2009 and 2011a). After induction of pneumo-peritoneum at a maximum of 15 mmHg, a 12 mm operative laparoscope was introduced through the umbilicus. Three supplementary 5 mm trocars were placed supra-pubically, left and right, respectively, at approximately two fingers medially from the spina ischiadica anterior superior. All visible endometriosis was
excised with a CO₂ laser (Lumenis Inc, USA: Compact 40W CO₂ laser) at a power density of 15 Watt Super pulse. Normal anatomic relations and function of the pelvic organs were restored as much as possible by excision of all peritoneum infiltrated by endometriosis. If perforation of the vaginal vault occurred, it was laparoscopically sutured by the reproductive surgeon (C.M.). The presence of endometriosis was scored and staged according to the rAFS classification system of the ASRM (rAFS, 1997).

In a second step, after all endometriotic lesions were resected by the reproductive surgeon (C.M.), it was up to the urologist (B.V.C.) to evaluate the ureters and the bladder. Seromuscular injury, perforation of the bladder or ureter injuries were sutured laparoscopically. Next to this, a re-implantation of a ureter in the bladder could be performed in case of extensive intramural invasion of endometriosis in the ureter-wall where suturing was not indicated (Boari plasty).

In a third step, the colorectal surgeon (A.D.) evaluated the integrity of the rectosigmoid colon. Depending on the type of lesions and their extensions, he decided whether or not to resect the involved segment with primary re-anastomosis. The indications for bowel resection and reanastomosis were described before (Meuleman et al., 2011a and b). The decision of bowel resection and reanastomosis was taken in the following conditions: large direct full-thickness trauma to the colorectal wall too extensive to be sutured without impact on the functionality of the bowel, extensive lesion to the bowel wall musculature in the absence of full-thickness damage but with impact on functionality, and extensive lateral dissection compromising the colorectal wall vascularity and/or innervation.

Bowel resection was performed laparoscopically as described before (Meuleman et al., 2009 and 2011a). The dissection was conducted merely as close to the bowel as possible (Landi et al., 2006). Only fibers of the resected segment of the bowel were cut, minimizing denervation. If nerve branches were impacted in the endometriosis, they were sacrificed to avoid leaving behind endometriotic tissue. A histological examination was performed on all resected tissue specimens.

**Postoperative procedure**

Postoperative appointments were arranged with the surgical team (B.V.C., A.D. and C.M.). A low dose oral contraceptive or a levonorgestrel-releasing intrauterine device was prescribed in
case postoperative contraception was desired (Vercellini et al., 2005) to minimize menstruation. Patients were asked to take an oral contraceptive until break-through bleeding and then to stop for seven days (Vercellini et al., 2003).

In women younger than 36 – 38 years with a regular ovulatory cycle, normal tubal function and a male partner with a normal sperm analysis, spontaneous conception was expected within 6 months to one year. In case of normal tubal function but ovulatory dysfunction or mild male factor infertility, controlled ovarian stimulation with low dose gonadotropins combined with intra-uterine insemination was performed during 3 cycles. If this treatment was not successful, IVF was proposed. In all cases of compromised ovum pick-up and transport capacity and/or major sperm problems and/or advanced female age (> 36 - 38 years), IVF was proposed after the patient had recovered from the intervention.

**Statistical analysis**

The chi-square test was used for the comparison of groups with regards to proportions; the fisher exact test was used in case of small cell counts. The Mann-Whitney U test was used for the comparison of groups with respect to continuous variables. The cumulative pregnancy rate and the cumulative recurrence rate were calculated using Life Table analysis.

Linear mixed models were used for the statistical analysis of the questionnaire data with the respective scales score as response variable and the time of measurement, the tAFS stage, and the reintervention status (yes or no) as explanatory variables. Additionally, interaction effects between the time of measurement and the tAFS class are tested. Given that 10 outcome scales were considered, correction for multiple testing was performed using the rough false discovery rate (RFDR). A Bonferroni correction was used at the level of the post-hoc comparisons. All tests are two-sided and considered significant with p-values smaller than 0.05. Analyses have been performed using the MIXED procedure in SAS (version 9.2 of the SAS System for Windows)
Results

Patient population operated at the LUFc during the study period

Of the 435 patients who were operated between September 1, 2006 and September 30, 2008 at the LUFc, a tertiary reference centre for fertility exploration and treatment and fertility surgery/endometriosis surgery, 124 patients (n = 124/435; 28.5%) did not have endometriosis including 56 women (56/435; 13%) with a completely normal pelvis, and 68 women (68/435; 16%) with non-endometriotic fertility reducing problem. These fertility reducing problems included uterine (fibromas, n = 12); ovarian [teratomas (n = 3), cystadenomas (n = 3) or ovarian absence (n = 8)] or tubal pathology [thick-walled hydrosalpinx (n = 14), thin-walled hydrosalpinx (n = 6), cornual occlusion (n = 3), previous sterilisation (n = 11), phymosis (n = 3) and peritubal/periadnexal adhesions (n = 36)].

The other 311 (311/435; 72%) patients were laparoscopically diagnosed with endometriosis (rAFS I: n = 34, rAFS II: n = 74, rAFS III: n = 67, rAFS IV: n = 136). Of these 311 (72%) patients with endometriosis, approximately 35% (n = 108/311) had minimal to mild endometriosis (rAFS I or rAFS II, respectively) and 65% (n = 203/311) had moderate to severe endometriosis (rAFS III or IV, respectively). In this latter group, 33% (n = 67/203) and 67% (n = 136/203) was classified as rAFS III or IV, respectively, and 37% (n = 76/203) underwent bowel resection and reanastomosis.

Response rate to the questionnaires

The initial response rate (preoperative questionnaire) of the selected patient population (rAFS III and IV) was 83% (168/203). In the group of patients who underwent bowel resection (n = 76), 68 completed the questionnaire (89%), compared with 79% (n = 100/127) of the patients who did not undergo bowel resection. Thirty-five patients (n = 35/203; 17%) did not respond. One patient with vision problems (bad eyes) could not complete the questionnaire, 1 patient found the questions to difficult to understand (mentally retarded), 5 patients moved abroad, 1 patient had a psychological crisis due to family problems, 7 patients did not speak Dutch and 20 patients did not want to collaborate.

Six months after surgery, the questionnaire was completed by 67% (n = 135/203) of the patients: 75% (n = 57/76) and 61% (n = 78/127) of the patients who underwent bowel resection and those who did not, respectively. 56% (n = 114/203), 36% (n = 73/203) and 24%
(n = 49/203) of the patients completed the questionnaire 12, 18 and 24 months after surgery, respectively. The patients who underwent bowel resection were more compliant with 65% (n = 49/76), 51% (n = 39/76) and 34% (n = 26/76) of them having completed the questionnaire 12, 18 and 24 months after surgery, respectively, compared with 51% (n = 65/127), 27% (n = 34/127) and 18% (n = 23/127) of the patients not undergoing bowel resection.

**Study population (rAFS III/IV, n = 203)**

The median age at the moment of intervention of the 203 patients diagnosed with rAFS III/IV, was 32.4 ± 4.8 years (range 20 - 47 years). Most patients (62%, n = 162/203) were referred to our centre by their gynaecologist, 30% (n = 60/203) came on their own initiative and only 8% (n = 17/203) were referred by a family doctor. The mean follow-up time was 19 ± 12 months (< 1 month – 45 months). Most of the patients (n = 143/203; 70%) were previously operated on for endometriosis elsewhere at least once before undergoing treatment in our centre; 90, 31 and 19 patients underwent 1, 2 or 3 previous surgeries for endometriosis, respectively. Three patients were operated on for endometriosis more than 3 times (4, 5 and 12 interventions, respectively).

**Preoperative characteristics of the study population (rAFS III/IV) with respect to pain, reproductive wishes and previous surgery**

Most patients (n = 162/203; 80%) underwent surgery because of pain in combination with an unfulfilled child wish. This pregnancy wish was present as either active infertility or a child wish in the near future (n = 116/162; 72%), or in the distant future (n = 46/162; 28%). Only 14 (n = 14/203; 7%) patients were operated because of pain only (10 and 4 in the non-bowel resection group and in the bowel resection group, respectively); 8 (n = 8/14; 57%) of them had their family completed and 6 (6/14; 43%) were childless but without any further pregnancy wish. Only 27 (n = 27/203; 13%) patients had no pain at all but underwent surgery because of an active unfulfilled child wish (n = 25/27; 93%) or a passive future child wish (n = 2/27; 7%) after an abnormal clinical and ultrasound examination. In the group of patients who underwent bowel resection, only 4 patients did not suffer from pain (n = 4/76; 5%).

Pain symptoms retrieved from the medical files (available in 185 patients) included dysmenorrhea (degree II and III) (n = 159/185; 86%), chronic pelvic pain (n = 104/185; 56%), deep dyspareunia (101/185; 55%), dysuria (n = 37/185; 20%) and hematuria (n = 6/185; 3%).
Symptoms regarding abnormal bowel function included constipation/diarrhoea (n = 43/185; 23% and n = 20/185; 11%), dyschezia (n = 102/185; 55%), and cyclical rectal bleeding (n = 21/185; 11%).

In the group of patients who underwent bowel resection, 70% (n = 47/67), 29% (n = 19/65) and 32% (n = 22/68) preoperatively suffered from dysmenorrhea (degree II and III), deep dyspareunia and chronic pelvic pain, respectively. In the group of patients who did not undergo bowel resection, this was 60% (n = 57/95), 26% (n = 25/96) and 19% (n = 19/99), respectively. For these three types of pain, the proportions of patients suffering pain were not significantly different between the two groups (p > 0.05).

**Preoperative tests**

**Vaginal examination**

Vaginal examination was performed in 186/203 (92%) patients. During this vaginal examination, abnormalities were found in 71% of the patients (132/186); 80% (55/69) in the group of patients who underwent bowel resection, compared with 66% (77/117) in the group who did not undergo bowel resection (p = 0.044). Of these 132 patients, an adnexal mass was observed in 11 (8%), 12 (9%) and 7 (5%) patients at the left, right and on both sides of the ovaries, respectively. Induration of the Douglas pouch (fornix posterior) was observed in 16 patients (12%); nodules on the Douglas pouch were found in 52 (39%) patients. Induration of the left and right SUB occurred in 36 (27%) and 23 (17%) patients, respectively. Nodules at the left and right SUB were observed in 28 (21%) and 18 (14%) of the patients, respectively. Induration of the left and right fornix lateralis, the rectovaginal septum and the fornix anterior was noticed in 6 (5%), 3 (2%), 9 (7%) and 12 (9%) of the patients, respectively. Twenty-four (18%) and 1 (1%) patients showed nodules in the rectovaginal septum and fornix anterior, respectively.

**Gynaecological transvaginal ultrasound**

The gynaecological transvaginal ultrasound examination was performed in 183 patients (n = 183/203; 90%). For 129 (70%) patients, abnormal findings were reported. This was the case for 74/115 (64%) and 55/68 (81%) of the patients who did not undergo bowel resection and those who did, respectively. Endometriomas were found left, right and bilaterally in 33 (26%), 29 (22%) and 20 (16%) patients, respectively. Nodules on the bladder, Douglas pouch, left SUB, right SUB, rectovaginal septum and rectum were observed in 5 (4%), 28 (22%), 7
(5%), 5 (4%), 15 (12%) and 32 (25%) patients, respectively. Vesico-uterine nodules were found in 3 (2%) patients.

Bowel barium enema
A bowel barium enema with double contrast was performed in 138/203 (68%) patients based on evidence from previous interventions, symptoms, clinical exam and/or ultrasound suggestive for colorectal endometriosis. Findings were abnormal in 89/138 (65%) patients: 61 (n = 61/68; 90%) patients who underwent bowel resection and 28 (n = 28/70; 40%) patients who did not. Transmural invasion of the bowel wall at the level of the sigmoid, rectosigmoid and rectum was clearly demonstrated in 25 (18%), 28 (20%) and 16 (12%) patients, respectively. Serosal invasion at the level of sigmoid, rectosigmoid and rectum was noticed in 5 (4%), 7 (5%), and 6 (4%) patients, respectively. The majority of these invasions could be observed in the bowel resection group (59 patients compared with 19 patients in the non-bowel resection group; p < 0.0001). The number of transmural invasions per patient was 1 for 56 patients, 2 for 5 patients and even 3 for 1 patient. The number of serosal invasions per patient was 1 for 15 patients and 2 for 2 patients. External compression (slightly abnormal findings) were observed in 9 (13%) and 2 (3%) patients of the non-bowel resection and the bowel resection group, respectively.

Intravenous pyelogram
In 145 of the 203 patients (71%) an intravenous pyelogram (IVP) was performed based on evidence from previous interventions, symptoms, clinical exam and/or ultrasound suggestive for ureteral and/or bladder endometriosis. IVP outcome was abnormal in 67/145 (46%) patients, including 53 slightly abnormal findings [ureter dislocation (n = 37/67, 55%) and diminished expansion of the pelvic segment (n = 16/67; 24%)] and 14 very abnormal observations including ureteral stenosis (n = 3/67; 5%) and hydro-uretero-nephrosis (n = 11/67, 16%). Based on the IVP results, surgeries were planned with operation time for the urologist for the 14 (10%) patients with very abnormal IVP findings. Abnormal findings were reported for 23/75 (31%) and 44/70 (63%) of the non-bowel resection and bowel resection group, respectively.

Intra-operative staging of endometriosis and surgical procedures
The surgical procedures the reproductive surgeon performed on the study patients are summarized in Table I. All abnormal tissue (e.g. peritoneum, adhesions, cysts, noduli) was
surgically removed and histologically analyzed. The mean rAFS score for the patients with moderate to severe endometriosis (rAFS III/IV) was 58 ± 31 (range 16 - 162). In the group of patients with moderate endometriosis (rAFS III, n = 67), the mean rAFS score was 27 ± 9 (range 16 - 56), while this score was 73 ± 26 (range 38 - 162) for the patients with severe endometriosis (rAFS IV, n = 137). In the group of patients who underwent bowel resection (n = 76), the mean rAFS score was 73.4 ± 31 (range 16 - 162), whereas the mean score was 48.3 ± 26 (range 16 - 126) for the group of patients who did not undergo bowel resection (p < 0.001).

The urologist (B.V.C.) placed Double J stents bilaterally (n = 100) or unilaterally [left (n = 5) or right (n = 2)] into the ureters in 107 out of the 203 patients (53%). An intervention was performed by the urologist in 22 (11%) patients: 20 laparoscopic interventions and 2 interventions by laparotomy. The urologist sutured the bladder in 7 (3%) patients (perforation) and performed 4 (2%) reinforcement sutures of the bladder. Additionally, 9 (4%) sutures of the ureter were performed (perforation), 6 on the left and 3 on the right. In the 2 patients who underwent a laparotomy, the ureter was reimplemented (Boari plasty) (1 left and 1 right).

The colorectal surgeon (A.D.) performed 85 surgical interventions (42%) by laparoscopy (n = 74), laparoscopy in combination with laparotomy (n = 7; 4 patients with ileum resection and 3 patients in whom a Pfannenstiel incision was required due to technical problems), or by laparotomy only (n = 4). In 2 of these 4 patients a laparoconversion was required: in one patient with a BMI of 41, laparoscopic resection was not considered as safe due to presence of a huge amount of abdominal fat; the other patient had a very low reaching nodulus combined with a narrow pelvis. The other 2 laparotomies were performed in a patient with endometriosis at the level of the umbilicus and in a patient undergoing an ureter reimplant. A total of 80 bowel resections were performed: 3 caecum bottom resections, 5 resections of the small intestine, 9 sigmoid resections, 53 colorectal resections (of which 48 end-to-end and 5 end-to-side) and 8 colon pouch resections (of which 6 with an temporary ileostoma [according to our protocol and the work load on the operation program of the colorectal surgeons, closed after 6 weeks to 3 months], and 2 without a stoma). Additionally, 7 appendectomies were performed. Seven reinforcement sutures were performed: 1 in the sigmoid, 2 in the rectosigmoid and 4 in the rectum.
Included ovarian endometriomas were removed in 74 patients (31 left, 32 right, 11 bilaterally). Invaginated ovarian endometriomas were eliminated in 42 patients (18 left, 17 right, 7 bilaterally). In total, 41 vaginal perforations occurred, which were sutured laparoscopically by the reproductive surgeon (CM).

**Histology**

In all 203 patients, the presence of endometriosis was confirmed by histological examination of the resected tissue. Bowel resection was performed in 76 patients (37%); in 4 patients, 2 bowel segments were resected. The average length of the resected segment was 119.2 ± 45.8 mm (range 35 – 290 mm) (n = 76). Perforations were observed in 30 (30/80; 38%) resected segments: 27, 2 and 1 segments showed 1, 2 and 3 perforations, respectively. In 73/80 specimens (91%), remaining endometriotic tissue was observed microscopically. In 3 (4%), 2 (3%), 37 (46%), and 21 (26%) specimens, the depth of infiltration of the endometriosis was at the serosal, subserosal, muscular, and submucosal level, respectively. Mucosal infiltration of endometriosis was not observed. In 5 samples, remaining endometriosis was present, but the depth of infiltration was not mentioned in the histological report. After bowel resection, margins positive for endometriosis were observed in 16/80 (20%) specimens (14 unilateral, 2 bilateral). In 12 of these 16 specimens (75%), no remaining endometriotic tissue was observed in other places besides the margins.

**Postoperative complications (within 42 days after surgery)**

Postoperative complications requiring additional surgical interventions (major complications) occurred in 4 patients (4/203, 2%). Other (minor) complications (9/203; 4%) were managed conservatively without reintervention.

At the level of the fertility surgery, 8 postoperative complications occurred (3 major and 5 minor). One patient (1/203; 1%) developed a unilateral lower leg compartment syndrome requiring surgery after she had not been scheduled for a multidisciplinary approach and had therefore not been correctly installed according to standard procedures reported before (Tomassetti et al., 2009). One postoperative bleeding occurred, requiring a repeat laparoscopy. In a third patient, the vaginal fold needed resuturing. Five patients (n = 5/203; 2%) were treated with intravenous antibiotics after showing biochemical signs of infection during blood analysis (increased leucocytosis and CRP levels), possibly related to the presence of a hematoma visualized by ultrasound in 4 of them.
Only 1 major complication was related to the bowel surgery (n = 3/203; 1%). For this 1 patient, a reintervention was required to perform laparoscopic stapling of a leakage after suture of a small transmural lesion of the wall of the rectum. Following this reintervention, a small rectovaginal fistula occurred which closed spontaneously after conservative management.

Four (n = 4/203; 2%) patients showed minor urological complications: 2 bladder leakages (treated conservatively), and 2 bladder atony (spontaneous recuperation).

Overall, major complications occurred in 3% (n = 2/76) and 2% (n = 2/127) of the patients who underwent bowel resection and those who did not, respectively. Minor complications occurred in 1% (n = 1/127) and 11% (n = 8/76), respectively (p = 0.0019).

Duration of multidisciplinary intervention
Due to a switch in the registration system of the hospital during the study period, the duration of surgery could not be calculated exactly prospectively and was estimated retrospectively based on operation notes from the surgeons.

The median total duration was 140 (60 - 180) minutes with operation times of 120 (60 - 180) and 20 (0 - 60) minutes for the gynaecologist and the urologist, respectively in case no bowel resection anastomosis was required. In case bowel resection anastomosis was required, the median total duration was 300 (170 - 450) minutes with operation times of 150 (90 - 210), 30 (20 - 60) and 120 (60 - 180) minutes for the gynaecologist, the urologist and the abdominal surgeon, respectively.

Reintervention and Recurrence
Three months after surgery, 1 patient had renal insufficiency, requiring a reintervention. This patient had only one functional kidney and during the primary surgery it was decided to free the ureter from the endometriosis and not to re-implant the ureter in the bladder. However, after the postoperative development of peri-ureteral fibrosis and a threat for the patient’s only kidney, a reintervention was required (boariplasty).

A total of 10 (n = 10/203, 5%) repeat laparoscopies [8 (6%) in the non-bowel resection group and 2 (3%) in the bowel resection group; p = 0.33]. were performed to diagnose and treat...
potential recurrent disease in patient with recurrence of pain (n = 5), ultrasound evidence of ovarian endometrioma (n = 2) or in preparation for treatment with ART (n = 3).

Surgical reintervention without clinical or histological evidence of endometriosis (category 3 in Material and Methods) was performed in 2 patients, both belonging to the non-bowel resection group.

Recurrence of endometriosis was observed in 8 patients (8/203, 4%) (category 5 in Materials and Methods) including peritoneal endometriosis with adhesions (n = 2), recurrent endometriomas (n = 3), hematosalpinx with histological tubal endometriosis (n = 1) and bowel endometriosis (n = 2) at the submucosal level (n = 1) or in the muscularis propria (n = 1). The latter 2 patients received a bowel resection during reintervention but not during primary surgery.

Using life table analysis, the cumulative reintervention rate was 1, 7 and 10% after 1, 2, and 3 years, respectively, and the cumulative recurrence rate of endometriosis was 1, 6 and 8% after 1, 2 and 3 years, respectively.

**Fertility outcome after surgery**

Of the 203 patients, 148 (73%) wanted to become pregnant after surgery. At the end of the study, 51% (n = 75/148) of these patients had conceived, with 81% giving live birth (n = 61/75). For 19 patients (n = 19/148, 13%), the pregnancy status was unknown. Using life table analysis, the cumulative pregnancy rate was 44, 58 and 73% after 1, 2 and 3 years, respectively (Figure I). The cumulative live birth pregnancy rate was 36, 50 and 67% after 1, 2 and 3 years, respectively. Among the patients with at least 1 functional tube (evaluated during surgery) (n = 169), 74% (n = 125/169) had a child wish; 66 of these patients (53%) conceived. Among the patients who underwent bowel resection (n = 76), 54 (71%) wanted to become pregnant, which is similar to the patients who did not undergo bowel resection (n = 94/127; 74%). Of the patients with a child wish in the bowel resection and non-bowel resection group, 27 (n = 27/54 or 50%) and 48 (n = 48/94 or 51%), respectively, became pregnant after surgery. The mode of conception for these different patient subgroups is shown in Table II.

The median follow-up period after multidisciplinary CO₂ laser surgery was 19.5 months (< 1 month – 45 months). For the EHP30 questionnaire and all its modules (except for module
B), a significant improvement could be observed between the results obtained prior to and 6 months after surgery. Module B (on the relationship with children) was not applicable for 84% of the patients prior to surgery. As data were available for only 29 patients, no calculations could be made on this module. In general, the average outcome at the 4 postoperative occasions was significantly better compared to the preoperative outcome. The improvement extended after the intervention with significant better average functioning after 12 to 24 months compared to 6 months after surgery. However, further improvement after 12 months was not observed (Table III). No differences were observed between the bowel resection and non-bowel resection subgroups or between patients with and without reintervention.

The postoperative VAS scores for chronic pelvic pain, dysmenorrhea and deep dyspareunia were significantly lower than the preoperative scores (p < 0.0001). Over the four postoperative measurements, average VAS scores were significantly lower than prior to surgery. After 12 months following the intervention, the level of pain remained stable as no difference was observed between these VAS scores after 12, 18 and 24 months after surgery (p > 0.05). No differences were observed between patients with and without reintervention (p > 0.05). For chronic pelvic pain, no difference was observed between the rAFS classes (p = 0.704). However, for dysmenorrhea and deep dyspareunia, a significant difference between rAFS classes III and IV was found, with a lower average pain level for the rAFS IV group (p = 0.017 and p = 0.020, respectively). No statistically significant difference was observed between the number of patients with dysmenorrhea, deep dyspareunia and chronic pelvic pain in the bowel and non-bowel resection subgroups pre- and postoperatively (p > 0.05).

After surgery, the VAS scores for chronic pelvic pain remained status quo, improved and worsened for 11% (n = 14/128), 64% (n = 82/128) and 25% (n = 32/128) of the patients, respectively. Complaints of dysmenorrhea remained status quo, improved and worsened for 8.0% (n = 10/125), 78.4% (n = 98/125) and 14% (n = 17/125) of the patients, respectively, whereas this was the case for 3.3% (n = 4/120), 68% (n = 81/120) and 29% (n = 35/120) of the patients, respectively for complaints of dyspareunia.
Discussion

The results of the present study show that radical (but fertility sparing) surgery in a multidisciplinary setting for the treatment of endometriosis is followed by a significant improvement of pain, QOL and sexual satisfaction. Additionally, we obtained a low major complication rate (2%) a low minor complication rate (4%), a low cumulative reintervention rate (1, 7 and 10% after 1, 2 and 3 years, respectively) and a low endometriosis recurrence rate (1, 6 and 8% after 1, 2 and 3 years, respectively) as well as a high cumulative pregnancy rate (44, 58 and 73% after 1, 2 and 3 years, respectively) and live birth rate (36, 50 and 67% after 1, 2 and 3 years, respectively).

No difference in outcome could be observed between the patients who underwent bowel resection in comparison with those who did not, except for a higher minor complication rate (11% compared with 1%, respectively). These study results confirm the data of our previous retrospective studies (Meuleman et al., 2009 and 2011a) and show that bowel resection does not have a negative effect on any of the outcome variables measured in our study.

The sum of these 3 studies [i.e. 2 retrospective studies on the same topic (Meuleman et al., 2009 and 2011a) and this prospective study] clearly indicate that our setting of a reproductive surgeon, backed-up by a colorectal surgeon and an urologist with a preoperative protocol describing the required preoperative exams and a common postoperative protocol for immediate postoperative care allows ‘radical’ surgery. This approach allows informing the patient on the probable extent of the intervention. Additionally, this approach, with every surgeon operating on his/her own domain, diminishes recurrence rate, with a low complication rate. However, this can only be obtained if each surgeon is aware of the typical characteristics of endometriosis forming a real multidisciplinary team, and not just a sum of three disciplines.

Comparison of the clinical outcome of different surgical managements of extensive forms of endometriosis is a major hurdle because of several reasons (Meuleman et al., 2011b). Firstly, in every study in literature, the best results of a surgeon are reported. Therefore, the quality of the different surgeons is compared (and not the quality of the different techniques). Secondly, it is impossible to directly compare the clinical outcome of a surgical technique versus an untreated control group [unethical in view of the pain suffered by patients and the results
achieved in cohort studies (Meuleman et al., 2011b), versus a control group treated by the same group of surgeons but with another technique (surgeons have their own skills and preferences) or versus another surgical group in the same hospital centre using a different technique (due to a lack of agreement on essential outcome variables). However, a comparison of the complication rate and recurrence rate by a clinical audit through a retrospective assessment of patient records (i.e. all patients with transmural invasion protocolled at bowel barium enema and treated with bowel resection and reanastomosis versus discoid excision and suturing) would be a possibility, but would be very difficult and time consuming. Therefore, the best solution seems to reach agreement on study design and objective reporting of clinical outcome data after endometriosis surgery (international consensus meeting planned in 2012) and to set up a multicenter study with clear patient identification and outcome parameters, based on a CONSORT-like checklist proposed in our systematic review (Meuleman et al., 2011).

The use of such a similar approach of the study design and outcome report might allow to compare the different available treatments at the level of complication, reintervention, recurrence and pregnancy rates and to decide upon what is in the best interest of the patient.

**Conclusion**

A before-after design was used to evaluate the impact of the surgical protocol on the patients QOL, pain and fertility (to evaluate the effectiveness of our multidisciplinary approach) focusing on the problems with surgical treatment of extensive endometriosis mentioned in literature: complication rate, reintervention/recurrence rate, QOL/pain and pregnancy rate.

Ideally, the surgical technique that we report should be exportable to another hospital/surgical team (applicability outside of the original study site). Therefore, a complete report (cfr. CONSORT, checklist SR) is necessary so that surgeons can adapt protocols of one another. In our opinion, it is best to reach an agreement on the study design and reporting of clinical outcome data after endometriosis surgery as well as to set up a multicenter study with clear patient ID in the near future.
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References


Figure 1: Time to first pregnancy after (first) intervention in function of bowel resection.
Table I: Overview of the different surgical procedures performed by the reproductive surgeon.

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<tr>
<td>Peeling total without vagina perforation</td>
<td>72</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vesico-uterine fold/bladder</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No surgery</td>
<td>178</td>
</tr>
<tr>
<td>Vaporization/coagulation</td>
<td>1</td>
</tr>
<tr>
<td>Peeling partial with bladder perforation</td>
<td>1</td>
</tr>
<tr>
<td>Peeling partial without bladder perforation</td>
<td>5</td>
</tr>
<tr>
<td>Peeling total with bladder perforation</td>
<td>6</td>
</tr>
<tr>
<td>Peeling total without bladder perforation</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bowel</th>
<th>Sigmoid</th>
<th>Rectosigmoid</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peeling with bowel perforation</td>
<td>3</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Peeling without bowel perforation</td>
<td>10</td>
<td>50</td>
<td>41</td>
</tr>
</tbody>
</table>
Table II: Mode of conception (for the first pregnancy) after surgery for endometriosis

<table>
<thead>
<tr>
<th>Mode of conception (first pregnancy)</th>
<th>All patients (n = 75)</th>
<th>Patients with at least 1 functional tube (n = 66)</th>
<th>Bowel resection (n = 48)</th>
<th>No bowel resection (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>31 (41%)</td>
<td>30 (45%)</td>
<td>18 (38%)</td>
<td>13 (48%)</td>
</tr>
<tr>
<td>Stimulation + HIUI</td>
<td>7 (9%)</td>
<td>7 (11%)</td>
<td>6 (13%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>IVF</td>
<td>24 (32%)</td>
<td>20 (30%)</td>
<td>14 (29%)</td>
<td>10 (37%)</td>
</tr>
<tr>
<td>IVF with donor sperm</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>ICSI</td>
<td>7 (9%)</td>
<td>6 (9%)</td>
<td>6 (13%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Cryo</td>
<td>3 (4%)</td>
<td>2 (3%)</td>
<td>1 (2%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Oocytes Reception</td>
<td>2 (3%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Table III: Comparison of the outcome of the EHP30 questionnaire and its different modules pre- and postoperatively: mean difference (standard deviation) and p-values

<table>
<thead>
<tr>
<th></th>
<th>EHP30</th>
<th>Mod A</th>
<th>Mod B</th>
<th>Mod C</th>
<th>Mod D</th>
<th>Mod E</th>
<th>Mod F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preop vs postop 1</strong></td>
<td>18.3 (1.8)</td>
<td>2.9 (0.4)</td>
<td>NC</td>
<td>3.2 (0.4)</td>
<td>4.5 (0.4)</td>
<td>2.5 (0.3)</td>
<td>0.5 (0.3)</td>
</tr>
<tr>
<td><strong>Preop vs average postop 1-4</strong></td>
<td>24.0 (1.9)</td>
<td>3.4 (0.4)</td>
<td>NC</td>
<td>3.8 (0.4)</td>
<td>4.0 (0.4)</td>
<td>2.4 (0.4)</td>
<td>1.3 (0.3)</td>
</tr>
<tr>
<td><strong>Postop 1 vs average postop 2-4</strong></td>
<td>7.6 (1.7)</td>
<td>0.7 (0.3)</td>
<td>NC</td>
<td>0.8 (0.3)</td>
<td>-0.6 (0.2)</td>
<td>-0.14 (0.3)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td><strong>Postop 2 vs average postop 3-4</strong></td>
<td>0.7 (1.5)</td>
<td>0.3 (0.3)</td>
<td>NC</td>
<td>-0.19 (0.4)</td>
<td>0.0 (0.3)</td>
<td>0.1 (0.4)</td>
<td>1.0 (0.3)</td>
</tr>
</tbody>
</table>

Legend: preop = 1 month prior to surgery; postop 1 = 6 months after surgery; postop 2 = 12 months after surgery; postop 3 = 18 months after surgery; postop 4 = 24 months after surgery; NC = not calculated.
2.9. Non-Health Care Costs associated with Endometriosis

Steven Simoens Ph.D., Christel Meuleman M.D., Thomas D’Hooghe M.D., Ph.D.
Human Reproduction, prepared for submission

Questionnaire: Non-Health Care Costs associated with Endometriosis
Abstract

**Background:** This study aims to quantify the non-health care costs of endometriosis in a sample of Belgian patients over a 30-month period.

**Methods:** A prospective, longitudinal study enrolled patients who underwent surgical treatment for endometriosis in University Hospitals Leuven. Self-reported patient questionnaires measured costs at one month prior to surgical treatment and at 6, 12, 18 and 24 months following treatment. The number of days of work absence was valued using gross monthly income to estimate costs of productivity loss. The analysis also included patient expenditure on support with household activities. Costs per patient were linearly extrapolated costs over six-month periods.

**Results:** Of 394 eligible patients, 180 participated in the study (response rate of 46%). The highest productivity loss was incurred during the six months prior to surgical treatment (€1,514 ± 2,576) and during the six months following treatment (€2,496 ± 4,144). Mean costs dropped to €115 - €225 during the following six-month periods. Similarly, costs of support with household activities peaked during the six months prior to surgical treatment (€982 ± 908) and during the six months following surgical treatment (€981 ± 1,085), after which they dropped to €500-€675 during the following six-month periods. Patients with severe endometriosis (rAFS stage IV) (€4,943) had higher total non-health care costs over the 30-month period than patients with minimal-to-moderate endometriosis (rAFS stages I - III) (€4,510) (p = 0.048).

**Conclusions:** As our study did not include a control population of women without endometriosis, patients were asked to report non-health care costs associated with endometriosis only. This study has demonstrated that the highest non-health care costs associated with endometriosis are incurred during the six months prior to and following surgical treatment.
**Introduction**

In an era of spiralling health care costs and limited resources, public policy makers and health care payers are concerned not only about the morbidity associated with endometriosis but also about the economic burden that endometriosis imposes on society. For instance, a cost-of-illness analysis estimated that annual endometriosis costs in the United States in 2002 amounted to $22 billion (Simoens *et al.*, 2007). The economic burden is not limited to health care costs, but also includes direct non-health care costs (e.g. child care costs while in treatment, transportation to health care provider) and indirect non-health care costs (e.g. absence from work, reduced productivity while at work, time lost from education and reduced ability to carry out day-to-day activities).

A literature review found that 85% of cost-of-illness analyses examined health care costs of endometriosis only (Gao *et al.*, 2006). In other words, little is known about the non-health care costs associated with endometriosis. Nevertheless, available estimates suggest that endometriosis may impose considerable non-health care costs. For instance, estimates of the number of hours missed from work due to endometriosis ranged from 19.2 to 86.4 hours per patient per year (Kunz *et al.*, 1995; Mathias *et al.*, 1996). The productivity loss of 86.4 hours translated into annual indirect costs of $1,023 per patient. The lack of attention to measuring indirect costs is a major concern given that patients suffering from endometriosis tend to belong to the working-age population (Bain, 2006). There is a need for a prospective collection of data on the productivity loss associated with endometriosis.

The aim of this study is to quantify the non-health care costs associated with endometriosis in a sample of Belgian patients over a 30-month period. The findings provide insight into one component of the economic burden associated with endometriosis. Furthermore, the cost data can be fed into economic evaluations, so that decision makers can ascertain the cost-effectiveness of various approaches to diagnosing and treating endometriosis by examining their effectiveness in relation to their costs.
Materials and Methods

This study was carried out in University Hospitals Leuven, a 1,900-bed university hospital where physicians and residents carry out more than 18,000 major procedures on patients per year.

A prospective, longitudinal study followed up patients over a period stretching from one month prior to surgical treatment for endometriosis to 24 months following treatment. All women who underwent surgery between September 1, 2006 and September 30, 2008 at the Leuven University Fertility Center and who had histologically proven endometriosis were asked to participate in this prospective follow-up study. Only patients who gave their written, informed consent for participation in the study were followed up. The study was approved by the ethical committee of University Hospitals Leuven.

Self-reported patient questionnaires (copies of the questionnaires are available from the corresponding author on request) enquired about costs associated with endometriosis and patient demographic characteristics at five time points: at one month prior to surgical treatment and at 6, 12, 18 and 24 months following treatment.

The questionnaire measured the number of days of work absence due to endometriosis during the previous six months. This productivity loss was valued using the gross monthly income reported by the patient. Direct non-health care costs related to patient expenditure on support with household activities (e.g. cleaning, ironing, childcare) during the previous four weeks. This covered support with household activities provided by professionals and provided by family, friends or neighbours. Cost questions were derived from a published questionnaire about the costs of renal transplantation (Cleemput et al., 2004) and were adapted to the case of endometriosis in collaboration with the health economist who had developed the renal transplantation questionnaire. Demographic characteristics included the highest level of education, occupation, gross monthly income and marital status. Endometriosis was staged based on hospital records using the rAFS score (rAFS, 1997).
A descriptive analysis linearly extrapolated costs per patient over six-month periods. The Kolmogorov-Smirnov test was applied to check for normality of cost data. If data were not normally distributed, the association between costs and demographic characteristics was explored using the Mann-Whitney U-test. All data were processed and analyzed using SPSS for Windows.

**Results**

At the moment of analysis, a total of 394 patients were eligible for inclusion in the study. Of those patients, 180 were willing to participate in this cost study and provided informed consent (response rate of 46%). The demographic characteristics of the patient sample are displayed in Table I. Around 50% of patients suffered from severe endometriosis (rAFS stage IV). The majority of patients (91%) had a relationship. With respect to the highest educational level, 31% of patients had attained upper secondary level, 40% had post-secondary level (except for university) and 20% had university level. Fifty-six percent of patients were white-collar workers. The gross monthly income was relatively evenly distributed across answer categories, although 25% of patients were not able or not willing to report their income.

A number of patients dropped out of the study due to disappearance of endometriosis symptoms after surgery and/or pregnancy (both aims of the surgery), lack of time or lack of interest. As a result, the number of patients decreased from 180 patients at one month prior to surgical treatment to 142 patients at six months, 116 patients at 12 months, 67 patients at 18 months and 49 patients at 24 months following treatment.

Table II reports non-health care costs per patient during successive six-month periods. These data show that the highest productivity loss was incurred during the six months prior to surgical treatment (€1,514 ± 2,576) and during the six months following treatment (€2,496 ± 4,144). Mean costs dropped substantially to €115 - €225 during the following six-month periods. Similarly, the costs of additional support with household activities peaked during the six months prior to surgical treatment (€982 ± 908) and during the six months following surgical treatment (€981 ± 1,085), after which they dropped to €500 - €675 during the following six-month periods.
Total non-health care costs over the 30-month period were higher for patients suffering from severe endometriosis (rAFS stage IV) (€4,943) than for patients suffering from minimal-to-moderate endometriosis (rAFS stages I - III) (€4,510) (p = 0.048). No statistically significant association was found between non-health care costs and the highest level of education.

Discussion

This prospective, longitudinal analysis has demonstrated that endometriosis is associated with substantial non-health care costs in the form of productivity loss and additional support with household activities. Due to limitations in design and scope, our study has likely underestimated the non-health care costs of endometriosis given that the costs of reduced productivity while at work and the costs of transportation to the health care provider were not included. In addition, our study did not consider the non-health care costs that endometriosis imposes on the partner, family or friends of patients (e.g. a husband who takes leave from work to care for a patient).

Our patient sample appears to be representative, even though patients were enrolled in a tertiary care centre which typically treats more complex and referred cases of endometriosis. Indeed, the proportion of women with minimal-mild (29%) and moderate-severe (71%) endometriosis in our study was comparable to the proportion of minimal-mild (37%) and moderate-severe (63%) in the whole Icelandic population over a 20-year period (Gylfason et al., 2010).

To the best of the authors’ knowledge, this is the first study that computes non-health care costs in patients with endometriosis over an extended time horizon of 30 months. This study has shown that the highest non-health care costs are incurred during the six months prior to and following surgical treatment. In addition to these non-health care costs, attention needs to be paid to the health care costs incurred during this period. Indeed, previous research has demonstrated that surgery accounts for most of the health care costs of endometriosis and that the well-documented long diagnostic delay between initial symptoms and diagnosis of endometriosis generates health care costs (Kennedy et al., 2005).
In order to fully appreciate these results, it is important to compare them with published cost estimates for other surgical diseases. A Belgian study quantified health care costs and costs of productivity loss from the year prior to diagnosis to five years following diagnosis (Broeckx et al., 2011). This study demonstrated that the costs of productivity loss accounted for 90% of total costs associated with breast cancer and that these costs were mainly incurred around the time of diagnosis and treatment. Costs of productivity loss of breast cancer patients converged with those of the general population at five years following diagnosis.

Ideally, the true cost of a disease is measured by the additional burden associated with that disease on society. Therefore, the questionnaires emphasized that patients should report non-health care costs associated with endometriosis only. Alternatively, a case-control study design could have been used. Due to practical and resource constraints, our study did not include a control population of women without endometriosis as is also the case in most other cost-of-illness analyses.

Our cost estimates need to be interpreted with caution. First, the costs of additional support with household activities are likely to be underestimated given that family, friends or neighbours who carry out these activities do not always ask for a financial compensation. Second, cost estimates were subject to large standard deviations as a result of for example differences in the number of days of work absence or differences in gross monthly income between patients. Third, our estimates were based on patient self-reported data. A patient questionnaire can be an efficient method to study a representative sample, but reliability of questionnaire data may be hindered by patients’ ability to recall resource use and expenditure related to a disease.

Future research needs to replicate our estimates of the non-health care costs associated with endometriosis in other settings or countries. There is also a need to examine the relationship between patient characteristics and non-health care costs. In particular, research is required that computes non-health care costs for different degrees of endometriosis severity as the relationship between endometriosis severity and costs is still unclear.
Cost estimates provided by this analysis can be used to determine priorities for and to inform future research on endometriosis. For instance, to reduce costs associated with endometriosis, attention needs to be focused on decreasing the productivity loss arising from endometriosis. The implementation of new techniques to prevent, diagnose, and treat endometriosis not only impact health care costs, but may also influence costs of productivity loss. Future studies exploring the impact of new techniques need to consider non-health care costs in addition to health care costs, and balance those costs against the effectiveness of techniques.

Acknowledgements

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The authors would like to express their gratitude to Lesley Behets, Julie Caerels, Fien Clarysse, Kristin Fraeyman, Sarina Heirbaut and Riet Van den Broeck for their contribution to data input and data analysis.

Authors’ roles

CM and TD conceived and designed the study, and were responsible for data collection. SS analysed and interpreted the data, and wrote the first draft of the manuscript. CM and TD critically revised the manuscript; TD supervised the study.
**Reference List**


### Table I: Patient characteristics (n = 180)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>rAFS stage</strong></td>
<td></td>
</tr>
<tr>
<td>Minimal (stage I)</td>
<td>8%</td>
</tr>
<tr>
<td>Mild (stage II)</td>
<td>21%</td>
</tr>
<tr>
<td>Moderate (stage III)</td>
<td>23%</td>
</tr>
<tr>
<td>Severe (stage IV)</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Living alone, without relationship</td>
<td>8%</td>
</tr>
<tr>
<td>Living alone, with relationship</td>
<td>3%</td>
</tr>
<tr>
<td>Living with partner</td>
<td>36%</td>
</tr>
<tr>
<td>Married</td>
<td>52%</td>
</tr>
<tr>
<td>Divorced</td>
<td>1%</td>
</tr>
<tr>
<td>Widowed</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Highest education level</strong></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>2%</td>
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<tr>
<td>Lower secondary</td>
<td>3%</td>
</tr>
<tr>
<td>Upper secondary</td>
<td>31%</td>
</tr>
<tr>
<td>Post-secondary, not university</td>
<td>40%</td>
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<tr>
<td>University</td>
<td>20%</td>
</tr>
<tr>
<td>Postgraduate</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
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</tr>
<tr>
<td>White-collar worker</td>
<td>56%</td>
</tr>
<tr>
<td>Blue-collar worker</td>
<td>5%</td>
</tr>
<tr>
<td>Executive staff</td>
<td>11%</td>
</tr>
<tr>
<td>Sales staff</td>
<td>9%</td>
</tr>
<tr>
<td>Intellectual or scientific staff</td>
<td>12%</td>
</tr>
<tr>
<td>Staff without educational degree</td>
<td>1%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>6%</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Percentage of patients</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Less than €625</td>
<td>4%</td>
</tr>
<tr>
<td>From €625 to €875</td>
<td>5%</td>
</tr>
<tr>
<td>From €875 to €1,125</td>
<td>6%</td>
</tr>
<tr>
<td>From €1,125 to €1,375</td>
<td>5%</td>
</tr>
<tr>
<td>From €1,375 to €1,625</td>
<td>10%</td>
</tr>
<tr>
<td>From €1,625 to €1,875</td>
<td>8%</td>
</tr>
<tr>
<td>From €1,875 to €2,125</td>
<td>9%</td>
</tr>
<tr>
<td>From €2,125 to €2,375</td>
<td>7%</td>
</tr>
<tr>
<td>From €2,375 to €2,625</td>
<td>1%</td>
</tr>
<tr>
<td>From €2,625 to €2,875</td>
<td>5%</td>
</tr>
<tr>
<td>More than €2,875</td>
<td>14%</td>
</tr>
<tr>
<td>Not able or not willing to report</td>
<td>25%</td>
</tr>
<tr>
<td>Voluntary work</td>
<td>1%</td>
</tr>
</tbody>
</table>
Table II: Non-health care costs of endometriosis (€)

<table>
<thead>
<tr>
<th>Costs of productivity loss</th>
<th>6 months prior to treatment (n = 180)</th>
<th>6 months after treatment (n = 142)</th>
<th>12 months after treatment (n = 116)</th>
<th>18 months after treatment (n = 67)</th>
<th>24 months after treatment (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1,514</td>
<td>2,496</td>
<td>117</td>
<td>223</td>
<td>184</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>2,576</td>
<td>4,144</td>
<td>398</td>
<td>841</td>
<td>475</td>
</tr>
<tr>
<td>Median</td>
<td>468</td>
<td>133</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Maximum</td>
<td>13,800</td>
<td>16,500</td>
<td>2,492</td>
<td>4,500</td>
<td>1,950</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs of household activities</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>982</td>
<td>981</td>
<td>513</td>
<td>607</td>
<td>675</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>908</td>
<td>1,085</td>
<td>352</td>
<td>507</td>
<td>170</td>
</tr>
<tr>
<td>Median</td>
<td>733</td>
<td>643</td>
<td>386</td>
<td>466</td>
<td>707</td>
</tr>
<tr>
<td>Minimum</td>
<td>32</td>
<td>135</td>
<td>129</td>
<td>193</td>
<td>450</td>
</tr>
<tr>
<td>Maximum</td>
<td>3,214</td>
<td>3,343</td>
<td>1,029</td>
<td>1,543</td>
<td>836</td>
</tr>
</tbody>
</table>
Appendix I: Gezondheidseconomische vragenlijst

Deze vragenlijst gaat over uw leven tijdens de laatste 6 maanden, dus tijdens de 6 maanden vooraleer u deze vragen beantwoordt.

Datum van invullen: Dag maand jaar

1. Welk opleidingsniveau heeft u op dit ogenblik?
   - Lager onderwijs
   - Lager secundair onderwijs
   - Hoger secundair onderwijs (algemeen vormend)
   - Hoger secundair onderwijs (beroeps/technisch)
   - Hoger, niet-universitair, onderwijs van het kort type
   - Universitair onderwijs of hoger onderwijs van het lange type
   - Postuniversitair onderwijs

2. Tot welke beroepscategorie behoort u op dit ogenblik?
   - Bedrijfsleiders en hoger kaderpersoneel
   - Intellectuele en wetenschappelijke beroepen
   - Ondergeschikt personeel in intellectuele en wetenschappelijke beroepen
   - Bedienden
   - Dienstverlenend en verkoopspersoneel
   - Ambachtslieden en ambachtelijke vakarbeiders
   - Fabrieksarbeiders, machine- en montagearbeiders
   - Ongeschoold personeel
   - Geen beroep

3. Wat is uw bruto inkomen per maand op dit ogenblik?
   - Minder dan 625€ in de maand
   - Tussen 625€ en 875€ in de maand
   - Tussen 875€ en 1125€ in de maand
   - Tussen 1125€ en 1375€ in de maand
   - Tussen 1375€ en 1625€ in de maand
   - Tussen 1625€ en 1875€ in de maand
   - Tussen 1875€ en 2125€ in de maand
   - Tussen 2125€ en 2375€ in de maand
   - Tussen 2375€ en 2625€ in de maand
   - Tussen 2625€ en 2875€ in de maand
   - Meer dan 2875€ in de maand
   - Ik weet mijn inkomen niet of wil het liever niet zeggen
   - Ik deed vrijwilligerswerk
4. Bent u op dit ogenblik:
   o Alleenstaand, zonder relatie
   o Alleenwonend, doch met een relatie
   o Samenwonend
   o Getrouwd
   o Gescheiden
   o Weduwe

5. Welk opleidingsniveau heeft uw partner op dit ogenblik?
   o Lager onderwijs
   o Lager secundair onderwijs
   o Hoger secundair onderwijs (algemeen vormend)
   o Hoger secundair onderwijs (beroeps/technisch)
   o Hoger, niet-universitair, onderwijs van het kort type
   o Universitair onderwijs of hoger onderwijs van het lange type
   o Postuniversitair onderwijs

6. Tot welke beroepscategorie behoort uw partner op dit ogenblik?
   o Bedrijfsleiders en hoger kaderpersoneel
   o Intellectuele en wetenschappelijke beroepen
   o Ondergeschikt personeel in intellectuele en wetenschappelijke beroepen
   o Bedienden
   o Dienstverlenend en verkoopspersoneel
   o Ambachtslieden en ambachtelijke vakarbeiders
   o Fabrieksarbeiders, machine- en montagearbeiders
   o Ongeschoold personeel
   o Geen beroep

7. Wat is het bruto inkomen per maand van uw partner op dit ogenblik?
   o Minder dan 625€ in de maand
   o Tussen 625€ en 875€ in de maand
   o Tussen 875€ en 1125€ in de maand
   o Tussen 1125€ en 1375€ in de maand
   o Tussen 1375€ en 1625€ in de maand
   o Tussen 1625€ en 1875€ in de maand
   o Tussen 1875€ en 2125€ in de maand
   o Tussen 2125€ en 2375€ in de maand
   o Tussen 2375€ en 2625€ in de maand
   o Tussen 2625€ en 2875€ in de maand
   o Meer dan 2875€ in de maand
o Ik weet zijn inkomen niet of wil het liever niet zeggen
o Hij deed vrijwilligerswerk

8. Heeft u zich in de afgelopen zes maanden afwezig gemeld op het werk wegens het probleem waarvoor u zal geopereerd worden of werd geopereerd:

O Niet van toepassing (indien u geen job met een loon had)
O Neen
O Ja Aantal volledige werkdagen afwezig: …………….dagen/6mnd

Reden van ziekmelding:
- Raadpleging/onderzoek………………werkdagen/6mnd
- Ziekenhuisopname……………………werkdagen/6mnd
- Werkongeschiktheid onafhankelijk van raadpleging, onderzoek of ziekenhuisopname
  ………………………………………werkdagen/6mnd

Werd u in deze periode door iemand vervangen op het werk

O Ja O Neen

9. Bent u tijdens de laatste zes maanden wegens het probleem waarvoor u zal geopereerd worden of werd geopereerd; (duidt aan wat op u van toepassing is – u mag ook meerdere punten aanduiden)

o Arbeidsongeschikt geworden (met vervangingsinkomen)(zelfstandigen)
o Arbeidsongeschikt geworden (met arbeidsongeschiktheidsuitkering) (bedienden en arbeiders)
o Arbeidsongeschikt geworden (met werkloosheidsuitkering) (i.g.v. ontslag)
o Van werkgever veranderd
o Naar een lagere functie overgestapt
o Naar een hogere functie overgestapt
o Niet in aanmerking gekomen voor een job (als werkzoekende indien u werkloos was of indien u van job wou veranderen (andere werkgever)
o Niet in aanmerking gekomen voor een promotie (bij dezelfde werkgever)
o Deeltijds gaan werken
o Opnieuw gaan werken na een periode van werkloosheid
o Opnieuw gaan werken na een periode van arbeidsongeschiktheid
10. Is uw inkomen tijdens de laatste zes maanden wegens het probleem waarvoor u zal geopereerd worden of werd geopereerd:
(duidt aan wat op u van toepassing is en beantwoordt de bijhorende vraag, weet dat indien u punt a) beantwoordt deze gegevens door het onderzoeksteam, overeenkomstig de wet op de Privacy, in alle discreetie zullen behandeld worden)

- Gedaald:
  - ja
  - neen

Zo ja,
  - a) hoeveel euro per maand(bruto) verdiende u voordien
  - en
  - hoeveel euro per maand(bruto) verdient u nu

  b) indien u punt a) niet wenst te beantwoorden, kan u misschien wel vertellen met hoeveel procent uw maandelijks inkomen is gedaald

- Gestegen:
  - ja
  - neen

Zo ja,
  - a) hoeveel euro per maand(bruto) verdiende u voordien
  - en
  - hoeveel euro per maand(bruto) verdient u nu

  b) indien u punt a) niet wenst te beantwoorden, kan u misschien wel vertellen met hoeveel procent uw maandelijks inkomen is gestegen

11. Bent u tijdens de laatste zes maanden wegens het probleem waarvoor u zal geopereerd worden of werd geopereerd:
(duidt aan wat op u van toepassing is)

- Meer gaan werken
- Minder gaan werken
- Noch meer, noch minder gaan werken

U werkte meer dan zes maanden geleden: %
U werkt nu: % (100% = voltijds werken)
Dit onderdeel van de vragenlijst heeft betrekking op de vier weken voorafgaande aan het invullen van deze vragenlijst

**Kolom 1:**

Welk van de onderstaande activiteiten doet u normaal zelf, maar hebt u in de afgelopen 4 weken niet kunnen doen vanwege het probleem waarvoor de ingreep werd gepland of werd uitgevoerd.

**Kolom 2:**

Hebben anderen deze taken (deels) van u overgenomen tijdens deze periode (de afgelopen 4 weken) vanwege het probleem waarvoor de ingreep werd gepland of werd uitgevoerd. Voor hoeveel uren hebt u deze hulp ongeveer gekregen?

**Kolom 3:**

Indien u deze perso(o)n(en) hebt betaald voor deze taken, hoeveel hebt u in totaal tijdens de laatste 4 weken hiervoor betaald?

<table>
<thead>
<tr>
<th>Taken</th>
<th>Kolom 1 Doe ik normaal zelf</th>
<th>Kolom 2 Heeft iemand deels van mij overgenomen</th>
<th>Kolom 3 Betaalde verloning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huishoudelijk werk (koken,poetsen,wassen, strijken)</td>
<td>Ja</td>
<td>ja/neen</td>
<td>………..uur</td>
</tr>
<tr>
<td></td>
<td>Neen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boodschappen doen (winkelen,bank,post-kantoor)</td>
<td>Ja</td>
<td>ja/neen</td>
<td>………..uur</td>
</tr>
<tr>
<td></td>
<td>Neen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klussen en karweien (in huis,tuin, aan voertuigen)</td>
<td>Ja</td>
<td>ja/neen</td>
<td>………..uur</td>
</tr>
<tr>
<td></td>
<td>Neen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verzorgin van uw kinderen (indien van toepassing)</td>
<td>ja</td>
<td>ja/neen</td>
<td>………..uur</td>
</tr>
<tr>
<td></td>
<td>Neen</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
12. Werd u tijdens de afgelopen 4 weken gehinderd bij uw vrijetijdsbesteding door het probleem waarvoor de ingreep werd gepland of werd uitgevoerd?
   (duidt aan wat op u van toepassing is en vul zo nodig de tijdsduur in)
   O Neen
   O Ja
   O Ik heb mijn vrijetijdsbesteding slechts …uur/week kunnen uitvoeren, in plaats van …uur/week, zoals normaal.
   O Ik heb mijn vrijetijdsbesteding niet kunnen uitvoeren.

13. Kreeg u tijdens de laatste vier weken verzorging thuis (door familieleden, thuisverpleegkundigen, vrijwilligers…)?
   (duidt aan wat op u van toepassing is en beantwoordt zo nodig de vragen)
   O Neen
   O Ja
   O Door wie?
   O Hoeveel uur? (in totaal tijdens deze vier weken)
   O Hoeveel heeft dit u gekost? (in totaal tijdens deze vier weken)
Chapter 3

Deeply Infiltrative Endometriosis: Pathways to Possible Prevention in Adolescents and in Young Adults
3.1 Study approach

Based on the concept that endometriosis is a progressive disorder in at least 50% of women and in nonhuman primates (D’Hooghe, 1997; Koninckx et al., 1991), early diagnosis and treatment of endometriosis appears to be relevant. However, the diagnostic delay between the onset of symptoms and definitive diagnosis can last up to 12 years (Arruda et al., 2003; Hadfield et al., 1996; Husby et al., 2003) due to aspecific symptoms considerably overlapping with other conditions such as Irritable Bowel Syndrome and Pelvic Inflammatory Disease and the fact that definitive diagnosis made by laparoscopy requires general anesthesia.

A relevant question is to which extent early diagnosis and complete surgical excision of endometriotic lesions during adolescence in a well selected patient group might prevent severe pain and infertility later in life. It is obvious that such an approach has to be weighed against the risks of general anaesthesia and surgery in adolescent girls or young women. On the other hand, early diagnosis and treatment during adolescence might diminish the number of young women with pain, decrease disease progression and prevent subsequent fertility problems and, as a consequence, diminish the cost of this disease. At present, in any case, very few gynaecologists, family doctors, health care workers, or female youngsters themselves are aware of the possible presence of endometriosis in adolescents and young adults.

Since there are indications that adults with DIE suffered from severe pelvic pain as an adolescent (Chapron et al., 2010; Treloar et al., 2010), endometriosis is one of the possible causes when adolescents complain of disabling menstrual cycle related pelvic pain.

A literature search was performed (Chapter 3.2) to learn more about the prevalence, the pathogenesis and the clinical manifestations of endometriosis in adolescents. The importance of a thorough history taking, a vaginal examination and technical investigations to diagnose endometriosis in adolescents is discussed as well as different options to treat the complaints of the adolescent. A flow chart based on this literature search is proposed for the management of diagnosis and treatment in adolescents with chronic pelvic pain suggestive for the presence of endometriosis.
After a systematic review (Chapter 3.3) on the prevalence of endometriosis confirmed by laparoscopy in adolescents/young women, a survey was done among 13 year old adolescents participating in an ongoing larger epidemiological study in Flanders aimed at documenting health and disease in Flemish children (Chapter 3.4) and among third year high school adolescent girls and first year university female students in Leuven (Chapter 3.5). The aim of this survey was to determine the prevalence of severe menstrual cycle related pelvic pain, considered to be a symptom suggestive for the presence of endometriosis.

Based on this survey, a specific questionnaire was developed (Chapter 3.6) to assess menstruation-related problems in this population. The development of a questionnaire allows detecting signals that possibly refer to the presence of endometriosis in adolescents and young adults.
Reference List


3.2. Literature Review: Chronic Pelvic Pain and Endometriosis in Adolescents - Onderbuikpijn en Endometriose bij Adolescenten

Dieter Mortier, M.D., Christel Meuleman, M.D., Thomas D’Hooghe, M.D., Ph.D.

Gunaïkeia, Volume 15, Nummer 3, 2010, Pagina’s 87-90
Inleiding

De term ‘endometriose’ duidt op de aanwezigheid van endometriale klierbuizen en stroma buiten de uteriene caviteit met inbegrip van het myometrium. Dit ectopisch endometrium bevindt zich hoofdzakelijk in het kleine bekken, maar kan op elke plaats in het lichaam voorkomen. De aandoening kan zowel asymptomatisch als symptomatisch zijn. Ondanks talrijke studies blijft er veel controverse bestaan over de prevalentie, pathogenese en klinische manifestaties van endometriose bij adolescenten. Verder gaan we in op het belang van een goede anamnese, klinisch onderzoek en bijkomende diagnostische middelen. We focussen ook op de mogelijke therapeutische benaderingen. Tot slot willen we een schema voorstellen voor de diagnostische en therapeutische aanpak bij een adolescent met pelvische pijn suggestief voor endometriose.

Prevalentie/Incidentie

De prevalentie in de algemene populatie is niet bekend. Schattingen variëren naargelang van de studiepopulatie (symptomatisch versus asymptomatisch) en de methoden van diagnose (klinisch versus heelkundig). In één studie werd endometriose gevonden bij 1% van alle vrouwen in de reproductieve leeftijd die om welke gynaecologische indicatie chirurgie ondergingen, en bij 12-32% van de vrouwen in de reproductieve leeftijd die een laparoscoopie ondergingen omwille van pelvische pijn (1). Er wordt geschat dat 4-17% van de postmenarchale vrouwen endometriose heeft (2).

Specifiek wat betreft endometriose bij adolescenten zijn er studies die aantonen dat 25-38% van de adolescenten met chronische pelvieve pijn endometriose heeft (3, 4). Deze prevalentie stijgt tot 50-70% bij adolescenten met pelvieve pijn die niet kon gecontroleerd worden met OAC (orale anticonceptie) of NSAID’s (niet-steroidale anti-inflammatoire drugs) (5-7). Alhoewel in het verleden verondersteld werd dat endometriose zich slechts presenteerde na enkele jaren menstrueren, zijn er artikelen die endometriose beschreven hebben voor de menarche (8), 1 maand (9) en 5 maanden na de menarche (10).

Pathogenese

Sommige adolescenten kunnen een genetische predispositie hebben voor de ontwikkeling van endometriose. In een studie werd endometriose gezien bij 7% van de vrouwelijke eerstegraadverwanten van endometriosepatiënten, en slechts bij 1% bij verwanten van een controlegroep (11). Wat de exacte pathogenese betreft, zijn er verschillende theorieën, maar geen enkele kan alle gevallen van endometriose verklaren.

De implantatie- of retrograde menstruatietheorie van Sampson stelt dat tijdens de menstruatie endometriaal weefsel doorheen de tubae wordt getransporteerd en zo in de peritoneale holte kan implanteren (12). Deze theorie wordt ondersteund door de observatie dat endometriose het meest wordt vastgesteld in de laagste pelvieve delen. Bovendien zijn er obstructieve anomalieën van de vrouwelijke genitale tractus die gepaard gaan met een verhoogde retrograde menstruatie en die geassocieerd zijn met endometriose bij de adolescent (9, 13, 14). Schifrin et al. identificeerden zes adolescenten met Mullerianse afwijkingen die geassocieerd waren met endometriose. De jongste
Tieners zich zelden presenteren met de klassieke triade dysmenorree – dyspareunie – infertiliteit.

Tijdige herkenning van deze symptomen kan het tijdsinterval tussen aanvang van de symptomen en presentatie van klachten en het tijdsinterval tussen presentatie van klachten en diagnose verkorten. Idealerl zal een vroege diagnose van endometriose de langetermijn effecten (chronische pijn, endometrioma’s en infertiliteit) verbergen en dus ook de kwaliteit van leven bij adolescenten en volwassen vrouwen. Dit dient echter nog bewezen te worden met prospective trials.

aan het gebruik van OAC; deze zijn veilig voor adolescenten en zorgen voor verlichting van acue en bescherming tegen ongewenste zwangerschap [22]. OAC zijn dus zeker bruikbaar bij adolescenten die tevens anticonceptie nodig hebben. Soms kunnen ouders echter bezwaar tegen het gebruik van OAC hebben als empirische therapie, omdat dit volgens hun beleving de drempel tot coïtus zou verlagen. In de counseling dienen de andere aspecten benadrukt te worden. Als alternatief voor OAC kan de contraceptive patch of de vaginale ring gebruikt worden. OAC verminderen de dysmenorrhea door de groei van het endometrium te limiteren en zo de hoeveelheid endometriaal weefsel te beperken dat prostaglandines en leukotrienen kan produceren. Tevens inhiberen OAC de ovulatie en de daaropvolgende progesteronproductie, en leiden ze tot tijdelijke inhibtie en inactivatie van endometrioletesels [22].

Falen empirische behandeling

Bij patiënten waar de pijn na drie maanden proeftherapie persisteert, is verdere evaluatie in het kader van endometriose aangezien. Een laparoscopie is essentieel om endometriose te diagnosticeer, het is de gouden standaard. Deze procedure kan veilig uitgevoerd worden bij de adolescent. Gynaecologen die een laparoscopie uitvoeren bij adolescenten met plevié pijn, dienen vertrouwd te zijn met de atypische letsels van endometriose bij adolescenten, die eerder rood, helder, of wit zijn in tegenstelling tot atypische letsels van endometriose bij adolescenten met pelviene pijn, dienen vertrouwd te zijn met de atypische letsels van endometriose bij adolescenten, die eerder rood, helder, of wit zijn in tegenstelling tot het endometrium te limiteren en zo de hoeveelheid en-

De behandeling met NSAID's is het meest effectief wanneer het 1-2 dagen voor de te verwachten menstruatie wordt gestart.

OAC kunnen continu genomen worden om dysmenorrhea te verminderen. Een 30 of 35 microgram monofase pí is meer effectief dan lager gedoseerde of trifasische pillen. Bovendien is er minder kans op doorbraakbloedingen [20]. Overigens zijn er nog bijkomende voordelen verbonden met formule, CRP en bezinkingssnelheid kunnen hel-

Wat betreft bijkomende diagnostiek, kunnen er ook laboratoriumtesten worden verricht. Dit kan belangrijk zijn voor het uitsluiten van andere aandoeningen. Een compleet met formule, CRP en bezinkingssnelheid kunnen hel-

Eerste/empirische behandeling

Medische interventie is aangezien, zelfs indien er nog geen historische diagnose is, bij adolescenten die een verstoring hebben van de normale activiteiten omwille van pijn. De behandeling van dysmenorrhea moet de eerste stap zijn bij adolescenten met niet-acute gynaecologische pijn. De ACOG (American College of Gynaecologists and Obstetricians) beveelt een proeftherapie aan van OAC voor SOA's (seksueel overdraagbare aandoeningen) zoals chlamydia en gonorroe.

CT-scan (computeromgrafie) kan helpen om appendix uit te sluiten in gevallen van acute pijn, in andere gevallen is het van weinig nut [19].

MRI (magnetic resonance imaging) is heel bruikbaar voor de evaluatie van genitale anomalieën. Gezien de kostprijs van dit onderzoek, dient dit enkel aangevraagd te worden wanneer er voldoende klinische of echografische verdenking is [20].

Overigens zijn er nog bijkomende voordelen verbonden met formule, CRP en bezinkingssnelheid kunnen hel-

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triose wordt best uitgestippeld vanaf het moment van de diagnose totdat de kinderwens voltooid is (21). De details van deze verderegezette medicamenteuze therapie zijn kort samengevat in figuur 1 en behoren niet tot het bestek van dit artikel.

Conclusie

De prevalentie en incidentie van endometriose bij adolescenten zijn tot op heden niet gekend. Wel werden een aantal literatuurdata hieromtrent gepresenteerd. Wat betreft de pathogenese van deze aandoening zijn er verschillende theorieën, die echter tot op heden niet alle gevallen van endometriose kunnen verklaren. Wellicht is de oorzaak van dit artikel.

3.3. Systematic Review: Prevalence of Endometriosis diagnosed by Laparoscopy in Adolescents
Anna Rijkers, M.Sc., Christel Meuleman, M.D., Thomas D’Hooghe, M.D., Ph.D.
Submitted for publication
Abstract

**Background and Aim:** Endometriosis associated with pain symptoms in adolescents has been reported, but the exact prevalence is unclear because pain symptoms may be atypical and endometriosis can only be diagnosed by laparoscopy. The aim of this paper is to provide a systematic review on the prevalence of endometriosis diagnosed by laparoscopy in adolescents.

**Methods:** A systematic literature search was carried out for relevant articles published 1980 – 2010 in the databases PUBMED and EMBASE based on keywords “endometriosis”, “laparoscopy”, “adolescents” and “pelvic pain”. In addition, the reference lists of the selected articles were examined.

**Results:** Based on 15 selected studies, the overall prevalence of endometriosis in adolescents was 62% (n = 557/893; range 24 - 100%) and was significantly higher (p < 0.001) in girls with CPP resistant to treatment with OCPs (76%; n = 238/314) and in girls with dysmenorrhea (72 %; n = 115/159) than in those with CPP only (49%; n = 204/420). The overall prevalence of ASRM classified moderate-severe endometriosis was 32% (n = 82/259) and lower in girls with CPP resistant to treatment with OCPs/NSAIDs (16%; n = 17/108) or those with dysmenorrhea (29%; n = 21/74) than in the subgroup with CPP (57%; n = 44/77).

**Conclusion:** Nearly two third of adolescents with CPP or dysmenorrhea have laparoscopic evidence of endometriosis. About one third of adolescents with endometriosis have moderate-severe disease. The value of early detection of endometriosis in symptomatic adolescents requires more research.
Introduction

Endometriosis is a gynaecological disorder defined by the presence of endometrial glands and stroma outside the uterus, associated with pelvic pain (dysmenorrhea, non-menstrual pain, and dyspareunia) and subfertility, which can be chronic and progressive in a significant subset of patients (Doyle et al., 2009; Kennedy et al., 2005; Reese et al., 1996). The prevalence of endometriosis is approximately 10 - 15% among women of reproductive age (Crosignani et al., 2006; Mao and Anastasi, 2010; Vigano et al., 2004) and up to 35 - 50% among women with pelvic pain, infertility, or both (Treloar et al., 2010). The exact cause of endometriosis remains unknown although many theories have been developed to explain this issue. No single theory can explain all cases of endometriosis, and likely the aetiology is multi-factorial. The most popular and widely accepted theory is that of Sampson, who proposed that during menstruation, endometrial cells regurgitate through the fallopian tubes and implant on the surrounding pelvic viscera (Sampson, 1927). Other theories such as immunological and genetic mechanisms have been proposed (Fraser, 2008). Endometriosis can only be diagnosed by visual inspection during laparoscopy, ideally confirmed by histology, and can present as peritoneal disease with typical or subtle lesions, ovarian endometriotic cysts (endometriomas) or DIE. The degree of endometriosis can be staged laparoscopically as minimal, mild, moderate or severe according to the classification of the American Society of Reproductive Medicine [ASRM – former American Fertility Society, (rAFS, 1997)]. Alternative or historical classification systems include the Endoscopic Endometriosis Classification I - IV by Semm [EEC I - IV, (Semm, 1984)], the Acosta classification (Acosta et al., 1973) or the staging system: proposed by Kistner and associates (Kistner et al., 1977) on a scale of I to IV, respectively.

Endometriosis does not only affect adult women but also adolescent girls. Symptoms in adolescents may differ from adults in that there may be cyclic or acyclic pain, irregular menses, dyspareunia, gastrointestinal symptoms, vaginal discharge, bladder dysfunction and urinary tract symptoms (Black and Jamieson, 2002; Laufer et al., 2003; Unger and Laufer, 2010). The principal manifestation of endometriosis among teenagers is CPP (Attaran et al., 2002; Bourdel et al., 2006; Kontoravdis et al., 1999; Vercellini et al., 1989) or/and dysmenorrhea (Bourdel et al., 2006; Laufer et al., 1997; Propst and Laufer, 1999). Recent evidence suggests that early dysmenorrhea is positively associated with endometriosis (Treloar et al., 2010). The pattern of pelvic pain in adolescents with endometriosis differs...
from that in adults. Whereas adults mention rather an increasing pain during the menstruation, adolescents indicate the pain rather as cyclic and acyclic (not menstruation-related). In an earlier study (Laufer et al., 1997), 9.4% of adolescents had the adult pattern of cyclic pain with menses, whereas 65.5% had both acyclic and cyclic pain and only 28.1% had acyclic pain (Laufer et al., 2003). This pelvic pain can occur unpredictably and intermittently or continuously throughout the menstrual cycle, and can be dull, throbbing, or sharp, and exacerbated by physical activity (Broach et al., 2009; Giudice, 2010).

Because endometriosis can only be diagnosed at laparoscopy, a relatively new addition in the field of adolescent gynaecology, the true prevalence of endometriosis among adolescents remains still unknown (Dovey and Sanfilippo, 2010; Gylfason et al., 2010; Kalu et al., 2008; Pandis et al., 2009). According to a previous review paper (Rijkers, 2011), the prevalence of endometriosis varies between 25%-38.3% in adolescents with chronic pelvic pain and dyspareunia and increases to 50%-70% in adolescents undergoing laparoscopy for pelvic pain not responding to non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraception (Laufer et al., 2003).

There has been limited research on endometriosis in adolescents. Previous reviews have mainly focused on the following items: 1) management and approach of chronic pelvic pain due to endometriosis (Attaran et al., 2002; Greco, 2003; Solnik, 2006) 2) treatment recommendations (Dovey and Sanfilippo, 2010; Laufer et al., 2003; Sanfilippo, 1997) 3) approaches to diagnosis and management of endometriosis (Black and Jamieson, 2002; Laufer et al., 2003; Laufer, 2008; Sanfilippo, 1997) 4) Adenomyosis (Dietrich, 2010) 5) endometriosis from thelarche to their sixteenth birthday (Batt and Mitwally, 2003) and 6) the incidence and diagnosis of endometriosis in adolescents (Propst and Laufer, 1999). However, to the best of our knowledge, there has not been a systematic effort to assess the prevalence of endometriosis in adolescents. Therefore, the overall aim of this paper is to present a systematic review of the prevalence of laparoscopically confirmed endometriosis in adolescents, based on studies reporting originally collected data only.
Materials and Methods

Search strategy
The literature review was conducted in two steps. First, an extensive search of the electronic databases including PUBMED and EMBASE at The Biomedical Libraries of the University Hospital of Leuven was performed for research articles published between January 1980 and August 2010. Following Medical Subject Heading (Agarwal and Fong, 2008) terms were used in different combinations: ‘endometriosis’, ‘adolescent’, ‘laparoscopy’, ‘chronic pelvic pain’ were used. Additionally, a search with the terms “endometriosis”, “Afro-American”, and “Asian” was done to look more specifically to other cultures than Caucasian.

Inclusion and exclusion of publications
The search was limited to articles in the English language that were published in full and addressed the research question at hand as primary outcome variable (prevalence of laparoscopically proven endometriosis in adolescents). Articles were only considered to be relevant if they reported original research. Therefore, manuscripts that did not contain empirical quantitative results, such as letters to the editor, brief reports, case studies, qualitative designs, opinions of experts, etc. were excluded. The reference lists of all selected articles were reviewed to identify additional relevant papers.

Outcome measures
The primary outcome measure was the prevalence of laparoscopically confirmed endometriosis in adolescent girls. Secondary outcome measures included the classification of endometriosis (Table II).

Critical appraisal
The studies were subsequently assessed independently by the author (AR) for methodological quality using the Critical Appraisal Skills Programme (CASP) for cohort studies (The NHS Public Health Resource Unit Critical Appraisal Skills Programme Oxford, UK). This CASP is a key skill required to evaluate the quality of cohort studies to make evidence-based decisions by setting of 3 major questions: 1) are the results of the study valid, 2) what are the results, 3) will the results help me locally? The appraisal questions were graded “+” when the criterion was fulfilled, “+/−” when the criterion was unclear and “−” when the criterion was not fulfilled.
Results

Characteristics of studies
The process of literature identification and selection is shown in Figure I. A PUBMED and EMBASE search with the above mentioned MESH terms provided 967 hits. Based on title and abstract content, 84 papers were withheld. After reading the articles, 68 more articles were excluded for the following reasons: no inclusion of specific data on adolescents (n = 15), review (n = 23), case reports (n = 6), case series (n = 1), descriptive studies and/or opinion papers without a laparoscopic intervention (n = 8), studies containing information not relevant to the research question (n = 11), and studies that were not published as a full text paper (n = 4). Finally, 15 articles were included in this review (Figure I, Table I). No additional papers were identified after checking the reference lists of these selected papers.

The 15 selected articles were observational studies published between 1980 and 2010 and were conducted between 1974 and 2009. Seven studies were conducted in the USA (Chatman and Ward, 1982; Davis et al., 1993; Doyle et al., 2009; Goldstein et al., 1980; Laufer et al., 1997; Reese et al., 1996; Ventolini et al., 2005), six studies in Europe (Chan et al., 2009; Emmert et al., 1998; Kontoravdis et al., 1999; Stavroulis et al., 2006; Vercellini et al., 1989e), one in New Zealand (Roman, 2010) and 1 in Asia (Bai et al., 2002). Data were retrospectively collected by reviewing medical records in nine studies (Bai et al., 2002; Davis et al., 1993; Doyle et al., 2009; Emmert, et al., 1998; Kalu et al., 2008; Laufer et al., 1997; Reese et al., 1996; Stavroulis et al., 2006; Vercellini et al., 1989), prospectively in five cohort studies (Chatman and Ward, 1982; Goldstein et al., 1980; Kontoravdis et al., 1999; Ventolini et al., 2005; Vicino et al., 2010) and one comparative cohort study comparing data from adolescents and adult women with endometriosis treated surgically during the same period (Roman, 2010).

Critical appraisal
All selected studies used a cohort study design to describe the prevalence of endometriosis among adolescent girls. Although this is a more robust study design than case series, considerable biases still exist. All selected studies were interpreted with caution using CASP criteria for observational studies. The overall appraisal of selected studies was more than acceptable and gave answers on the major 3 questions ‘are the results valid’, ‘what are the results en ‘will the results help locally’. The results of the studies were valid with the
exception of the study of Kontoravdis (Kontoravdis et al., 1999), were clearly described with the exception of three studies (Bai et al., 2002; Doyle et al., 2009; Kontoravdis et al., 1999) and the results can be applied to the local population except for the studies of Bai and Chatman (Bai et al., 2002; Chatman and Ward, 1982). Some authors (Emmert et al., 1998; Kontoravdis et al., 1999; Stavroulis et al., 2006) did not clearly mention or describe the potential risk of confounders (e.g. age, culture, the severity of the environmental toxins, dietary habits).

A summary of the critical appraisal of the 15 articles withheld can be found in Table III.

**General Patient characteristics**

Included subjects were adolescent girls (n = 893) with pelvic pain, aged 10 - 21 years, with Caucasian (n = 811/893, 91%), African (n = 43/893, 5%) or Asian (n = 39/893, 4%) ethnic origin. The number of patients included in the 15 studies varied between 20 (Roman, 2010) and 140 (Goldstein et al., 1980).

A total of 557 cases of endometriosis were found (184 in prospective studies, 353 retrospective studies and 20 in the comparative cohort study).

The term “adolescents” was present in the title of all articles, except two (Stavroulis et al., 2006; Vicino et al., 2010), but was defined differently in each study, with age groups varying between 10 - 19.25 years (Goldstein et al., 1980), 16 - 19 years (Kontoravdis et al., 1999), 21 - 22 years (Laufer et al., 1997; Vicino, Parazzini et al., 2010) and < 24 years (Doyle et al., 2009).

The main symptom leading to laparoscopic investigation was either chronic pelvic pain (Bai et al., 2002; Emmert et al., 1998; Goldstein, et al., 1980; Kontoravdis et al., 1999; Vicino et al., 2010), chronic pelvic pain not responding to medical therapy with NSAIDs and OCPs (Doyle et al., 2009; Kalu et al., 2008; Laufer et al., 1997; Reese et al., 1996; Stavroulis et al., 2006; Ventolini et al., 2005) or dysmenorrhea (Chatman and Ward, 1982; Davis et al., 1993; Roman, 2010; Vercellini et al., 1989) (Table II). Histological confirmation was reported in eleven studies (Chatman and Ward, 1982; Davis et al., 1993; Emmert et al., 1998; Goldstein et al., 1980; Laufer et al., 1997; Reese et al., 1996; Roman, 2010; Stavroulis et al., 2006; Ventolini et al., 2005; Vercellini et al., 1989; Vicino et al., 2010) but was not mentioned in 3 other studies (Doyle, et al., 2009; Kalu et al., 2008; Kontoravdis et al., 1999).
Details of the studies (Author, age menarche, sample size, study objective, study period and design, care setting and outcome measure) are summarized in Table I. The average menarche was mentioned very clearly in only 5 studies (Bai et al., 2002; Emmert, et al., 1998; Goldstein et al., 1980; Laufer et al., 1997; Reese et al., 1996) and ranged between 11.8 - 14.2 years.

**Prevalence of endometriosis**
The prevalence of endometriosis was highly variable (24.5% - 100%) among the selected studies. The overall prevalence of endometriosis in all patients included in all studies was 62% (n = 557/893). The prevalence was significantly higher (p < 0.001; chi square test) in girls with CPP resistant to treatment with OCPs/NSAIDs (76%; n = 238/314) and in girls with dysmenorrhea (72%; n = 115/159) than in those with CPP only (49%; n = 204/420).

**The classification and stage of endometriosis**
Endometriosis was staged laparoscopically (Table II) according to different classification systems. The AFS/ASRM classification system [ASRM – former American Fertility Society (rAFS, 1997)] was used in 8/15 studies (Bai et al., 2002; Doyle et al., 2009; Laufer et al., 1997; Reese et al., 1996; Roman, 2010; Ventolini et al., 2005; Vercellini et al., 1989; Vicino et al., 2010), whereas the ACOSTA classification (Acosta et al., 1973) was used in only 2 of the 15 studies (Chatman and Ward, 1982; Stavroulis et al., 2006). Only one study applied a combination of the AFS/ACOSTA classification (Davis et al., 1993), the Semm ECC (Endoscopic Endometriosis Classification [Emmert et al., 1998]) or the Kistner classification system (Goldstein et al., 1980). Classification of endometriosis was not mentioned in 2/15 studies (Kalu et al., 2008; Kontoravdis et al., 1999).

When only the ASRM classification was taken into account, the adolescents with endometriosis, taken together from all studies, had either minimal (42%, n = 108/259), mild (27%, n = 69/259), moderate (18%, n = 47/259) or severe (14%, n = 35/259) endometriosis. The distribution of minimal, mild, moderate and severe endometriosis was different (p < 0.001, chi square test) between the subgroups with CPP (14%, 29%, 31%, 26%, respectively), CPP resistant to treatment with OCPs/NSAIDs (62%, 22%, 14%, 2%, respectively), and the subgroup with dysmenorrhea (41%, 31%, 11%, 18%, respectively). The overall prevalence of ASRM classified moderate-severe endometriosis was 32% (82/259) and lower in girls with CPP resistant to treatment with OCPs/NSAIDs (16%; n = 17/108) or those with dysmenorrhea (29%; n = 21/74) than in the subgroup with CPP (57%; n = 44/77).
The laparoscopic presentation of the more severe forms of endometriosis was only noted in 3 studies with the following surgical findings. In the first study 50% (n = 18/36) had moderate to severe- endometriosis according to the Acosta classification or stage III - IV when classified by the r-AFS system, marked by the presence of rectal lesions (sever endometriosis according to Acosta classification) and tubo-ovarian adhesions (Davis et al., 1993). In the second study only 5% (n = 3/66) of adolescents had stage r-AFS IV endometriosis marked by extensive disease of the peritoneum, ovaries and tubes as well as involvement of surrounding structures (Goldstein et al., 1980). In the third study, 54.5% (n = 6/11) of adolescents had severe endometriosis (Acosta classification) associated with rectovaginal-, uterovesical-, bowel- and ureteric endometriosis (Stavroulis et al., 2006).

**Discussion**

In this systematic review the prevalence of laparoscopically confirmed endometriosis in adolescents was high (62%), especially in girls with CPP resistant to medical treatment (76%) or those with dysmenorrhea (62%). Our study is characterized by several strengths.

Firstly, we only included studies documenting prevalence of endometriosis in adolescents as primary outcome variable and analyzed theses studies on the level of originally collected patient data. Other reviews on adolescent endometriosis were not based on a systematic approach and were focused on other endometriosis-related topics in adolescents: diagnosis and management (Black and Jamieson, 2002; Laufer et al., 2003; Laufer, 2008; Sanfilippo, 1997), management of chronic pelvic pain (Attaran et al., 2002; Greco, 2003; Solnik, 2006), specific treatment recommendations (Dovey and Sanfilippo, 2010; Laufer et al., 2003; Sanfilippo, 1997), adenomyosis or evolution of endometriosis from thelarche to age 16 (Batt and Mitwallly, 2003).

Secondly, all selected studies were largely comparable with regard to gender, age, pain symptoms, and laparoscopic assessment of endometriosis (Table I - II).

Thirdly, a total of 893 adolescents with chronic pelvic pain were included in this review, a numbers sufficiently large to draw meaningful conclusions.

Only a limited number of articles (n = 15) met the inclusion criteria of our study and are associated with a number of limitations.
Firstly, data were collected retrospectively by reviewing medical records in nine of the 15 studies (Bai et al., 2002; Davis et al., 1993; Doyle et al., 2009; Emmert et al., 1998; Kalu et al., 2008; Laufer et al., 1997; Reese et al., 1996; Stavroulis et al., 2006; Vercellini et al., 1989) and could bias the accuracy of the results by an overestimation of the prevalence of endometriosis (positive selection bias).

Secondly included data were based largely on adolescents from Caucasian origin (n = 811/893, 91%), and it is impossible to conclude anything about the prevalence of endometriosis in adolescents from non-Caucasian origin, as the total study population included only a small proportion of adolescents from African (n = 43/893, 5%) or Asian (n = 39/893, 4%) ethnic origin derived from only 2 (Bai et al., 2002; Chatman and Ward, 1982).

Thirdly, histological analysis of endometriosis biopsies obtained during laparoscopy was not done in 33% (n = 5/15) of studies, and the histological confirmation rate was variable in the other studies.

Fourthly, the severity of endometriosis was classified in most studies (n = 13/15) using variable systems, most commonly the staging system of the American Society of Reproductive Medicine (rAFS, 1997) (n = 8/13) but other classification systems were used in a significant proportion (n = 5/13) of other studies.

Fifthly, selection bias occurred because, in the absence of a standardized care protocol, patients were allocated to laparoscopy based on subjective criteria like pain symptoms and the surgeon’s personal discretion and experience. It is not imaginary that a higher surgical level of experience could lead to an increased recognition and better treatment of endometriosis with potentially lower complication rates. Also the opposite is true (Katsuno et al., 2009; Markides et al., 2010).

Sixthly, the term ‘adolescents’ was not defined in any of the included studies. Interestingly, the age of an adolescent is defined differently according to different sources: 13 - 18 years (PubMed), 13 - 17 years (Embase), 10 - 19 years (WHO) or 15 - 20 years (Van Dale Large Dictionary of the Dutch Language).
Seventhly, 3 of the 15 studies were published in the 80’s, at a time when the laparoscopic recognition of subtle endometriotic lesions was limited, which could have resulted in an underestimation of endometriosis in those studies (Koninckx et al., 1991).

Our observation that the prevalence of endometriosis was significantly higher (p < 0.001) in girls with CPP resistant to treatment with OCPs (76%; n = 238/314) and in girls with dysmenorrhea (72 %; n = 115/159) than in those with CPP only (49%; n = 204/420) warrants further discussion. We hypothesize that CPP, defined differently in the included studies, is a more heterogeneous clinical symptom which may be less specific for endometriosis than dysmenorrhea (menstrual pain only) or CPP resistant to OCPs/NSAIDs (selected “worse” cases).

This hypothesis is supported by recent evidence showing that dysmenorrhea at an early age is a risk factor for endometriosis in general (Treloar et al., 2010) and that both the incidence and duration of oral contraceptive use for severe primary dysmenorrhea during adolescence is higher in women who later develop DIE that in women without DIE (Chapron et al., 2010).

Our observation that the overall prevalence of ASRM classified moderate-severe endometriosis was 32% (n = 82/259) was not expected, as it is commonly accepted that endometriosis in adolescents is limited to peritoneal lesions with an inflammatory component (Kennedy et al., 2005). Unfortunately, only 3 studies included some description of the type of lesions observed that led to their classification as moderate-severe endometriosis. While adhesions were reported in these studies, it is not clear to which ovarian endometriotic cysts or DIE contributed to this classification. Furthermore, it is not clear why the prevalence of moderate-severe endometriosis was lower in girls with CPP resistant to treatment with OCPs/NSAIDs (16%; n = 17/108) or those with dysmenorrhea (29%; n = 21/74) than in the subgroup with CPP (57%; n = 44/77). We speculate that treatment with OCPs and/or NSAIDs may not only lead to pain relief but also limit the progression to moderate-severe disease in some adolescents.

Overall, the high prevalence of endometriosis with a substantial proportion of moderate-severe disease demonstrated in our review among adolescents with pelvic pain has important consequences for clinical practice. We advocate that adolescents with CPP and/or dysmenorrhea, especially if resistant to OCPs or NSAIDs, should be taken seriously and that
diagnostic laparoscopy with simultaneous surgical treatment should be offered, after the adolescents and their parents have been fully informed about potential risks and benefits. Prospective studies are needed to identify the adolescent population at risk for the development of endometriosis and to develop a clinical pathway to care for them in collaboration between nurses, school doctors, student doctors, family physicians and gynaecologists specialized in endometriosis. These studies will provide the organizational basis to test the hypothesis that early laparoscopic diagnosis and surgical treatment of adolescent endometriosis can prevent the progression to moderate-severe disease associated with debilitating pain and infertility.

Acknowledgements
The idea for this study originated from the Centre for Health Services and Nursing Research. There is no conflict of interest between the first author, the co-authors, the Centre for Health Services and Nursing Research, the LUFc and the Department of Obstetrics and Gynaecology of the University Hospitals Leuven, Belgium. This review was performed without funding.


Figure I. The process of literature identification and selection
<table>
<thead>
<tr>
<th>Author et al., Year</th>
<th>Age patient (years)</th>
<th>Menarche (mean years)</th>
<th>Sample (n)</th>
<th>Study objective</th>
<th>Study period</th>
<th>Design</th>
<th>Care setting</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al., 1980</td>
<td>10 - 19.25</td>
<td>11.8</td>
<td>140</td>
<td>To describe experience in adolescents who have endometriosis.</td>
<td>1974, 1979</td>
<td>Prospective</td>
<td>Boston Children’s Hospital Medical center</td>
<td>Symptoms</td>
</tr>
<tr>
<td>Chatman &amp; Ward, 1982</td>
<td>12 - 19</td>
<td>NS</td>
<td>43</td>
<td>To outline the magnitude of the problem of endometriosis.</td>
<td>?</td>
<td>Prospective</td>
<td>Department Obstetrics and Gynecology, University of Chicago</td>
<td>Surgical findings</td>
</tr>
<tr>
<td>Vercellini et al., 1989</td>
<td>11 – 19 (18.7)</td>
<td>NS</td>
<td>47</td>
<td>To add additional information about etiology of endometriosis To determine the incidence of endometriosis.</td>
<td>1983, 1987</td>
<td>Retrospective</td>
<td>First Department Obstetrics and Gynecology, University, Milan</td>
<td>Stage, Symptoms, Surgical findings</td>
</tr>
<tr>
<td>Davis et al., 1993</td>
<td>13 – 20 (16.6)</td>
<td>NS</td>
<td>49</td>
<td>Study to describe stage and treatment type</td>
<td>?</td>
<td>Retrospective</td>
<td>Phoenix integrated residency program in obstetrics and gynecology, Arizona</td>
<td>Lesion type, Stage</td>
</tr>
<tr>
<td>Reese et al., 1996</td>
<td>11 - 19</td>
<td>12.5</td>
<td>67</td>
<td>To determine the incidence, clinical stage and lesion type of endometriosis</td>
<td>1992, 1994</td>
<td>Retrospective</td>
<td>Emory University Affiliated Hospital Atlanta, Georgia</td>
<td>Lesion type, Stage, Symptoms</td>
</tr>
<tr>
<td>Emmert et al., 1998</td>
<td>11 – 19 (17.3)</td>
<td>12.2</td>
<td>105</td>
<td>To determine the incidence, type, clinical stage of endometriotic lesions.</td>
<td>1996, 1997</td>
<td>Retrospective</td>
<td>Carl Thiem-Clinic and Gynecological Endoscopy Training center Cottbus Germany</td>
<td>Age, Incidence, Lesion type, Stage, symptoms</td>
</tr>
<tr>
<td>Laufer et al., 1997</td>
<td>&lt; 22</td>
<td>12.3</td>
<td>46</td>
<td>To evaluate adolescent girls with CPP not responding to medical therapy.</td>
<td>1990, 1994</td>
<td>Descriptive retrospective</td>
<td>Pediatric adolescent gynecology and reproductive endocrine academic practice</td>
<td>Stage</td>
</tr>
<tr>
<td>Kontoravdis et al., 1999</td>
<td>16-19</td>
<td>NS</td>
<td>98</td>
<td>To evaluate the role of laparoscopy as a diagnostic procedure and findings in adolescent with CPP</td>
<td>1993, 1997</td>
<td>Prospective</td>
<td>University of Athens</td>
<td>Role of laparoscopy</td>
</tr>
<tr>
<td>Bai et al., 2002</td>
<td>14 - 21 (20.1)</td>
<td>14.2</td>
<td>39</td>
<td>To evaluate the age distribution, diagnosis, clinical stage, treatment of endometriosis.</td>
<td>1990, 1999</td>
<td>Retrospective</td>
<td>Yonsei University Medical College, Korea</td>
<td>Age, Stage, Symptoms</td>
</tr>
<tr>
<td>Study</td>
<td>Age Range</td>
<td>Sample Size</td>
<td>Study Type</td>
<td>Hospital/Institution</td>
<td>Focus Areas</td>
<td></td>
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<tr>
<td>Stavroulis et al., 2005</td>
<td>13 – 20 (16.5)</td>
<td>NS 31</td>
<td>Retrospective</td>
<td>Elizabeth Garrett Anderson and Obstetric Hospital, London</td>
<td>To determine the frequency and severity of endometriosis in girls with CCP unresponsive to medical treatment.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventolin et al., 2005</td>
<td>12 - 18</td>
<td>NS 52</td>
<td>Prospective</td>
<td>Department Obstetrics and Gynecology, University, Wright University, Ohio</td>
<td>To compare mild and severe forms of endometriosis and to follow up their fecundability on long-term.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalu et al., 2008</td>
<td>15 - 21</td>
<td>NS 28</td>
<td>Retrospective</td>
<td>The Chelsea and Westminster Hospital, London</td>
<td>To describe the clinical features and treatment outcome following the laparoscopic treatment of endometriosis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doyle et al., 2009</td>
<td>12 - 24</td>
<td>NS 90</td>
<td>Retrospective</td>
<td>Two academic medical centers Boston</td>
<td>To evaluate the effect of combined surgical-medical treatment on endometriosis progression in adolescents.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Roman et al., 2010</td>
<td>17.4</td>
<td>NS 20</td>
<td>Comparative cohort</td>
<td>Braemar Hospital, Hamilton, New Zealand</td>
<td>To describe the experience with laparoscopic excision and to compare with a non-adolescent population.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vicino et al., 2010</td>
<td>≤ 21</td>
<td>NS 38</td>
<td>Prospective</td>
<td>University and General hospitals.Italy</td>
<td>To analyze the clinical manifestations of endometriosis in adolescents.</td>
<td></td>
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</tr>
<tr>
<td>TOTAL</td>
<td>10 - 24</td>
<td>11.8 - 14.2</td>
<td>Propective n=5</td>
<td>Symptom n = 6; Stage n = 11; Surgical findings n = 4; Lesion type n = 5; Age n = 3; Adhesions n = 1; Recurrence n = 1; Future fecundability n = 1; Role of laparoscopy n = 1; Incidence n = 1</td>
<td>Experience, magnitude, severity, clinical manifestations, incidence, stage, role of laparoscopy, age, lesion type among adolescents with endometriosis.</td>
<td></td>
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</tr>
</tbody>
</table>

NS: not specified
Table II. Prevalence, clinical presentation and laparoscopic classification of endometriosis in adolescents

<table>
<thead>
<tr>
<th>Main symptoms leading to laparoscopy</th>
<th>Author Year</th>
<th>Definition of pain</th>
<th>N</th>
<th>N patients with visually confirmed endometriosis/N (%)</th>
<th>N with histological confirmed endometriosis/N with visually confirmed endometriosis (%)</th>
<th>Classification N patients/total N patients with endometriosis (%)</th>
<th>rAFS (%)</th>
<th>Acosta (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1Goldstein DP et al., 1980</td>
<td>The criterion for admission was 3 separate visits to ER/clinic/consultation because of pain</td>
<td>140</td>
<td>66/140 (47%)</td>
<td>66/66 (100%)</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td></td>
<td>2Emmert et al., 1998 Kontoravdis A et al., 1999 Bai SW et al., 2002 Vicino M. et al., 2010</td>
<td>Chronic pelvic pain was defined as the presence of non-cyclic pelvic pain for ≥ 6 months.</td>
<td>105</td>
<td>37/105 (35%)</td>
<td>14/37 (38%)</td>
<td>4/39 (10%)</td>
<td>17/39 (44%)</td>
<td>11/39 (28%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98</td>
<td>24/98 (25%)</td>
<td>NA</td>
<td>7/38 (18.4%)</td>
<td>5/38 (13%)</td>
<td>13/38 (34%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>39/39 (100%)</td>
<td>39/39 (100%)</td>
<td>11/77 (14%)</td>
<td>22/77 (29%)</td>
<td>24/77 (31%)</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>420</td>
<td>204/420 (49%)</td>
<td>149/204 (73%)</td>
<td>11/77 (14%)</td>
<td>22/77 (29%)</td>
<td>24/77 (31%)</td>
</tr>
</tbody>
</table>
### CPP UNRESPONSIVE TO MEDICAL THERAPY

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Pain during 3 months</th>
<th>67/49 (73%)</th>
<th>3/67 (5%)</th>
<th>39/49 (60%)</th>
<th>6/49 (12%)</th>
<th>3/49 (6%)</th>
<th>1/49 (2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reese KA et al., 1996</td>
<td>67</td>
<td>49/67 (73%)</td>
<td>3/67 (5%)</td>
<td>39/49</td>
<td>6/49</td>
<td>3/49</td>
<td>1/49</td>
<td>2%</td>
</tr>
<tr>
<td>Laufer MR et al., 1997</td>
<td>46</td>
<td>32**/46 (70%)</td>
<td>1/32 (3%)</td>
<td>24/31**</td>
<td>7/31**</td>
<td>0/31**</td>
<td>0/31**</td>
<td></td>
</tr>
<tr>
<td>Stavroulis AI et al., 2005</td>
<td>31</td>
<td>11/31 (36%)</td>
<td>6/11 (55%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ventolin G et al., 2005</td>
<td>52</td>
<td>28/52 (54%)</td>
<td>28/52 (54%)</td>
<td>4/28</td>
<td>11/28</td>
<td>12/28</td>
<td>1/28</td>
<td></td>
</tr>
<tr>
<td>Kalu E et al., 2008</td>
<td>28</td>
<td>28/28 (100%)</td>
<td>NA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Doyle JO et al., 2009</td>
<td>90</td>
<td>90/90 (100%)</td>
<td>NA</td>
<td>74%***</td>
<td>-</td>
<td>-</td>
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### DYSMENORRHEAL

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Dysmenorrhea was defined as severe cramping uterus with concomitant abdominal pain</th>
<th>28/43 (65%)</th>
<th>18/28 (64%)</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>-</th>
<th>14/28 (50%)</th>
<th>11/28 (39%)</th>
<th>3/28 (11%)</th>
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<tbody>
<tr>
<td>Chatman DL &amp; Ward AB, 1982</td>
<td>43</td>
<td>28/43 (65%)</td>
<td>18/28 (64%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14/28 (50%)</td>
<td>11/28 (39%)</td>
<td>3/28 (11%)</td>
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<td>47</td>
<td>18/47 (38%)</td>
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<td>Davis GD et al., 1993</td>
<td>49**/49 (100%)</td>
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<tr>
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### Subtotal

| Total of main symptoms       | 893          | 557**/893 (62%)                                                          | 265/557 (48%) | 108/259 | 69/259 | 47/259 | 35/259 | 50/75 | 25/75 |

1. Measures: Mild and moderate endometriosis were counted together; **Classification score was not measured in all cases with visually confirmed endometriosis; ***No detailed information available; -: not reported; NA: Not Applicable.

2. The Kistner classification system (Kistner, Siegler et al., 1977): stage I (58%, 38/66), stage II (38%, 25/66), stage III (0%, 0/66) and stage IV (4%, 3/66).

2. Endometriosis Classification I - IV by Semm (EEC): stage I (92%, 34/37), stage II (8%, 3/37) and stage III-IV (0%, 0/37)
### Table III. Critical appraisal of the articles included in the review

<table>
<thead>
<tr>
<th>Did the study address a clearly focused issue?</th>
<th>Did authors use an appropriate method to answer their question?</th>
<th>Was the cohort recruited in an acceptable way?</th>
<th>Was the outcome accurately measured to minimize bias?</th>
<th>Have they taken account of the confounding factors in the design and/or analysis?</th>
<th>Are the results of this study clear?</th>
<th>Were results precise?</th>
<th>Do you believe the results?</th>
<th>Can the results be applied to the local population?</th>
<th>Were all important outcomes considered (policy makers, professionals, family)?</th>
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*+Yes; +/- Cannot tell; - No*
3.4. Prevalence of Menstrual Cycle-Related Pain in 12 Years Old Girls in Flanders

Anna Rijkers, M.Sc., Karel Hoppenbrouwers, M.D., Ph.D., Mathieu Roelants, M.SC., Christel Meuleman, M.D., Thomas D’Hooghe, M.D., Ph.D.

Prepared for submission
Abstract

Background: Pelvic pain is the main presenting symptom, and possibly a risk factor or even a clinical marker for endometriosis in adolescents. The prevalence of important pelvic pain related to the menstrual cycle is however not well known. Pelvic pain related to the menstrual cycle is often neglected by medical professionals, which may explain the 5 - 10 years delay between the onset of pain symptoms and the diagnosis of endometriosis.

Objective: The aim of this study was to investigate the prevalence of menstrual cycle-related pain in 12 years old girls who were resident in Flanders (the Dutch speaking northern part of Belgium).

Method: Quantitative descriptive, observational survey of pelvic pain, its relation to menstrual cycle characteristics, and its impact on quality of life in 769 12 years old girls (mean age 12.8 ± 0.3 years, range 12.2 – 13.6 years). This study is part of a larger longitudinal cohort study.

Results: In this cohort, 363 girls (47.2%) had reached menarche, of whom 41.6% (95% CI: 36.4 – 47.0%) reported painful menstruations. The likelihood of painful menstrual periods decreased approximately 50% if the age at menarche increased with a year (OR: 0.48; 0.33 - 0.68; p < 0.001). Painful menstruation was also positively correlated with the duration of the menstrual flow and the amount of blood loss. One in four girls indicated a negative impact of the menstruation on social activities, but this number was significantly higher in girls who experienced the menstruation as painful (41.3%) compared to those who did not (14.2%).

Conclusion: Painful menstruation affects more than one third of 12 years old girls in Flanders and had a negative effect on social life in more than 40% of those affected.
Introduction

Endometriosis is a gynaecological disorder defined by the presence of endometrial glands and stroma outside the uterus (Kennedy et al., 2005; Reese et al., 1996; Doyle et al., 2009). The prevalence of endometriosis is approximately 10 - 15% among women of reproductive age (Crosignani et al., 2006; Mao and Anastasi, 2010; Vigano et al., 2004) and up to 35 - 50% among women with pelvic pain, infertility, or both (Treloar et al., 2010). The exact cause of endometriosis remains unknown although many theories have been developed to explain this issue (Laufer, 2010). No single theory can explain all cases of endometriosis, and likely the etiology is multifactorial. The most popular and widely accepted theory is that of Sampson, who proposed that during menstruation, endometrial cells migrate through the fallopian tubes and implant on the surrounding pelvic structures viscera (Sampson, 1927). Endometriosis can only be diagnosed by visual inspection during laparoscopy, ideally confirmed by histology, and can present as peritoneal disease with typical or subtle lesions, ovarian endometriotic cysts (endometriomas) or DIE.

Endometriosis does not only affect adult women but also adolescent girls. According to a previous review paper, the prevalence of endometriosis varies between 25% - 38.3% in adolescents with chronic pelvic pain and dyspareunia and increases to 50% - 70% in adolescents undergoing laparoscopy for pelvic pain not responding to non-steroidal anti-inflammatory drugs (NSAID) and oral contraception (Laufer, 2003). According to a more recent systematic review (Rijkers et al., 2011) the prevalence of laparoscopically confirmed endometriosis in adolescents with pelvic pain was 62% (n = 557/893). Symptoms in adolescents may differ from adults in that they may include cyclic or acyclic (not menstruation-related) pain, irregular menses, dyspareunia, gastrointestinal symptoms, vaginal discharge, bladder dysfunction and urinary tract symptoms (Black et al., 2002; Unger et al., 2010; Laufer et al., 2003). The principal manifestation of endometriosis among teenagers is chronic pelvic pain (CPP) (Vercellini et al., 1989; Kontoravdis et al., 1999; Bourdel et al., 2006; Attaran et al., 2002) or/and dysmenorrhea (Laufer et al., 1997; Propst and Laufer, 1999; Bourdel et al., 2006). Recent evidence suggests that early dysmenorrhea is positively associated with endometriosis (Treloar et al., 2010). In an earlier study (Laufer et al., 1997), 9.4% of adolescents had the adult pattern of cyclic pain with menses, whereas 65.5% had both acyclic and cyclic pain and 28.1% had acyclic pain only (Laufer 2003). This pelvic pain can occur unpredictably and intermittently or continuously throughout the menstrual cycle, and
can be dull, throbbing, or sharp, and exacerbated by physical activity (Giudice, 2010; Broach et al., 2009).

Underestimation of pelvic pain in adolescents is a significant issue for a number of reasons. First, this pelvic pain has the potential to impact upon their lives and their uncertainty about the normality of the menstrual pattern. Young people do not like to discuss these personal and intimate complaints with their parents but rather talk to other adult persons or friends who they can trust (American Academy of Pediatrics, 2006). Second, endometriosis can only be diagnosed at laparoscopy, which is often considered as too invasive in the context of adolescent gynaecology (Pandis et al., 2009; Kalu et al., 2008; Dovey and Sanfilippo, 2010; American College of Obstetricians and Gynecologists, 2005; Gyfason et al., 2010). Third, the laparoscopic recognition is difficult because endometriosis lesions in adolescents can be less typical than in adults with the majority having minimal or mild endometriosis (Deligeoroglou and Tsimaris, 2010; Rijkers et al., 2011SR). Fourth, there is a lack of awareness among medical practitioners that endometriosis is a significant cause of pelvic pain in adolescents which contributes to delayed diagnosis (Attaran et al., 2002).

Menstrual pain complaints are the most important cause of school absences, with a possible impact on school performance and on social activities (Harel, 2006; Song and Advincula, 2005). An abnormal menstruation pattern can also become apparent later in life and have a negative influence on the health on the longer term (American Academy of Pediatrics, 2006). Complaints related to endometriosis can have a negative influence on quality of life and social relationships (Meuleman et al., 2009; Crosignani et al., 2006; Gao et al., 2006) and can also result in feelings of uncertainty (Denny, 2009).

In view of emerging evidence that endometriosis is correlated with early dysmenorrhea (Treloar et al., 2010) and that a positive family history of endometriosis and absenteeism from school during menstruation is associated with deeply infiltrative endometriosis later in life (Chapron et al., 2010), it is important to assess the prevalence of primary dysmenorrhea and other pain symptoms related to the menstrual cycle. The aim of this study was to investigate the prevalence of menstrual cycle-related pain in 12 years old girls who were resident in Flanders (the Dutch speaking northern part of Belgium).
Methods

Subjects
Participants were recruited as part of a larger multidisciplinary cohort study ('JOnG!') in eight regions in Flanders. Each region represent about 1000 births a year, and was selected according to the degree of urbanization, poverty and ethnic diversity. Parents of all 5056 girls, born in the year 1996, and officially resident of a selected region, were contacted by mail in March - June 2009 with information on the study and a request to participate. Upon agreement, both the parent and the youngster had to complete and return a questionnaire on health, development, behaviour, education and care trajectories. For girls, the questionnaire was supplemented with questions regarding the menstrual cycle and possibly associated pelvic pain. The questionnaire was returned by 792 girls (participation rate 15.7%), but 23 questionnaires were additionally excluded because none of the items related to menstruation were answered, leaving 769 subjects fit for analysis (mean age 12.8 ± 0.3 years, range 12.2 – 13.6 years).

Ethical approval
The JOnG! study was approved by the Medical Ethics Committees of the Katholieke Universiteit Leuven and of the University of Ghent on 15 December 2008 (Belgian number B32220084551).

Questionnaires
Information on the menstruation was collected with a semi-structured questionnaire. The questionnaire contained items on menarche, duration of the menstrual flow and the menstrual cycle, abundance of the menstrual flow and the presence of chunks, menstrual pain, and the impact of the menstrual period on social activities (Table I). This set of questions could be answered in 2 - 3 minutes, but completion of the full questionnaire required 30 – 60 minutes.

Statistical analysis
For the descriptive analysis, percentages are presented with a 95% confidence interval, and means with the standard deviation. Unless otherwise specified, missing answers were not taken into account. The association of painful menstruation according to characteristics of the menstruation was analyzed with simple logistic regression. The results are expressed as odds ratios with a 95% confidence interval. For the logistic regression analysis, age at menarche
was considered as a continuous variable, and duration of the menstruation, menstrual cycle and amount of blood loss as ordinal variables coded as 1, 2, 3, etc., and treated as continuous. Statistical significance was considered for p-values below 0.05. The age of menarche was estimated with probit analysis on current status (status quo) data (Finney, 1952). The mean age at menarche is the age where half of the girls have reached their menarche; the standard deviation is the reciprocal of the probit regression slope. The statistical analysis was done with R version 2.8 (R foundation for statistical computing, Vienna, Austria, 2008).

Results

Menarche
The question “Have you had your first menstrual period yet?” was answered 363 times positively (47.2%; 43.6 – 50.8%) and 406 times negatively (52.8%; 49.2 – 56.4%). The respondents who claimed to have had their first menstrual period mentioned a mean age of menarche of 11.7 ± 0.62 years (range 9 -13 years) (n = 358; 5 girls did not specify the age). Figure I shows the observed proportion of girls with menarche according to age and the proportion estimated with of the corresponding probit regression model. With probit regression, the mean age at menarche was estimated at 12.9 ± 1.3 years.

Characteristics of the menstrual cycle
The duration of menstruation during the 3 months prior to completion of the questionnaire (N = 346; 17 missing) was specified as 1 - 2 days (n = 12; 3.5%), 3-4 days (n = 104; 30.0%), 5-6 days (n = 174; 50.3%) up to more than 6 days (n = 56; 16.2%). The length of the menstrual cycle (n = 323; 40 missing) was less than 25 days (n = 50; 15.5%), 25-32 days (n = 174; 53.9%), 32-38 days (n = 52; 16.1%) or more than 38 days (n = 47; 14.6%). The amount of menstrual flow during the 3 months before completion of the questionnaire (n = 346; 17 missing) was perceived to be “average” (n = 222; 64.2%), “little (n = 58; 16.8%), or “abundant” (n = 66; 19.1%). Of the 66 girls with abundant blood loss 43 (69.4%) also mentioned also the presence of clots (four girls did not answer this question). The size of the clots was indicated 38 times as “smaller than a 1 euro coin” (approximately 23 mm in diameter), 4 times “larger than 1 euro” and 3 times not specified.
Painful menstruation
The question about painful menstruation was answered by 351 girls (12 missing), of whom 146 (41.6%; 36.4 – 47.0%) indicated history of painful menstruation, including pain starting from the first menstrual period (n = 90/143, 62.9%) or pain starting at a later age (n = 53/143, 37.1%) (3 missing). In the latter group, the painful menstruation started at the age of 11 years (n = 9; 17.6%), 12 years (n = 32; 62.7%), or 13 years (n = 10; 19.6%). On two questionnaires this age was not specified. When the menstruation was not painful from the start, this occurred at the same age as menarche (n = 22), or one (n = 27) or two (n = 2) years later (2 missing).

The relation between painful menses and a number of characteristics of the menstruation are listed in Table II. The likelihood of painful menstrual periods decreased approximately 50% if the age at menarche increased with a year (OR: 0.48; 0.33 - 0.68; p < 0.001). The prevalence of painful menstruation also increased with the average duration of the menstruation (p < 0.01) and with the amount of blood loss (p < 0.001), but not with menstrual cycle length or the presence of blood clots (Table II).

Impact of menstruation on quality of life during the 3 months before completion of the questionnaire
A total of 87 girls (25.4%) mentioned a negative impact of the menstruation on social activities (21 girls did not answer this question). The type of activity that was specified was missing school (n = 11), not being able to do sports (n = 60), not being able to do things with friends (n = 18), and other (n = 6) (multiple answers per respondent may apply). Five girls did not specify the activity, and 10 girls gave two or more answers. A negative impact on social life was reported more frequently by girls with painful menstruation (n = 59/143; 41.3%) than by those without painful menstruation (n = 27/190; 14.2%, p < 0.001) (30 girls did not answer both questions).

Discussion
In this study, we reported a high prevalence of painful menstruation in young girls aged 12 - 13 years, which is often associated with negative effects on quality of social life. We also observed that the likelihood of painful menstrual periods is higher in girls with a younger age at menarche, a longer duration of the menstruation and more abundant blood loss.
The design of our study is marked by several strengths. Firstly, recall bias was limited in this study as most of the retrospective data were related to activities occurring during the last three menstrual cycles. Secondly, the adolescents participating in the JOnG!-study will be followed with additional yearly questionnaires during the next 3 years, which will allow a follow-up of the prevalence of painful menstruation and its impact on social life in this cohort longitudinally. Thirdly, the sample size for this survey was fairly large and representative for Flanders, as eligible participants came from eight different representative and geographically defined Flemish regions covering a wide socioeconomic range.

A limitation of our study was the low participation response (15.6%) in completing and returning the JOnG! questionnaire, possibly because the questionnaire is fairly long (30 pages) and deals with various aspects of health, development, behaviour, education and care and these issues may not be of primary interest to 12 - 13 years old children. The external validity of our study remains to be proven, as eligible participants were 12 years old girls resident in Flanders (the Dutch speaking northern part of Belgium).

The mean menarchal age reported by the girls participating in this study, 11.7 ± 0.62 years, was considerably lower than the average menarchal age in Flanders (13.13 ± 1.3 years, Roelants, Hauspie, & Hoppenbrouwers, 2009), as it includes only those girls who already had their menstruation at the moment of this study, and is therefore biased downwards. For this reason age at menarche was estimated by probit analysis on status presence data, which indicates a more realistic mean age at menarche of 12.9 ± 1.3 (Figure I). This estimate of menarchal age is in agreement with results reported in other studies. Indeed, menarchal ages of 13.1 - 13.5 and 12.0 - 12.6 years have been reported for Northern European and Southern European countries (France, Italy, Spain, and Greece), respectively (Parent et al. 2001). It has been suggested that menarche tends to appear earlier in life as the sanitary, nutritional and economic conditions of a society improve (Kaplowitz, 2006; Zegeye et al., 2009) or that biological, cultural and social factors could influence the menstrual pattern (Zhu et al., 2010), with a higher menarchal age (p < 0.001) in Chinese girls (14.2 ± 1.4) than in Australian girls (12.7 ± 1.5) (Zhu et al., 2010).

Menstrual pain was positively correlated with other menstrual characteristics in our study. The strongly positive (p = 0.009) correlation between menstrual pain and duration of the bleeding period observed in our study was also reported in other studies (Balbi et al., 2000;
Zegeye et al., 2009). Our observation of a significant correlation between painful menstruation and the heaviness of flow \( (p < 0.001; \text{Table II}) \) also confirms previous research showing a significant correlation between menstrual flow and intensity of pain \( (r = 0.19, p = 0.003) \) (Zhu et al., 2010). Interestingly, our study did not show a correlation between menstrual pain and presence of blood clots \( (p = 0.8) \), which is consistent with previous data (Zhu et al., 2010). Moreover, it is also possible that it is not even clear for teenagers what was meant by of little or abundant blood loss as even adult women experience a number of uncertainties about whether or not their bleeding is heavy (Garside et al., 2008). Women usually define their periods as ‘heavy’ based on a change from previous experience in amount, duration or frequency and this change is a key, in deciding whether their experience is normal, or more severe than normal (Garside et al., 2008). This change is still unclear for 12 years old girls since they lack the historical perspective. Also the objectively measuring menstrual blood flow when relying on self-reporting is difficult given its variability and the variety of sanitary products available (Zhu et al., 2010). In our present study, both the girls with average-and abundant blood loss, indicate the presence of clots.

Primary dysmenorrhea was defined as painful menstruation and is characterized by crampy pelvic pain beginning shortly before or at the onset of menses and lasting one to three days. The prevalence of painful menstruation of 40% in our study is somehow lower than the prevalence reported in older girls (review presented in Table III) probably because the age of our study participants was lower than the age of adolescents participating in the studies list in Table III.

Our observation that the prevalence of painful menstruation decreased with later onset of the menarche \( (p < 0.001) \) is consistent with earlier research findings. Firstly, a significant association was found between menarche age and the severity of primary dysmenorrhea. Early menarche was related to an increase in the severity primary dysmenorrhea (Balbi et al., 2000). Secondly, a positive association has been observed between earlier menarche age and greater intensity of menstrual pain \( (p < 0.05. \text{in Chinese girls (Ge et al., 2003; Zhu et al., 2010). Thirdly, menarche after age of 14 years was strongly and inversely associated with endometriosis (odds ratio, 0.3; 95% confidence interval, 0.1 – 0.6), whereas the risk for endometriosis was increased in women who had early onset dysmenorrhea when they were girls (Treloar et al. 2009).} \)
Our study revealed an important impact of dysmenorrhea on various aspects of social life among 12-13 years old girls. Overall, one of four respondents (25%) reported a negative influence on the social life. The type of activity that was specified was missing school (n = 11), not being able to do sports (n = 60), not being able to do things with friends (n = 18), and other (n = 6) (multiple answers per respondent may apply). A negative impact on social life was reported more frequently by girls with painful menstruation (59/143; 41.3%) than by those without painful menstruation (27/190; 14.2%, p < 0.001). Our data confirm earlier reports that negative experiences regarding menstruation were associated with higher rates of school absenteeism (p = 0.0790) and missed activities (p = 0.0297) (Houston et al., 2006).

The school absenteeism rate in our study was similar to the rate previously reported in 12 - 17 years old girls (14%, Klein and Litt, 1981), lower than the rate reported in 12 - 21 years old girls (46%, Johnson et al., 2006), and higher than the rate reported in girls with mean age of 20.745 ± 1.823 years (16.731 – 26.902 years) (6%, Cakir et al., 2007). Dysmenorrhea is a major cause of activity restriction and school absence in adolescent girls (Davis et al., 2001). In a questionnaire study of 182 U.S. high school girls, 59% reported that cramps caused them to be less active, 45% reported ever missing school or work due to cramps, and 40% reported missing class in the past year due to cramps (Johnson, 1988). In a sample of Swedish school girls ages 14 – 19 yr, 15% reported being unable to participate in normal activities, 10% reported school absence. (Svanberg et al., 1980). In a prospective cohort study among first year university students aged 17 - 19 years (Harlow et al., 1996), menstrual pain led to ever missing school in 25% of subjects. In a review paper (Song and Advincula, 2005) the prevalence of school absence due to dysmenorrheal varied between 10 - 25% at an age group of 12 - 19 years, and was about 48% in the age group 14 - 19 years. Logically, absence of school seemed to be more prevalent among adolescents (14 - 19 years) with moderate to serious dysmenorrhea (68%) than those with mild dysmenorrheal (43.4%) (Zegeye et al., 2009).

Some of the participants of our study are very likely to develop endometriosis, as dysmenorrheal, heavy menstrual bleeding and early menarche can be considered to be risk factors for endometriosis (Treloar et al., 2009; Chapron et al., 2010). Adolescent care providers should explain the menstrual cycle, menstruation associated symptoms, and physiologic etiology of dysmenorrhea to every girl who suffers from menstrual cramps and/or other menstruation associated symptoms. Adolescent girls with significant pelvic pain should
be asked about age at menarche, menstrual pattern, onset and character of menstrual cramps and other menstruation associated symptoms like school absenteeism, and family history of menstrual disorders (Chapron et al., 2010; French, 2005).

**Conclusion**

It becomes clear that menstrual-related complaints occur more often among adolescent girls than generally thought. Painful menstruation affects about one in five 12 years old girls in Flanders and frequently results in a negative impact on social activities. These above mentioned data indicate a considerable need for tools that can accurately assess menstrual cycle related pain symptoms in at-risk adolescent girls.

Given the fact that recent evidence showed that endometriosis is correlated with early dysmenorrhea (Treloar et al., 2010), a positive family history of endometriosis and absenteeism from school during menstruation is associated with deeply infiltrative endometriosis later in life (Chapron et al., 2010), it is important to focus in future research on determining optimal approaches of identifying a possible endometriosis as soon as possible. These approaches should be integrated into routine developmental surveillance practices of healthcare workers who take care for adolescent girls. In this way an early diagnosis of endometriosis can be made, adolescents can be referred to an expert centre and an appropriate treatment can be established.

**Declaration of interest/funding**

The authors report no conflicts of interest. This investigation was conducted with the support of the clinical research fund UZ Leuven, the fund for research Flanders, and the particular research fund KU Leuven. The JOnG! cohort study was conducted in the framework of the Policy Research Centre of Welfare, Public Health and Family, funded by the Flemish Government.
References


Denny E (2009) I never know from one day to another how I will feel: pain and uncertainty in women with endometriosis. Qual Health Res, 19, 985-995.


Figure 1. Cumulative proportion of girls with menarche according to age. Bars indicate the observed proportion of girls with menarche in each age group; the line shows the cumulative distribution curve estimated with probit regression.
Table I. Questions related to menarche, pelvic pain and menstrual cycle characteristics, integrated in the JOnG! questionnaire, 2009

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<tr>
<th>Question</th>
<th>Response Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you had your first menstrual period yet?</td>
<td>(Yes / No)</td>
</tr>
<tr>
<td>2. At what age did you have your first menstrual period?</td>
<td>(Number of years)</td>
</tr>
<tr>
<td>3. Had you ever or now menstrual pain?</td>
<td>(Yes/No)</td>
</tr>
<tr>
<td>If yes, since when?</td>
<td>(From my first period onwards/From the age of…..years)</td>
</tr>
<tr>
<td>4. On average, what was the number of days of menstrual flow during the last 3 months?</td>
<td>(1 or 2 / 3 or 4 / 5 or 6 / More than 6)</td>
</tr>
<tr>
<td>5. On average, what was the number of days of your menstrual cycle during the last 3 months?</td>
<td>(Less than 25 / 25 to 32 / 38 to 45 / More than 45)</td>
</tr>
<tr>
<td>6. How abundant was your menstrual flow during the last 3 months?</td>
<td>A little / Average / A lot</td>
</tr>
<tr>
<td>If a lot: chunks present?</td>
<td>(Yes / No)</td>
</tr>
<tr>
<td>If chunks present, How big?</td>
<td>(Smaller than a 1 Euro coin, Bigger than a 1 Euro coin)</td>
</tr>
<tr>
<td>7. Have you experienced a negative influence on social life because of your menstruation during the last 3 months?</td>
<td>(Yes / No)</td>
</tr>
<tr>
<td>If yes, tick: (Missing school / nor being able to do sports / Nor being able to do things with friends / Other: …)</td>
<td></td>
</tr>
</tbody>
</table>
Table II: Prevalence of painful menstruation according to age at menarche and characteristics of the menstrual cycle (logistic regression)

<table>
<thead>
<tr>
<th></th>
<th>Total number</th>
<th>Painful menses (percentage)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at menarche</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>0/1 (0%)</td>
<td>0.48 (0.33 – 0.68)**</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>7/10 (70%)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>105</td>
<td>57/105 (54.3%)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>215</td>
<td>81/215 (37.7%)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>17</td>
<td>1/17 (5.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of menstruation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 2 days</td>
<td>11</td>
<td>2/11 (18.2%)</td>
<td>1.68 (1.24 – 2.30)**</td>
</tr>
<tr>
<td>3 – 4 days</td>
<td>98</td>
<td>33/98 (33.7%)</td>
<td></td>
</tr>
<tr>
<td>5 – 6 days</td>
<td>172</td>
<td>73/172 (42.4%)</td>
<td></td>
</tr>
<tr>
<td>7 days or more</td>
<td>56</td>
<td>33/56 (58.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of the menstrual cycle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25 days</td>
<td>49</td>
<td>23/49 (46.9%)</td>
<td>0.92 (0.75 – 1.14)</td>
</tr>
<tr>
<td>25 tot 32 days</td>
<td>171</td>
<td>79/171 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>32-38 days</td>
<td>51</td>
<td>19/51 (37.2%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 38 days</td>
<td>46</td>
<td>20/46 (43.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Amount of menstrual blood loss</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little</td>
<td>56</td>
<td>7/56 (12.5%)</td>
<td>5.0 (3.17 – 8.24)**</td>
</tr>
<tr>
<td>Average</td>
<td>214</td>
<td>83/214 (38.7%)</td>
<td></td>
</tr>
<tr>
<td>Abundant</td>
<td>66</td>
<td>51/66 (77.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Presence of clots</strong></td>
<td>62<strong>ab</strong></td>
<td></td>
<td>1.35 (0.36 – 4.66)</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>14/19 (73.7%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
<td>34/43 (79.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*excluding missing: age at menarche (n = 15), duration of menstruation (n = 26), length of cycle (n = 46), amount of blood loss (n = 27), presence of clots (n = 4)

**only applies for girls with abundant blood loss

*** simple logistic regression: p < 0.001
<table>
<thead>
<tr>
<th>Author /year</th>
<th>Country</th>
<th>Sample (n)</th>
<th>Age (range in years)</th>
<th>Prevalence of dysmenorrhea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Art et al., 2010</td>
<td>Austria</td>
<td>255</td>
<td>9-16</td>
<td>29</td>
</tr>
<tr>
<td>Svanberg et al., 1981</td>
<td>Sweden</td>
<td>502</td>
<td>10 - 19</td>
<td>43</td>
</tr>
<tr>
<td>Agarwal &amp; Venkat, 2009</td>
<td>Singapore</td>
<td>5561</td>
<td>12 - 19</td>
<td>83.2</td>
</tr>
<tr>
<td>Klein et al., 1981</td>
<td>US</td>
<td>2699</td>
<td>12 - 17</td>
<td>60</td>
</tr>
<tr>
<td>Zegeye et al., 2009</td>
<td>Ethiopia</td>
<td>612</td>
<td>14 - 19</td>
<td>72</td>
</tr>
<tr>
<td>Campbell &amp; McGrath, 1997</td>
<td>Canada</td>
<td>291</td>
<td>14 - 21</td>
<td>93</td>
</tr>
<tr>
<td>Parker et al., 2010</td>
<td>Australia</td>
<td>1051</td>
<td>14.75 – 19.25</td>
<td>93</td>
</tr>
<tr>
<td>Chan, 2009</td>
<td>Hong Kong</td>
<td>5609</td>
<td>15.1</td>
<td>68.7</td>
</tr>
<tr>
<td>Wilson &amp; Keye, Jr., 1989</td>
<td>US</td>
<td>88</td>
<td>15</td>
<td>91</td>
</tr>
<tr>
<td>Robinson et al., 1992</td>
<td>US</td>
<td>308</td>
<td>16</td>
<td>79.6</td>
</tr>
<tr>
<td>Hillen, et al, 1999</td>
<td>Australia</td>
<td>384</td>
<td>15 - 17</td>
<td>80</td>
</tr>
<tr>
<td>Banikarim et al., 2000</td>
<td>US</td>
<td>706</td>
<td>16</td>
<td>85</td>
</tr>
<tr>
<td>Harlow &amp; Park, 1996</td>
<td>US</td>
<td>165</td>
<td>17 – 19</td>
<td>71.6</td>
</tr>
<tr>
<td>Andersch &amp; Milsom, 1982</td>
<td>Sweden</td>
<td>596</td>
<td>19</td>
<td>72</td>
</tr>
<tr>
<td>Cakir et al., 2007</td>
<td>Turkey</td>
<td>391</td>
<td>20.75</td>
<td>89.5</td>
</tr>
<tr>
<td>Eryilmaz et al., 2010</td>
<td>Turkey</td>
<td>1951</td>
<td>13 - 18</td>
<td>68.1 – 72.2</td>
</tr>
<tr>
<td>Ortiz, 2010</td>
<td>Mexico</td>
<td>1539</td>
<td>20.4 ± 2.0</td>
<td>62.4</td>
</tr>
</tbody>
</table>
3.5. The Prevalence of Complains Suggestive for the Presence of Endometriosis in Adolescents and Young Adults

Christel Meuleman, M.D., Marie Elisabeth Smet, M.D., Mariet Vandersanden, M.Sc., Steffen Fieuws, Ph.D., Maura Sisk, M.D., Veerle Van Gerven, M.D., Karel Hoppenbrouwers, M.D., Ph.D., Thomas D’Hooghe, M.D., Ph.D.

Prepared for submission
Abstract

Aim of the study: Adults with extensive endometriosis often mention during history taking, that cycle related complaints started during adolescence or young adulthood. The purpose of this study was to determine the prevalence of complaints suggestive for the presence of endometriosis in adolescents and young adults.

Materials and methods: In a questionnaire-based quantitative study with descriptive-observational cross-sectional research design, 172 adolescents (13 - 16 years) and 1028 young adults (17-21 years) completed an online questionnaire.

Results: The prevalence of frequently perceived dysmenorrhea was 40% (adolescents) and 52% (young adults), which was associated with severe pain (VAS score ≥ 7) in 17% (adolescents) and 16% (young women). The prevalence of frequently perceived lower back pain during menstruation was 25% (adolescents) and 37% (young adults), which was associated with severe pain (VAS score ≥ 7) in 8% (adolescents) and 13% (young women). Relief for menstrual pain was the indication for use of OCPs in 44% (adolescents) and 39% (young adults). However, menstrual pain was resistant to OCPs or painkillers (4% adolescents and 5% young adults) and to the combination of OCPs and painkillers (1% adolescents and 3% young adults). An impaired QOL caused by menstrual cycle related discomfort was observed in 11% of adolescents and 12% of the young women.

Conclusions: The data from our study demonstrate that both adolescent girls and young adults experience severe discomfort due to menstrual cycle related pelvic and back pain, associated with reduced QOL. Additional gynaecological investigation, including diagnostic laparoscopy could be recommended to those with pain not responsive to treatment with either NSAIDs and/or hormonal contraception.
Introduction

Endometriosis, first described by von Rokitansky in 1860, is a gynaecological disease in which endometrial glands and stroma are located outside the endometrial cavity (Laufer et al., 2003; French, 2008). Due to the influence of ovarian hormones, the ectopic endometrial tissue monthly grows and starts to bleed (Koninckx et al., 1991; Vercellini et al., 1997). It can be located at nearly any place in the body, but most often in the pelvis. This disorder affects approximately 7 - 10% of women worldwide (Baldi et al., 2008), is strongly associated with pelvic pain and infertility, and can affect any woman in the reproductive age, regardless of ethnic, social or cultural background. Endometriosis does not exclusively affect adult women. Studies report that the prevalence of endometriosis among adolescents varies between 17 - 73% (Bulun, 2009; Laufer, 2008; Pandis et al., 2009). However, a single case can be found describing the occurrence of endometriosis in premenarcheal girls (Marsh and Laufer, 2005). Symptoms may vary between adults and adolescents. Adults commonly indicate symptoms like severe dysmenorrhea, menorrhagia, dyspareunia, cyclical mictalgia and dyschezia, sub- and infertility (De Hondt et al., 2006). Meanwhile, in adolescents isolated cyclic pain is less common and the most frequent presentation of endometriosis consists of a chronic pelvic pain, meaning pelvic pain occurring in the menstrual and non-menstrual phase and lasting up for more than 6 months (Laufer et al., 1997). Dyspareunia and infertility are obviously not mentioned by adolescents or young women.

The first step to the diagnosis of endometriosis is to understand and to recognize the disease throughout a careful history and clinical examination. In case of cystic ovarian endometriosis, ultrasound can confirm the diagnosis. Unfortunately, the mainstay of diagnosis still consists of visual diagnosis of endometriosis during laparoscopy or laparotomy and histological confirmation of the excised lesions (Kennedy et al., 2005 - ESHRE Guidelines). Laparoscopic appearance of endometriosis can vary between peritoneal lesions, cystic ovarian endometriotic cysts and deeply invasive endometriosis with extension to bowel and urological organs. According to the American Society of Reproductive medicine, endometriosis can be classified, depending on location, depth of the implants, presence and severity of adhesions or ovarian endometriomas, in 4 stages (stage I - minimal, II - mild, III - moderate and IV - severe endometriosis) (Attaran et al., 2002; rAFS, 1997).

When questioning women with endometriosis, they generally admit to be suffering for many years. In 1998, the Endometriosis Association registered the data of 4000 adult women with
endometriosis, showing that 78% of them experienced their first symptoms before 20 years of age and 38% even before the age of 15. Also, the condition seems to be more severe with an earlier onset (Arvanitis et al., 2003): dysmenorrheal and pelvic pain at a young age have been identified as risk factors for (advanced) endometriosis later in life (Treloar et al., 2010; Chapron et al., 2010). Moreover there is suggestive evidence that endometriosis is a dynamic and moderately progressive disease with the majority of patients having AFS classification stage I or II disease when diagnosed at young age (Koninckx et al., 1991). In view of the fact that endometriosis is a progressive disease in a substantial group of women (at least 50%) (Kyama et al., 2007), it is reasonable to state that diagnosis and treatment at an early stage of minimal to mild endometriosis would reduce the incidence of severe endometriosis at later age, improve reproductive outcome and QOL (Koninckx et al., 1991). Unfortunately, there seems to be a big delay between the onset of symptoms and diagnosis of endometriosis, especially in our youngsters. In girls younger than 19 years old, the time interval between symptoms and visit to a physician was 2 years, and it took another 9 years to make a surgical diagnosis of endometriosis (Arruda et al., 2003). This is partly explainable by the fact that young girls might feel uncomfortable reporting symptoms as dyspareunia, but in particular because physicians fail to recognize dysmenorrhea in the younger population as a possible expression of an underlying disease and tend to classify it as a physiological condition. In women aged 30 or more, generally less time expires before being diagnosed, with a median interval of 3.3 years (Arruda et al., 2003).

Dysmenorrhea is the most common cause of recurrent school delay (French, 2008; Emmert et al., 1998) and impaired school, social and sportive activities. Therefore, it is worth considering early diagnosis of endometriosis between 15 and 18 years with significant dysmenorrhea or other pelvic pain symptoms associated with the menstrual cycle, especially if these symptoms are refractory to pain killers and/or hormonal treatment with oral contraception. The main purpose of this survey was to document the prevalence of menstrual and non-menstrual pain problems suggestive for the presence of endometriosis and their effect on QOL in adolescents and young adults.
Materials and methods

Study design
This study was devised as a questionnaire-based quantitative study with descriptive-observational cross-sectional research design. The protocol for this study (Clinical Trials.gov ID: NCT00590811) was approved by the Ethical Commission of Leuven University.

Participants and setting
The study was conducted between November 2007 and January 2010 in female adolescents and young women (first year university students from the University of Leuven).

Female adolescents from the 3rd year of 4 junior high schools in Leuven (Paridaens Instituut, Sint-Pieterscollege, Heilig Drievuldigheidscollege and Mater Dei Instituut), which were connected with the vCLB Leuven (Vrij Centrum voor Leerlingenbegeleiding, Free Centre for Student Guidance, Leuven), were all eligible for participation in this study. Study information and informed consents were sent by letter to these students and their parents, prior to the required visit to the CLB Leuven. The parents decided whether their daughter could participate to this study and signed the informed consent form. When the adolescents were visiting the center, informed consents were gathered and the physicians invited the participating girls one by one to fill in the online questionnaire using a computer with exclusive access to the website of the survey. Pre-menarcheal adolescents were excluded from the study.

Young female adults eligible for this study (first year university students) were informed about this survey when they visited the Student Doctor Office of Leuven University for their medical examination. After completion of an informed consent form and deposition of this form in the Student Doctor Office, the students filled in the questionnaires in the waiting room either before or after their medical examination using 2 computers with exclusive access to the website of the survey.

Questionnaire
A quantitative, descriptive observational survey was used to document the prevalence of menstrual cycle related pain symptoms in young adults and adolescents (Appendix I). The questionnaire consisted of nine questions, referring to several topics such as the menogram (cycle length, amount of blood loss, and influence on QOL), gynaecological pain, as well as
the use of hormonal contraceptives and/or pain killers. Furthermore, we investigated whether or not the girls consulted a physician for their specific complaints. Three additional questions about sex-related problems were included for the young adults.

Most questions were to be answered by ‘never’, ‘sometimes’, ‘often’, ‘mostly’ or ‘always’. Specific questions about menstrual or non-menstrual pelvic pain and lower back pain contained Visual Analogue Scales to evaluate the severity of pain. The survey was completed electronically and took about 10 minutes to complete.

Statistical analysis
The primary outcome variable of this study was the prevalence of pain symptoms that were perceived to be severe (VAS ≥ 7) and/or to occur frequently. A frequently occurring pain symptom was defined as a pain symptom which occurred 'often', 'mostly' or 'always'). The secondary outcome variable was the prevalence of pain symptoms unresponsive to NSAIDs and/or OCP treatment.

Non-parametric tests were applied to evaluate the normal distribution of the data. Mann-Whitney U tests were used to compare ordinal, continuous and dichotomous variables. To assess the relation between categorical variables, Fisher Exact Tests were performed. The p-values were cut-off at a significance level of 0.001 and 0.05. Analyses were performed using SAS software, version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). A latent variable model was fitted using the ltm package in R (Bartholomew et al., 2002; Rizopoulos, 2006).

Results
Adolescents
In total, 172 adolescents (mean age 15.2 ± 6.88 years) participated to this study. They reported a mean age at menarche of 12.5 ± 0.96 years. Eighteen girls (10.4%; n = 18/172) actually used hormonal contraception. The mean age to start pill use was 14.6 ± 1.59 years. Hormonal contraception was taken for decreasing pain symptoms in 44% (n = 8/18) and mitigation of premenstrual syndrome in 22% (n = 4/18) of the girls using hormonal contraception (Table I). The reported average length of cycle was 25 to 32 days (57%; n = 98/172), menstruation generally lasted for 5 to 6 days (57%; n = 98/172) (Table II).
Abundant periods appeared in 14% (n = 25/172) of the adolescents. In this group, 5.8% (n = 10/172) mentioned loosing blood clots.

**Pelvic Pain**

During menstruation, frequently perceived pelvic pain was observed in 40% (n = 68/172) of the participants, especially on the first and second day of menstruation (Table III). Nineteen (n = 19/172, 11%) of the youngsters suffered from dysmenorrhea during the entire menstruation. The mean VAS score of the girls with complaints was 4.34, with a VAS score ≥ 7 among 22% (n = 38/172) of the girls. Frequently perceived dysmenorrhea was associated with severe pain (VAS score ≥ 7) in 17% (n = 30/172) of the adolescents. To relieve their symptoms, 38% (n = 66/172) among them used analgesics without prescription and 6.4% (n = 11/172) with a prescription of a physician.

In the non-menstrual phase, 8.7% (n = 15/172) of the girls reported pelvic pain with an average VAS score of 3.23 and 10% (n = 17/172) reporting a score ≥ 7 (Table III). The percentage of girls with frequently perceived pelvic pain and a high VAS score (≥ 7) was 2.3% (n = 4/172). Painkillers were needed without a prescription among 10% (n = 18/172) of the girls, while 2.3% (n = 4/172) of them used analgesics requiring a prescription.

**Lower back pain**

During menstruation, lower back pain was frequently present in 25% (n = 43/172) of the respondents, mostly on the first day of menstruation, with a mean VAS score of 4 and a score ≥ 7 in 8.7% (n = 15/172) of the adolescents (Table III). Severe cyclic lower back pain (VAS ≥ 7) occurred with a frequent pattern in 8.1% (n = 14/172) of the respondents. Analgesics without prescription were used in 15% (n = 25/172) of the cases, whereas a prescription was needed in 3.5% (n = 6/172) of the girls.

In the non-menstrual phase of the cycle, 12% (n = 21/172) of the adolescents experienced lower back pain frequently, with an average VAS score of 3.63 and a score ≥ 7 in 7.0% (n = 12/172) of them (Table III). 14% (n = 24/172) of the girls asked for painkillers without and 9.3% (n = 16/172) with a prescription to relieve their pain.

**QOL**

In general, menstruation had a negative influence on QOL in 33% (n = 56/172) of the studied population (Table IV). 12% (n = 20/172) of the girls reported this symptoms to occur.
frequently. Symptoms varied from feeling ill (51%; n = 87/172), over nausea (47%; n = 81/172) to fatigue and loss of energy (59%; n = 102/172). Seven individuals (4.1%; n = 7/172) mentioned these 3 symptoms occurring frequently.

Even in the non-menstrual period, the QOL was impaired by illness (13%; n = 22/172), nausea (41%; n = 70/172), fatigue and loss of energy (46%; n = 79/172). Two of these symptoms co-existed frequently in 3 girls (1.7%).

**Urological symptoms**

During menstruation, urological problems existed frequently among 26% of the youngsters (n = 45/172). The main problems were polyuria (17%; n = 30/172) and (partial) retention (16%; n = 27/172) (Table IV). Urological problems existed less frequently in the non-menstrual period than during the menstrual period (Table IV). Most of the girls (8.1%, n = 14/172) suffered only from one single urological problem.

**Intestinal symptoms**

When questioning the girls about bowel symptoms during menstruation, 24 (14%; n = 24/172) of them mentioned complaints appearing frequently (Table IV). The most frequently reported symptoms were polydefecation (6.4%; n = 11/172), dyschezia (5.2%; n = 9/172) and troubles postponing defecation in 4.1% (n = 7/172). In the non-menstrual period, less symptoms were reported than in the menstrual period with nineteen girls (11%; n = 19/172) suffering from 1 or more intestinal symptoms.

**Physician Consultation**

To relieve their complaints, 13% (n = 23/172) of the adolescents needed medical help during menstruation, while the presence of symptoms on the non-menstrual period prompted 11% (n = 18/172) of the teenagers to consult a physician.

**Number of complaints**

We observed that severe cyclic complaints were mostly limited to a single problem (21%; n = 6/172). However, 53 respondents (31%; n = 53/172) indicated they had to face 3 or more issues. A comparable pattern was observed in the non-menstrual phase with 37 (21.5%; n = 7/172) and 15 (8.7%; n = 15/172) participants coping with only 1 symptom or three or more problems, respectively.
Overall, 69% of the studied subjects (n = 118/172) experienced cycle related complaints, with the majority experiencing not more than two symptoms (58%; n = 99/172), while 73 of them (42%) had to stand three or more symptoms. Despite the use of hormonal treatment, 9 (50%; n = 9/18; p = 0.450) and 8 adolescents (44.4%; n = 8/18; p = 0.576) still showed severe and frequent symptoms during menstruation and their non-menstrual period, respectively.

Hormonal contraception
The correlation of the use of hormonal contraception and the appearance and severity of the different symptoms, including pelvic pain, lower back pain, QOL, urological and intestinal symptoms was calculated. These calculations were made for the use of hormonal contraception during the menstrual period and the non-menstrual phase. No statistically significant difference was observed in frequency or intensity of any of the symptoms between the girls using hormonal contraception and those who did not.

In the girls using hormonal contraception, dysmenorrhea and lower back pain during menstruation still occurred more than sometimes with a VAS-score of ≥ 7 among 6 girls (n = 6/18; 33%; p = 0.177). In the non-menstrual phase, only pelvic pain was reported more than sometimes with a VAS-score of ≥ 7 in 4 girls (n = 4/18; 22%; p = 0.061). Despite prior therapy consisting of painkillers and/or hormonal contraception, chronic pelvic pain was reported by 2 (1.2%) and 7 (4%) girls, respectively. Cyclic pelvic pain not responsive to painkillers and/or hormonal contraception was mentioned by 3 (1.7%) and 30 (17.4%) girls respectively.

Young adults
1028 young adults (mean age 19 years ± 5.32) participated to this study. The group of young adults reported their mean age at menarche to be 13 ± 1.36 years. Hormonal contraception (pill, ring or patch) was used by 94% (n = 969/1028) of them, with 681 participants currently using it (Table I). The age at start was generally 16 ± 1.30 years. Hormonal methods were used mainly as contraception (76%; n = 516/681) and to treat dysmenorrhea (39%; n = 266/681) (Table I). The average cycle length was 25 to 32 days, reported by 794 young adults (77%; n = 794/1028) (Table II). Most of the girls (53%; n = 548/1028) menstruated during 5-6 days, but 7.4% (n = 76/1028) experienced a menstruation length of more than 6 days. The prevalence of abundant periods was 9% (n = 92/1028). 41 girls (4%; n = 41/1028) reported bleeding with big clots.
Pelvic pain

Pelvic pain occurred frequently in 52% (n = 530/1028) of the interviewees during menstruation, mostly on the first and second day (44%; n = 457/1028), while 6.4% (n = 66/1028) of the young adults reported pelvic pain during the entire menstruation cycle (Table III). Taken into account only those girls with complaints, the mean VAS score was 4.56 and 186 girls (18%; n = 186/1028) reported a VAS score ≥ 7. A total of 165 girls (16%; n = 165/1028) suffered frequently from their complaints with a VAS score ≥ 7. In order to control their menstrual pain symptoms, 6.7% (n = 69/1028) of the girls needed analgesics with and 39% (n = 396/1028) of them without a prescription.

Non-menstrual pelvic pain existed frequently among 78 of the questioned women (7.6%; n = 78/1028) (Table III) and 5.4% (n = 55/1028) of the women reported ≥ 7 on the VAS scale with a mean score of 3.83. The number of women with frequent complaints combined with a high VAS score (≥ 7) was 10% (n = 107/1028). Non-menstrual pelvic pain forced 21 women (2.0%; n = 21/1028) to take prescription analgesics whereas 83 participants (8.1%; 83/1028) used over-the-counter analgesics.

Lower back pain

During menstruation, lower back pain was frequently reported by 37% of the girls (n = 382/1028); 85 girls were symptomatic during the entire menstruation cycle (Table III). The average VAS score was 4.2 and a score of ≥ 7 was indicated by 140 girls (14%; n = 140/1028). The frequent existence of lower back pain with a VAS score of ≥ 7 was reported in 129 women (13%; n = 129/1028). During menstruation, 13% (n = 135/1028) of the young women tried to relieve lower back pain using analgesics without and 27 youngsters (2.6%; n = 27/1028) with a prescription.

During the non-menstrual period, 15% of the young adults (n = 157/1028) frequently had lower back pain with a mean VAS score of 1.32. 101 (9.8%; n = 101/1028) teenagers reported a VAS score of ≥ 7. The appearance of lower back pain more than sometimes with a VAS score of ≥ 7 was reported by 75 participants (7.3%; n = 75/1028) apart from menstruation. Only 48 women (4.7%; n = 48/1028) asked for analgesics without while 14 women (1.4%; n = 14/1028) used prescription-free analgesics.
QOL
The appearance of painful menstruation reduced the QOL among 11% (n = 113/1028) of the women in the menstrual period (Table IV). There were 530 women (52%; n = 530/1028) who felt ill and 409 women (40%; n = 409/1028) who were nauseous while menstruating. Up to 121 young adults (12%; n = 121/1028) named the co-occurrence of more than three symptoms. In the non-menstrual period, 144 girls (14%; n = 144/1028) mentioned an impaired QOL, due to cycle-related problems. Only 23 (2.2%; n = 23/1028) girls reported more than three symptoms affecting them.

Urological symptoms
During menstruation, the most frequent urological disturbances included polyuria (16%; n = 161/1028), urgency for micturition (7.6%; n = 78/1028) and nycturia (7.2%; n = 74/1028) with 234 girls (22.8%; n = 234/1028) suffering from one or more different urinary problems (Table IV). During the non-menstrual days, the most frequently reported urological symptoms were the same as during menstruation: polyuria (2.3%; n = 24/1028), urgency for micturition (3.7%; n = 38/1028) and nycturia (7.2%; n = 74/1028). In 11.3% (n = 116/1028) of the studied, all of the former symptoms acted together (Table IV).

Intestinal symptoms
During menstruation, girls complained about an incomplete (6.0%; n = 62/1028) or difficult (5.5%; n = 57/1028) defecation, polydefecation (16%; n = 166/1028), pain during (5.4%; n = 55/1028) or after (2.1%; n = 21/1028) defecation and urgency for defecation (6.1%; n = 63/1028). 24% (n = 248/1028) of the young adults suffered frequently from more than one of these complaints. In the non-menstrual period, defecation seemed less problematic than in the menstrual period, with a lower prevalence of all symptoms (Table IV). A total of 103 young adults (10%; n = 103/1028) reported more than one of these above mentioned symptoms on a regular base.

Sexual behaviour
596 girls (58%; n = 596/1028) mentioned having relationships involving sexual intercourse. 89 girls (15%; n = 89/596) reported dyspareunia and 37 girls (6.2%; n = 37/596) noted a VAS score ≥ 7 (Table III). The mean VAS score was 3.38 ± 2.01. Dyspareunia, occurring immediately after the menstruation, was reported by 8.8% of the girls (n = 53/596) while 6.3% (n = 38/596) of the girls experienced pain 24 hours after sexual intercourse. For 14 girls
(2.3%; n = 14/596), dyspareunia led to the interruption of the intercourse and 141 girls (24%; n = 141/596) even avoided intercourse due to this kind of pain. In general, 50.7% (n = 302/596) of those having sexual relationships, declared having one or more cycle related sexual problems.

**Physician consultation**

Of the young adults interviewed, 24% (n = 245/1028) suffered from symptoms that required the consultation of a physician in order to relief their pain symptoms, whereas 2.3% (n = 24/1028) of the young adults resorted to medical attention to explore dyspareunia.

**Number of complaints related to the menstrual cycle**

In general, 760 young women (74%; n = 760/1028) complained about menstrual problems, with 20% (n = 205/1028) having only one problem. However, 38% (n = 390/1028) of the women suffered from more than 2 different problems. In the non-menstrual period, less young adults (35%; n = 364/1028) had problems than in the menstrual phase, with 17% reporting one symptom (n = 176/1028). Among 9.6% of the respondents (n = 99/1028), the presence of 3 or more symptoms could be observed. Although students used hormonal contraception, 73% (n = 497/681; p = 0.341; Fisher Exact test) of them still experienced menstrual related complaints and 37% had to deal with non-menstrual related complaints (n = 253/681; p = 0.715; Fisher Exact test).

**Hormonal contraception**

The correlation of the use of hormonal contraception with the appearance and severity of the different symptoms, including pelvic pain, lower back pain, QOL, urological and intestinal symptoms and sexual behaviour was calculated during the menstrual period and the non-menstrual phase. No statistically significant difference was observed in frequency or intensity of pelvic pain and lower back pain between the women using hormonal contraception and those who did not.

At the level of QOL, women using hormonal contraception, manifestly suffered from fewer menstrual complaints (49.6%; n = 338/681; p = 0.003) than the ones who did not use contraception. They were less often ill (9.7%; n = 66/681; p = 0.072) or nauseous (7.3%; n = 50/681; p = 0.010) and had more energy (29%; n = 197/681; p = 0.091) than the ones who did not use contraception. As a consequence, their social life was less disturbed by their
menstruation pattern (10%; n = 67/681; p = 0.061). Likewise they experienced less illness (2.1%; n = 14/681; p = 0.254) or nausea (2.8%; n = 19/681; p = 0.952) in the non-menstrual days. On the other hand, the ones using hormonal contraception were more tired and felt less energetic (14%; n = 93/681; p = 0.913) in the non-menstrual days than those who did not use hormonal contraception thereby, restricting the QOL of 15% (n = 102/681; p = 0.215) of the students.

Surprisingly, a significantly lower VAS score (4.1) for pelvic pain was reported in women who used hormonal methods than in non-users. However, 15% (n = 105/681) of the users still reported a score ≥ 7 (p = 0.021; Fisher Exact test). Significantly more girls using hormonal treatment (52%; n = 348/681) had to resist one or more symptoms in a frequent pattern (≥ sometimes) combined with a VAS ≥ 7) (p = 0.030; Fisher Exact test). Despite prior therapy consisting of painkillers or hormonal contraception, chronic pelvic pain was reported by 31 (3%; n = 31/1028) and 47 (4.6%; n = 47/1028) girls, respectively.

At the level of intestinal symptoms, defecation was generally more complicated during (23%; n = 156/681; p = 0.334) as well as besides (11%; n = 72/681; p = 0.370) menstruation amongst the 681 users of contraception compared with the non-users. However, cyclic occurrence of polydefecation (14%; n = 97/681; p = 0.343) and constipation (5.6%; n = 38/681; p = 0.427) are surprisingly less common in users of contraception. Furthermore, during menstruation, 6.0% (n = 41/681; p = 0.684) of the users still suffered from constipation, 6.8% (n = 46/681; p = 0.029) of them experienced dyschezia and 2.2% (n = 15/681; p = 0.432) suffered from pain after defecation. 6.2% (n = 42/681; p = 0.632) of those applying hormones, encountered an urgency for defecation. In the non-menstrual period, only dyschezia seemed more consistently present among those using hormones (1.9%; n = 13/681; p = 0.039) than those who did not use it.

**Discussion**

Pain occurring during the menstrual cycle is a common complaint among the examined population. NSAIDs and, especially among young adults, the use of OCPs is a popular therapy to relieve this pain, which is in line with data from an earlier study reporting that 18% of adolescent girls taking pain killers and OCPs for menstrual pain (Parker *et al.*, 2009). Unfortunately, pain resistant to treatment with OCPs or painkillers was observed in 7 adolescents (4.1%) and 47 (4.6%) young adults, whereas pain resistant to combined OCPs and
pain killers was present in 2 adolescents (1.2%) and 31 young adults (3.0%). The prevalence of severe CPP resistant to OCPs and NSAIDs was even more than 50% in a previous report (Black et al., 2002).

The high prevalence of dysmenorrhea in our data set (40% among adolescents and 52% among young adults) is similar to previous studies reporting a prevalence of 50 - 60% (Emmert et al., 1997; Eskenazi et al., 2001). The prevalence of nonmenstrual pelvic pain was less common, (5.2% among adolescents and 7.6% among young adults) than reported in another study where girls with endometriosis mentioned chronic pain rather than cyclic pain (Laufer et al., 2003).

Jones et al. (2004) reported that symptoms including mictalgia and dyschezia may be caused by endometriosis. 14% of the adolescents and 24% of the young adults in our study complained about gastrointestinal pain during the menstrual period. This is comparable to the data of Laufer et al. (1997), who reported a prevalence of 34% among adolescents. During menstruation, urological problems appeared more frequently in adolescents (26%), which is also comparable to previously reported data (Laufer et al., 1997; Arleen et al., 2005).

In our data, the mean age at menarche in adolescents and young adults was 12.5 years ± 0.96 and 13 years ± 1.36, respectively. The mean length of cycle in both groups was 25 to 32 days. Cycles lasting for more than 45 days occurred in 5.2% of the adolescents and 0.9% of the young adults. 14% of the adolescents and 10% of the young adults mentioned polymenorrhoea (cycles < 25 days). Menstruation usually lasted for 5 to 6 days, but 12% of the adolescents and 7.4% of the young adults suffered from abundant periods (menstruation > 6 days). According to Vercellini et al. (1997), patients with endometriosis seem to have a shorter (28 ± 4.2 days) length of cycle when compared to a non-endometriosis group (29.5 ± 6.5 days). Furthermore, they have reported a significant association between endometriosis and a longer menstrual flow in comparison with a healthy population (p = 0.03). Darrow et al. (1993) confirmed that women with menstruation lasting for 6 days or more are at a greater risk of endometriosis.

In our study, 10.4% of the adolescents and 66% of the young adults used hormonal contraception. The purpose of use slightly differed in both groups. Adolescents mainly used it to control their cycle (38%) or to relieve menstrual pain (33%). Among young adults,
hormonal contraception remained an important treatment for dysmenorrhea (39%), but the main indication for its use was contraception (76%). According to Harel (2008), oral contraceptive pills are a widely used treatment for primary dysmenorrhea in adolescence. Hillen et al. (1999) showed that medication is taken by 58% of the dysmenorrhoelic girls between 15 - 17 years to relieve their symptoms, in 4% among them, this medication consists of hormonal contraception. Of those girls, 53% took simple analgesics, 42% a NSAID, and 4% of them the pill.

Dyspareunia was reported to occur frequently by 15% of the young adults compared to 22% in a study of Eskenazi et al. (2001), 5.5% in a study of Arruda et al. (2003) and 6.75% reported by Roman (2009). When exploring this pain by surgery, Eskenazi et al. (2001) found ovarian endometriosis in almost every patient with dyspareunia.

Other cycle related problems reported by our questioned population, included nausea, fatigue and loss of energy. In general, 11% of the girls experienced a reduced QOL, especially in relation to sportive activities, school and social life. In a similar study of Hillen et al. (1999), 45% of the 309 girls with dysmenorrhea reported limited school activities, 48% were restricted in their sportive activities and 46% had an impaired social life due to gynaecological pain. The most commonly mentioned symptoms in their study were stomach cramps (90%) and fatigue (50%). Girls who experienced severe cramps were more likely to miss out on school than those with mild cramps (Harel, 2008; Parker et al., 2009). In a school-based survey including 182 adolescents with dysmenorrhea, 26% reported absenteeism from school or work due to this kind of pain (O’Connell et al., 2006).

In our study, we did not ask which complaint in particular was responsible for their altered QOL.

As we expected, the use of hormonal contraception seemed to be associated with a stronger requirement for NSAIDs to treat dysmenorrhea and chronic pelvic pain. Likewise, more urological problems, including polyuria and urgency for micturation, and more dyschezia in the menstrual as well as in the non-menstrual phase were observed among young adulthood compared to girls who did not take hormonal treatment. In the older population, the prevalence of avoiding sexual intercourse due to dyspareunia seemed to be higher among pill users than among non-users.
In general, we observed a rising number of complaints together with increasing age, especially in the menstrual phase. Therefore, we assume that girls already start suffering in adolescence and that the amount and severity of complaints increase during adulthood. A study with similar design (Bai et al., 2002) reported a higher prevalence of endometriosis among girls at the age of 20 to 21 years (48.6%) than among girls in the 14 - 19 age group (13%). Laufer et al. (2003) confirmed that the incidence of endometriosis among adolescents with chronic pelvic pain increased with age.

Youngsters are not likely to consult a physician concerning cycle related problems. In order to relieve their symptoms, more young adults (24%) searched medical help compared to the adolescents (13%). This was similar to the findings of O’Connell et al. (2006) who showed that only 14% consulted a physician about severe menstrual pain. However, a study of Parker et al. (2009) reported a higher prevalence (33%). Unfortunately, dysmenorrhea is still too often considered as a physiological condition. As a consequence, many physicians fail to recognize dysmenorrhea in the younger population as a possible expression of an underlying condition. Therefore, many of the young patients receive an inadequate treatment for their complaints and are often not correctly redirected to a specialist.

Considering our data and the literature, it seems appropriate to assume that endometriosis is a disease affecting the younger female population. Properly administered NSAIDs, whether or not in combination with oral contraceptives often alleviate the symptoms. When this treatment appears insufficient in order to relieve complaints, the girls should be offered laparoscopy, which remains the gold standard in the diagnosis of endometriosis. The latter is supported by the data of Ozaksit et al. (1995) and Black et al. (2002). If in the presence of a suggestive history, neither pelvic examination nor ultrasound showed evidence of endometriosis, they proved abnormal laparoscopic findings in 50% of these cases.

Taking all this into account, we would recommend additional gynaecological investigation, including diagnostic laparoscopy to the girls/women with pain not responsive to treatment with either NSAIDs and/or hormonal contraception.

The strength of our survey is the large number of young adults included. However, there are some limitations to our study: we only included well-educated young adults and girls who visited the school doctor or the physician of both centres. Additionally, the sample size of adolescents was rather limited.
A clear need exists for more information and guidance for young girls, that way encouraging them to consult a physician or endometriosis specialist when complaints due to menstruation affect their QOL. In the future, a questionnaire needs to be developed to allow physicians and school doctors consulted by young girls, to detect complaints suggestive for endometriosis, to appropriately select adolescents or young adults with a high likelihood to have endometriosis and to refer them to an endometriosis specialist so that more severe problems may be avoided and fertility may be preserved.

**Conclusion**

The main purpose of this survey was to detect the prevalence of menstrual cycle associated pain symptoms suggestive for the presence of endometriosis in adolescents and young adult. Our data indicate that a significant proportion of adolescents and young adults have frequently occurring and severe pelvic pain and lower back pain during menstruation, often resistant to medical treatment with hormonal contraception and/or analgesics. In our opinion, the latter group should be referred to an endometriosis specialist and may be offered laparoscopy.

**Acknowledgements**

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References


Parker MA, Sneddon AE, Arbon P (2009) The menstrual disorder of teenagers (MDOT) study: determining typical menstrual patterns and menstrual disturbance in a large population-based study of Australian teenagers. BJOG, 117, 185-192


<table>
<thead>
<tr>
<th>Use of hormonal contraception</th>
<th>N adolescents (%)</th>
<th>N young adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use</td>
<td>18/172 (10%)</td>
<td>681/1028 (66%)</td>
</tr>
<tr>
<td>Purpose of use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraception</td>
<td>6/18 (33%)</td>
<td>516/681 (76%)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>6/18 (33%)</td>
<td>266/681 (39%)</td>
</tr>
<tr>
<td>Control irregular cycles</td>
<td>7/18 (38%)</td>
<td>253/681 (37%)</td>
</tr>
<tr>
<td>Control premenstrual symptoms</td>
<td>4/18 (22%)</td>
<td>66/681 (9.7%)</td>
</tr>
<tr>
<td>Cure of acne</td>
<td>2/18 (11%)</td>
<td>29/681 (4.3%)</td>
</tr>
<tr>
<td>Non-menstrual pain relief</td>
<td>2/18 (11%)</td>
<td>20/681 (2.9%)</td>
</tr>
<tr>
<td>Therapy for menorrhagia</td>
<td>0/18 (0%)</td>
<td>6/681 (0.9%)</td>
</tr>
</tbody>
</table>

Table I: Use of hormonal contraception
## Table II: Menstrual patterns

<table>
<thead>
<tr>
<th>Menstrual pattern</th>
<th>Adolescents (%) (n = 172)</th>
<th>Young adults (%) (n = 1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of cycle</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle 25 - 32 days</td>
<td>98 (57%)</td>
<td>794 (77%)</td>
</tr>
<tr>
<td>Cycle &lt; 25 days</td>
<td>25 (14%)</td>
<td>99 (9.6%)</td>
</tr>
<tr>
<td>Cycle &gt; 45 days</td>
<td>9 (5.2%)</td>
<td>9 (0.9%)</td>
</tr>
<tr>
<td><strong>Duration of menstruation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - 6 days</td>
<td>98 (57%)</td>
<td>548 (53%)</td>
</tr>
<tr>
<td>&gt; 6 days</td>
<td>20 (12%)</td>
<td>76 (7.4%)</td>
</tr>
<tr>
<td>Abundant periods</td>
<td>25 (14%)</td>
<td>92 (8.9%)</td>
</tr>
<tr>
<td>Loss of big blood clots</td>
<td>10 (5.8%)</td>
<td>41 (4.0%)</td>
</tr>
</tbody>
</table>
Table III – Prevalence of chronic pelvic pain, lower back pain and sexual activity outcome for adolescents (n = 172) and young women (n = 1028) during the menstrual and non-menstrual period.

<table>
<thead>
<tr>
<th></th>
<th>Adolescents (n = 172)</th>
<th>Young women (n = 1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Menstrual %</td>
<td>Non-menstrual %</td>
</tr>
<tr>
<td><strong>Chronic pelvic pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>general prevalence</td>
<td>152 88</td>
<td>82 48</td>
</tr>
<tr>
<td>prevalent often/mostly/always</td>
<td>68 40</td>
<td>15 8.7</td>
</tr>
<tr>
<td>VAS ≥ 7</td>
<td>38 22</td>
<td>8 4.7</td>
</tr>
<tr>
<td>prevalent often/mostly/always or VAS ≥ 7</td>
<td>76 44</td>
<td>19 11</td>
</tr>
<tr>
<td>prevalent often/mostly/always and VAS ≥ 7</td>
<td>30 17</td>
<td>4 2.3</td>
</tr>
<tr>
<td>pain relief OTC</td>
<td>66 38</td>
<td>18 10</td>
</tr>
<tr>
<td>pain relief Rx</td>
<td>11 6.4</td>
<td>4 2.3</td>
</tr>
<tr>
<td>refractory to NSAID or OC</td>
<td>7 4.1</td>
<td>- -</td>
</tr>
<tr>
<td>refractory to NSAID and OC</td>
<td>2 1.2</td>
<td>- -</td>
</tr>
<tr>
<td>OC used as analgesic</td>
<td>8/18 44</td>
<td>- -</td>
</tr>
</tbody>
</table>

<p>| | | | | |
|                              |             |                |             |                |
| <strong>Lower back pain</strong>          |             |                |             |                |
| general prevalence           | 84 49      | 63 37         | 641 62      | 366 36         |
| prevalent often/mostly/always| 43 25      | 21 12         | 382 37      | 157 15         |
| VAS ≥ 7                      | 15 8.7     | 12 7.0        | 140 14      | 101 9.8        |
| prevalent often/mostly/always or VAS ≥ 7 | 44 26    | 25 15         | 393 38      | 183 18         |
| prevalent often/mostly/always and VAS ≥ 7 | 14 8.1    | 8 4.7         | 129 13      | 75 7.3         |</p>
<table>
<thead>
<tr>
<th></th>
<th>25</th>
<th>15</th>
<th>24</th>
<th>14</th>
<th>135</th>
<th>13</th>
<th>48</th>
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<tr>
<td>pain relief OTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain relief Rx</td>
<td>6</td>
<td>3.5</td>
<td>16</td>
<td>9.3</td>
<td>27</td>
<td>2.6</td>
<td>14</td>
<td>1.4</td>
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**Sexual activity (n = 596)**

<table>
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<tr>
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<th>NA</th>
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<th>NA</th>
<th>NA</th>
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<th>65</th>
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<tr>
<td>sexual dysfunction</td>
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<td></td>
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</tr>
<tr>
<td>avoidance of sexual intercourse</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>141</td>
<td>24</td>
</tr>
<tr>
<td>dyspareunia (often/mostly/always)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>89</td>
<td>15</td>
</tr>
<tr>
<td>dyspareunia (VAS ≥ 7)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>37</td>
<td>6.2</td>
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<tr>
<td>prevalent often/mostly/always or VAS ≥ 7</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
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<td>NA</td>
<td>94</td>
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<td>prevalent often/mostly/always and VAS ≥ 7</td>
<td>NA</td>
<td>NA</td>
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<td>32</td>
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Table IV – Prevalence of urological and intestinal symptoms and the impact of pain on the QOL of adolescents (n = 172) and young women (n = 1028) during the menstrual and non-menstrual period.

<table>
<thead>
<tr>
<th></th>
<th>Adolescents (n = 172)</th>
<th>Young women (n = 1028)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Menstrual %</td>
<td>Non-Menstrual %</td>
</tr>
<tr>
<td><strong>Urological symptoms</strong></td>
<td></td>
<td></td>
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<tr>
<td>mictalgia (general prevalence)</td>
<td>29 17</td>
<td>16 9.3</td>
</tr>
<tr>
<td>mictalgia (often/mostly/always)</td>
<td>4 2.3</td>
<td>1 0.6</td>
</tr>
<tr>
<td>polyuria (general prevalence)</td>
<td>80 47</td>
<td>40 23</td>
</tr>
<tr>
<td>polyuria (often/mostly/always)</td>
<td>30 17</td>
<td>11 6.4</td>
</tr>
<tr>
<td>urgency (general prevalence)</td>
<td>42 24</td>
<td>22 13</td>
</tr>
<tr>
<td>urgency (often/mostly/always)</td>
<td>16 9.3</td>
<td>4.0 2.3</td>
</tr>
<tr>
<td>nycturia (often/mostly/always)</td>
<td>11 6.4</td>
<td>6 3.5</td>
</tr>
<tr>
<td>partial bladder retention (often/mostly/always)</td>
<td>27 16</td>
<td>2 1.2</td>
</tr>
<tr>
<td>at least one urological symptom (often/mostly/always)</td>
<td>45 26</td>
<td>1 0.6</td>
</tr>
<tr>
<td><strong>Intestinal symptoms</strong></td>
<td></td>
<td></td>
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<tr>
<td>dyschezia (general prevalence)</td>
<td>25 15</td>
<td>10 6</td>
</tr>
<tr>
<td>dyschezia (often/mostly/always)</td>
<td>9 5.2</td>
<td>4 2.3</td>
</tr>
<tr>
<td>polydefecation (general prevalence)</td>
<td>61 35</td>
<td>43 25</td>
</tr>
<tr>
<td>polydefecation (often/mostly/always)</td>
<td>11 6.4</td>
<td>10 5.8</td>
</tr>
<tr>
<td>urgency (general prevalence)</td>
<td>39 23</td>
<td>27 16</td>
</tr>
<tr>
<td>urgency (often/mostly/always)</td>
<td>7 4.1</td>
<td>2 1.2</td>
</tr>
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**QOL**

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<td>5.2</td>
<td>-</td>
<td>-</td>
<td>38</td>
<td>3.7</td>
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Appendix I – Questionnaire

1. What is your date of birth? …day/…month/…year

2. How old were you at the time of your first menstruation (menses, period)? …years

3. Did you suffer or do you suffer now from a painful menstrual period?
   Yes / No

3.1. If yes, since when did you suffer from a painful menstrual period?
   • Since your first menstrual period
   • Since the age of …years

3.2. If not, Proceed with question 4

4. Are you currently using a hormonal treatment (tablet, ring or patch) (a medication used to control an irregular menstrual cycle, in case of painful menstruation and/or as contraceptive to avoid pregnancy)?
   Yes / No

4.1. If no:
   4.1.1. Did you ever use a hormonal treatment (tablet, ring or patch)?
       No  Proceed with question 5
       Yes  Proceed with the next question

   4.1.2. At what age did you start using a hormonal treatment (tablet, ring or patch)?
       … years

   4.1.3. When did you stop using a hormonal treatment (tablet, ring or patch)?
       < 3 months ago / between 3 and 6 months ago / between 6 and 12 months ago / between 1 and 2 years ago / between 2 and 3 years ago / > 3 years ago

       Proceed with question 5!
4.2. If yes:

4.2.1. Which hormonal treatment (tablet, ring or patch) are you currently using?

- Cilest
- Claudia
- Daphne
- Desorelle 20
- Desorelle 30
- Diane 35
- Femodene
- Gestodelle
- Gestofeme
- Gracial
- Harmonet
- Lowette
- Marvelon
- Meliane
- Mercilon
- Merck Elisa
- Microgynon 20
- Microgynon 30
- Microgynon 50
- Minulet
- Mirelle
- Ovidol
- Ovysmen
- Stederil-30
- Trigynon
- Tri-Minulet
- Trinordiol
- Trinovum
- Triodene
- Yasmin
- Yasminelle
o Nuvaring
o Evra
o Implanon
o I forgot the name
o Other

4.2.2. At what age did you start using a hormonal treatment (tablet, ring or patch)?
… years

4.2.3. Why are you using a hormonal treatment (tablet, ring or patch)? (More than one reason can be given!)
- Pain during the menstrual period
- Pain during the non-menstrual period
- Premenstrual complaints (this means: irritability, a bloated feeling, headache, ... during the days/week before menstruation)
- Irregular breakthrough of the menstruation
- As a contraceptive (to prevent pregnancy)
- Other…

5. What was the average duration of your menstruation (from the first day of clear red blood loss until the day you stopped loosing blood) during the last 3 months?

…days: 1 or 2 / 3 or 4 / 5 or 6 / > 6

6. What was the average duration of your menstrual cycle (from the first day of your menstruation until the last day of your menstruation) during the last 3 months?

…days: < 25 / 25 – 32 / 32 - 38 / 38 - 45 / > 45

7. How abundant was your menstruation during the last 3 months?
   - Little
   - Average
   - Abundant
      o Blood clots: Yes / No
If yes: smaller than a 1 euro coin
larger than a 1 euro coin

8. Did your menstruation have a negative impact on your social life during the last 3 months?

Yes / No

If yes, please indicate:
- Missing school
- Not being able to exercise
- Not being able to go out with friends
- Other…

9. Have you suffered from any of the following complaints during the last 3 months?

9.1. Complaints during the menstrual period

How often did you suffer from the following complaints during the last 3 months? The following answers are possible:
- never
- sometimes (less than 25% of the menstrual periods)
- often (between 25 and 50% of the menstrual periods)
- mostly (more than 50% of the menstrual periods)
- always

9.1.1. I suffered from pelvic pain

never

immediately proceed with question 9.1.2.

sometimes / often / mostly / always

please proceed with the next question

- When did the pelvic pain occur most often (during the last 3 months)?
  - 0 The 1st day only
  - 0 The 1st and the 2nd day
  - 0 The 1st and the 2nd and the 3rd day
0 During the entire menstrual period
0 Other (specify)…

- Indicate on the following scale the number that corresponds the most with the intensity of the pelvic pain you experienced during the menstrual period (during the last 3 months).
0 = no pain at all
10 = the worst pain one can imagine

- Did you take prescription free (OTC) pain killers for this pain?
Yes / No

- Did you take prescription required (Rx) pain killers for this pain?
Yes / No

9.1.2. I suffered from lower back pain
never  
sometimes / often / mostly / always  

immediately proceed with question 9.1.3.
please proceed with the next question

- When did the lower back pain occur most often (during the last 3 months)?
  0 The 1st day only
  0 The 1st and the 2nd day
  0 The 1st and the 2nd and the 3rd day
  0 During the entire menstrual period
  0 Other (specify)…

- Indicate on the following scale the number that corresponds the most with the intensity of the lower back pain you experienced during the menstrual period (during the last 3 months).
0 = no pain at all
10 = the worst pain one can imagine

- Did you take prescription free (OTC) pain killers for this pain?
Yes / No

- Did you take prescription required (Rx) pain killers for this pain?
Yes / No

9.1.3. I felt ill
Never / sometimes / often / mostly / always

9.1.4. I felt nauseous
Never / sometimes / often / mostly / always

9.1.5. I felt tired and had a lack of energy
Never / sometimes / often / mostly / always

9.1.6. It was impossible for me to completely empty my bladder at urination
Never / sometimes / often / mostly / always

9.1.7. I had to urinate often (within 2 hours after the previous urination)
Never / sometimes / often / mostly / always

9.1.8. I felt pain when urinating
Never / sometimes / often / mostly / always

9.1.9. I felt pain after urinating
Never / sometimes / often / mostly / always

9.1.10. It was hard for me to postpone urinating
9.1.11. I had to get up at night to urinate (at night means: from the moment you go to bed in the evening until the moment you get up in the morning)
Never / sometimes / often / mostly / always

9.1.12. It was impossible for me to completely empty my bowel when defecating
Never / sometimes / often / mostly / always

9.1.13. I defecated often (more than 1x per 24h)
Never / sometimes / often / mostly / always

9.1.14. It was difficult to defecate (less than 1 x every 3 days)
Never / sometimes / often / mostly / always

9.1.15. I felt pain during defecation
Never / sometimes / often / mostly / always

9.1.16. I felt pain after defecation
Never / sometimes / often / mostly / always

9.1.17. It was difficult for me to postpone defecation
Never / sometimes / often / mostly / always

If you had complaints of pain during the menstrual period, did you consult a physician?
Yes / No

9.2. Complaints during the non-menstrual period
How often did you suffer from the following complaints during the last 3 months? The following answers are possible:
- never
- sometimes (less than 25% of the non-menstrual periods)
- often (between 25 and 50% of the non-menstrual periods)
- mostly (more than 50% of the non-menstrual periods)
9.2.1. I suffered from pelvic pain

never  
immediately proceed with question 9.2.2.

sometimes / often / mostly / always  
please proceed with the next question

- When did the pelvic pain occur most often (during the last 3 months)?
  0 The 1st day only
  0 The 1st and the 2nd day
  0 The 1st and the 2nd and the 3rd day
  0 During the entire non-menstrual period
  0 Other (specify)…

- Indicate on the following scale the number that corresponds the most with the
  intensity of the pelvic pain you experienced during the non-menstrual period
  (during the last 3 months).
  0 = no pain at all
  10 = the worst pain one can imagine

  0     5     10

- Did you take **prescription free** (OTC) pain killers for this pain?
  Yes / No

- Did you take **prescription required** (Rx) pain killers for this pain?
  Yes / No

9.2.2. I suffered from lower back pain

never  
immediately proceed with question 9.2.3.

sometimes / often / mostly / always  
please proceed with the next question
- When did the lower back pain occur most often (during the last 3 months)?
  0 The 1st day only
  0 The 1st and the 2nd day
  0 The 1st and the 2nd and the 3rd day
  0 During the entire non-menstrual period
  0 Other (specify)…

- Indicate on the following scale the number that corresponds the most with the intensity of the lower back pain you experienced during the non-menstrual period (during the last 3 months).
  0 = no pain at all
  10 = the worst pain one can imagine

- Did you take prescription free (OTC) pain killers for this pain?
  Yes / No

- Did you take prescription required (Rx) pain killers for this pain?
  Yes / No

9.2.3. I felt ill
Never / sometimes / often / mostly / always

9.2.4. I felt nauseous
Never / sometimes / often / mostly / always

9.2.5. I felt tired and had a lack of energy
Never / sometimes / often / mostly / always

9.2.6. It was impossible for me to completely empty my bladder at urination
Never / sometimes / often / mostly / always
9.2.7. I had to urinate often (within 2 hours after the previous urination)
Never / sometimes / often / mostly / always

9.2.8. I felt pain when urinating
Never / sometimes / often / mostly / always

9.2.9. I felt pain after urinating
Never / sometimes / often / mostly / always

9.2.10. It was hard for me to postpone urinating
Never / sometimes / often / mostly / always

9.2.11. I had to get up at night to urinate (at night means: from the moment you go to bed in the evening until the moment you get up in the morning)
Never / sometimes / often / mostly / always

9.2.12. It was impossible for me to completely empty my bowel when defecating
Never / sometimes / often / mostly / always

9.2.13. I defecated often (more than 1x per 24h)
Never / sometimes / often / mostly / always

9.2.14. It was difficult to defecate (less than 1 x every 3 days)
Never / sometimes / often / mostly / always

9.2.15. I felt pain during defecation
Never / sometimes / often / mostly / always

9.2.16. I felt pain after defecation
Never / sometimes / often / mostly / always

9.2.17. It was difficult for me to postpone defecation
Never / sometimes / often / mostly / always
If you had complaints of pain during the non-menstrual period, did you consult a physician?

Yes / No

You have reached the end of this questionnaire.

In case you suffer too much from your menstrual cycle, please consult your general practitioner who can refer you to a gynaecologist.

Thank you for your cooperation.

(The next questions were only to be answered by the young women)

10. Did you already have sexual intercourse? No / Yes

   If no, please go to the end of the questionnaire.

   If yes, please proceed with question 11.

11. When was the last time you had sexual intercourse?

   - During the last 3 months
   - Between 3 and 6 months ago
   - More than 6 months ago

12. The next questions deal with pain during sexual intercourse.

   The following answers are possible:

   - never
   - sometimes (less than 25% of the sexual intercourses)
   - often (between 25 and 50% of the sexual intercourses)
   - mostly (more than 50% of the sexual intercourses)
   - always
12.1. How often do you feel pain during sexual intercourse?

Never / sometimes / often / mostly / always

- Indicate on the following scale the number that corresponds the most with the intensity of pain during sexual intercourse.
  
  0 = no pain at all
  10 = the worst pain one can imagine

- When is the pain during sexual intercourse the most intense?
  - immediately after the menstrual period
  - in the middle between two menstrual periods
  - just before the menstrual period
  - during the menstrual period
  - unknown

12.2. How often do you feel pain 24 hours after sexual intercourse?

Never / sometimes / often / mostly / always

- Indicate on the following scale the number that corresponds the most with the intensity of pain 24 hours after sexual intercourse.
  
  0 = no pain at all
  10 = the worst pain one can imagine

- When is the pain 24 hours after sexual intercourse the most intense?
  - immediately after the menstrual period
  - in the middle between two menstrual periods
- just before the menstrual period
- during the menstrual period
- unknown

12.3. Do you sometimes interrupt sexual intercourse because of pelvic pain?
   Never / sometimes / often / mostly / always

12.4. Do you sometimes avoid sexual intercourse because of pelvic pain?
   Never / sometimes / often / mostly / always

12.5. If you suffer from pain during sexual intercourse, did you already consult a
physician for this problem?
   Yes  Proceed with the next question
   No   Go to the end of the questionnaire
   Not applicable Go to the end of the questionnaire

12.5.1. If yes, did the physician investigate the uterus internally with a finger?
   No   Go to the end of the questionnaire
   Yes  Proceed with the next question

12.5.1.1. If yes, did you think this internal gynaecological investigation
was painful?
   Yes / No

You have reached the end of this questionnaire.

In case you suffer too much from your menstrual cycle, please consult your general
practitioner who can refer you to a gynaecologist.

Thank you for your cooperation.
3.6. Development of a questionnaire for the detection of significant menstrual and non-menstrual pain in adolescent girls at risk for endometriosis

Anna Rijkers, M.Sc., Christel Meuleman, M.D., Karel Hoppenbrouwers, M.D., Ph.D., Thomas D’Hooghe, M.D., Ph.D.
Gynecologic and Obstetric Investigation, prepared for submission

Rijkers questionnaire for the detection of significant menstrual and non-menstrual pain problems
Abstract

**Background:** Dysmenorrhea at a young age can have a negative effect on QOL and may be a risk factor for the development of endometriosis with associated pelvic pain and subfertility. It is important to identify those girls with severe dysmenorrhea who need additional counselling, medical treatment, and possibly, laparoscopic investigation.

**Methods:** Based on a systematic review and on locally developed questionnaires, we selected and analyzed the quality of 3 international and 3 national questionnaires focused on menstrual cycle related pain complaints in adolescent girls. This information was used for internal discussion amongst endometriosis experts, youth care experts and midwives, leading to the identification of relevant and common domains and to the development of a new questionnaire.

**Results:** The Rijkers questionnaire, aimed at the detection of significant menstrual and nonmenstrual pain in female adolescents and young women includes questions about menarche, menstrual cycle, menstruation duration, abundance of menstrual flow, acyclic and cyclic pelvic pain, chronic pelvic pain, associated pain symptoms, onset of dysmenorrhea or painful menstruation, medication use, first line relative with endometriosis, doctor’s visit, social life, fatigue and sexual life.

**Conclusion:** The Rijkers questionnaire has been developed specifically for the detection of significant menstrual and nonmenstrual pain in female adolescents and young women. This questionnaire now needs to be validated, pilot tested and used in appropriate places like high schools and higher education institutions, in order to test the hypothesis that this screening tool can identify girls affected by endometriosis and guide their referral to a gynaecologist specialized in endometriosis care.
Introduction

Endometriosis is a gynaecological disorder defined by the presence of endometrial glands and stroma outside the uterus (Kennedy et al., 2005; Reese et al., 1996; Doyle et al., 2009). The prevalence of endometriosis is approximately 10 - 15% among women of reproductive age (Crosignani et al., 2006; Mao and Anastasi, 2010; Vigano et al. 2004) and up to 35 - 50% among women with pelvic pain, infertility, or both (Treloar et al. 2010). The exact cause of endometriosis remains unknown although many theories have been developed to explain this issue (Laufer, 2010). Endometriosis can only be diagnosed by visual inspection during laparoscopy, ideally confirmed by histology, and can present as peritoneal disease with typical or subtle lesions, ovarian endometriotic cysts (endometriomas) or DIE.

Several studies have previously identified a long delay experienced by patients between the first onset of symptoms and eventual diagnosis of endometriosis (Arruda et al., 2003; Dmowski et al., 1997; Hadfield, et al., 1996; Husby et al., 2003). The average delay in diagnosis in women aged under 19 years is even greater than in women aged over 30 years (12.1 years versus 3.3 years) (Arruda et al., 2003). The delay is a significant issue for a number of reasons. First, it has the potential to impact upon the lives of women. Previous studies reveal that women diagnosed with endometriosis can experience concern, worry, anxiety, self-blame, financial and relationship difficulties and a reduced QOL (Abbott et al., 2003; Bodner et al., 1997; Denny and Mann, 2007; Garry et al., 2000; Jones et al., 2001; Strzempko et al., 2007).

Various explanations have been forwarded to explain the diagnostic delay, with both doctors and women being implicated. It has been mentioned that doctors normalize or underestimate women’s menstrual pain and do not take these symptoms seriously (Carlton, 1996; Hadfield et al., 1996). Some women might delay in seeking medical advice because they have difficulty distinguishing between ‘normal’ and ‘abnormal’ menstruation or are reluctant to disclose problems associated with their menstrual cycle (Seear, 2009; Denny, 2004). This long delay in diagnosis of endometriosis can lead to more painful symptoms, can worsen the prognosis for fertility (Matsuzaki et al., 2006) and may contribute to the large economic burden of the condition to society (Gao et al., 2006; Simoens et al., 2007).

According to a previous review, the prevalence of endometriosis in adolescent girls varies between 25% - 38.3 % in adolescents with chronic pelvic pain and dyspareunia and increases
to 50% - 70% in adolescents undergoing laparoscopy for pelvic pain not responding to NSAID and oral contraception (Laufer, 2003). A more recent systematic review shows an overall prevalence in adolescents with CPP/CPP unresponsive to medical treatment/dysmenorrhea of 62% (n = 557/893). Symptoms in adolescents may differ from adults in that there may be cyclic or acyclic pain, irregular menses, dyspareunia, gastrointestinal symptoms, vaginal discharge, bladder dysfunction and urinary tract symptoms (Black et al., 2002; Unger et al. 2010; Laufer et al., 2003). The principal manifestation of endometriosis among teenagers is CPP (Vercellini et al., 1989; Kontoravdis et al., 1999; Bourdel et al., 2006; Attaran et al., 2002) or/and dysmenorrhea (Laufer et al., 1997; Propst and Laufer, 1999; Bourdel et al., 2006).

Underestimation of pelvic pain in adolescents is a significant issue for a number of reasons. First, this pelvic pain has the potential to impact upon their lives and their uncertainty about the normality if the menstrual pattern. Young people do not like to discuss these personal and intimate complaints with their parents but rather talk to other adult persons or- friends who they can trust (American Academy of Pediatrics, 2006). Second, endometriosis can only be diagnosed at laparoscopy, which is often considered as too invasive in the context of adolescent gynaecology (Pandis et al., 2009; Kalu et al., 2008; Dovey and Sanfilippo, 2010; American College of obstetricians and Gynecologists, 2005; Gylfason et al., 2010). Third, the laparoscopic recognition is more difficult and because endometriosis lesions in adolescents can be less typical than in adults with the majority have in minimal or mild endometriosis (Deligeoroglou and Tsimaris, 2010; Rijkers et al., 2011). Fourth, there is a lack of awareness among medical practitioners that endometriosis is a significant cause of pelvic pain in adolescents which contributes to delayed diagnosis (Attaran et al., 2002).

Menstrual pain complaints are the most important cause of absences on school, with a possible impact on the school performances and on the social activities (Harel, 2006; Song and Advincula, 2005). A possible abnormal menstruation pattern, with impact on social living, comes to light at a later time in life and can have a negative influence on the health on the longer term (American Academy of Pediatrics, 2006). Complaints related to endometriosis can have a negative influence on QOL and social relationships (Meuleman et al., 2009; Crosignani et al., 2006; Gao et al., 2006) and can also result in feelings of uncertainty (Denny, 2009).
It becomes clear that endometriosis and menstrual-related complaints occur more often among adolescent girls than generally thought and even two-thirds of women with endometriosis report commencement of symptoms prior to the age of 20 years (Ballwegg, 2003). These above mentioned data indicate a considerable need for tools that can accurately assess menstrual cycle related pain symptoms in at-risk adolescent girls. Furthermore, these tools need to be accessible to providers working in settings where adolescents are treated (e.g., schools, emergency rooms, medical inpatient units, outpatient clinics). Specifically, measures need to (a) be short enough to be easily incorporated into busy acute clinical settings, (b) rely on sources that are readily available in the literature and (c) require minimal training to administer and interpret. The need for such an instrument that can be used by primary healthcare providers to identify girls requiring further investigation of menstrual disturbance has been highlighted recently (Parker et al., 2010).

Currently, there are a number of instruments for assessing QOL in women with endometriosis and/ or pelvic pain. However, the majority of these instruments is not developed specifically assess menstrual cycle related pain symptoms in adolescents that can be suggestive for endometriosis. The purpose of the current study was to develop a questionnaire, based on literature review, nationally developed questionnaires, and clinical experience, as a screening tool, which could be utilized in settings where adolescent girls are treated to identify quickly and easily those teenagers who could be at risk for endometriosis.

**Materials and Methods**

The development of the Rijkers questionnaire aimed at the identification of relevant symptoms in adolescents at risk for the development of endometriosis was done over 4 phases.

I. Systematic review of the literature to identify questionnaires measuring the QOL in women and girls suffering from endometriosis and chronic pelvic pain, leading to the selection of the 3 questionnaires with the highest relevance for our study.

II. Presentation of 3 questionnaires previously developed within Leuven University and Leuven University Hospitals in order to assess the presence of menstrual cycle associated pain symptoms in adolescents.

III. Comparison of the 6 selected questionnaires (3 international, 3 national) (Tables I - II).

IV. Development of the Rijkers questionnaire based on phases I - III and on discussion among authors of this paper.
Step I. Exploration of the literature (Systematic Review)

The aim of this systematic review was to evaluate validated and reliable questionnaires that can identify the QOL in women suffering from endometriosis and chronic pelvic pain.

Search strategy

The literature review was conducted in two steps. First, an extensive search of the electronic databases including Medline, Web of Science, CINAHL, EMBASE, Google and The Cochrane Library was conducted in December 2008 at The Biomedical Libraries of the University Hospitals of Leuven, The Medical Subject Hearing (MESH) Terms ‘endometriosis’ and chronic pelvic were used in different combinations with topics as ‘Dysmenorrhea’; ‘Questionnaires’; ‘Development’: ‘Adolescent’; ‘Menstrual Cycle’; ‘Pain’; ‘QOL’; ‘Instrument’ en ‘Menorrhagia’. A second step was screening the references of all selected articles to identify additional relevant papers.

Inclusion and exclusion of publications

The search was limited to articles in the English or French language, which were published in full and addressed the research question. Articles were only considered to be relevant if they were not older than 20 years, reported research on the topic gynaecology and QOL related to endometriosis and/or dysmenorrhea and/or chronic pelvic pain. Therefore, manuscripts that didn’t clearly describe the reliability and validity of the applied questionnaire nor had fully written questionnaire were excluded.

Quality appraisal

Quality appraisal of the measuring instruments, used in the articles was based on a checklist using all facets of a valid and reliable measuring instrument with regard to QOL. A checklist for quality assessment was designed, based on previous literature. Based on 12 questions we evaluated the properties of the measuring instruments. The qualitative measurement methods such as interviews were not included in the quality assessment given the fact that validity and reliability were unknown. The explanation of the checklist can be found in Table I (Clark et al., 2002; Streiner et al., 1993).
Results

The literature search with the above mentioned MESH en keywords provided 989 hits. Based on title, 132 papers were selected and after reading the abstract 37 were withheld for detailed evaluation. After reading the articles, more articles 20 were excluded for the following reasons: no scientific evidence (n = 5), no IMRD structure (n = 6), missing a description of validity (n = 7). No additional papers were identified after writing authors to obtain a complete version of de questionnaire paper (n = 2). Finally, 17 articles were included in this review (Ching-Hsing et al., 2004; Colwell et al., 1998; Dubernard et al., 2008; Fedele et al., 2007; Garry et al., 2000; Gehlert i 2006; Huntington et al., 2005; Jenkinson et al., 2008; Jones et al., 2004; Jones et al., 2004; Jones et al., 2004; Jones et al., 2001; Leplège et al., 1998; Perneger et al., 1995) of which 3 systematic reviews (Clark et al., 2002; Jones et al., 2002; Neelakantan et al., 2004). The process of literature identification and selection is detailed in Figure I.

The review identified questionnaires addressing the QOL in women with endometriosis or chronic pelvic pain.

Four non-specific questionnaires were identified (1) Short Form Health Questionnaire-36 (SF-36) (Dubernard, et al., 2008; Leplege et al., 1998; Perneger et al., 1995); (2) American Urological Association Symptom Index questionnaire (AUASI-Wikipedia, the questionnaire) (Fedele et al., 2007); (3) 5 d EuroQoL (EQ-5 d) (Garry et al., 2000); and (4) The Women's QOL Questionnaire (WOMQOL) (Gehlert et al., 2006).

Three specific questionnaires were identified: (1) The adolescent dysmenorrhic self-care scale (ADSC-scale, Ching-Hsing et al., 2004); (2) Health-related QOL instrument for endometriosis (HRQoL) (Colwell et al., 1998); (3) Endometriosis Health Profile-30 (EHP-30) (Jenkinson et al., 2008; Jones et al., 2004; Jones et al., 2001) including a short version of the EHP30 published as the Endometriosis Health Profile (EHP-5) questionnaire (Jones et al., 2004).

The Endometriosis Health Profile Questionnaire – 30 (Jones et al., 2001; Jones et al., 2004, Jones et al., 2008) includes 30 questions and concerns a validated, reliable, useful and disease-specific questionnaire which sounds to the possible negative impact of endometriosis
on the QOL at women of reproductive age. This questionnaire is easy to use and asks no extra training of care workers who must use them.

After an update of the systematic review on 7 February 2011, we identified 2 other relevant and published questionnaires (Nnoaham et al., 2009; Parker et al., 2010), These will be shortly reviewed in the next section.

**The Prevalence of Menstrual Disorder of Teenagers (MDOT) questionnaire** (Parker M et al., 2010) was developed by an Australian research group under the guidance of Melissa Parker (RN RM Nurse; Endometriosis coordinator and Researcher) as a preparation for a cross-sectional study and is related to the menstrual pattern of adolescents and the impact on their daily activities. The questionnaire, which confiscates approximately 20 minutes, has been structured with recurrences in topics and questions. It contains scales, open questions, propositions in the form of true/false; yes/no and questions. The questionnaire was tested in a pilot project but is not yet validated.

**The Global Study of Women’s Health questionnaire** (Nnoaham et al., 2009) was developed by an Oxford research team together with an international consortium and was used in a prospective epidemiologic study that examines the impact of risk factors for endometriosis in 14 countries in the world (Nnoaham et al., 2009). This questionnaire collects information on gynaecological symptoms, the impact on women, the use of health care, life quality, medical and family history and lifestyle. The questionnaire is focused on women between 18 - 45 years who will undergo a laparoscopy because of complaints, which can be suggestive for endometriosis or for a tuba sterilization. The research workers asked to fill in this questionnaire online or by writing before the participants will undergo their operation. It concerns a quantitative questionnaire existing of 67 items with mainly closed questions of ordinal categories or multiple-choice questions. Visually analogue scales or questions with dichotomous answers were regularly used. Filling in the questionnaire takes approximately 20 minutes.
Step II. Presentation of questionnaires previously developed within Leuven University and Leuven University Hospitals in order to assess the presence of menstrual cycle associated pain

This short questionnaire is an instrument developed to assess the presence of dysmenorrhea in female nulliparae students of 18-25 years to the K.U.Leuven in 1970. The instrument contains 7 questions, concerning painful menstruation [listed in Appendix II (English version) and IV (Dutch version)], with multiple choice format answers but was not validated or published.

2. The Leuven dysmenorrhea-questionnaire (Degroote K. en Hoppenbrouwers K., Department of Youth Health Care K. U. Leuven, 1996)
This questionnaire was developed to get more insight in the prevalence and seriousness of dysmenorrhea, in the attitude of young women/girls and to provide a contribution to a more efficient treatment. It focuses on several aspect of the menstrual pattern such as frequency, nature, influencing factors, impact of menstruation complaints as well as the use of medication and subject attitude during menstruation. It contains 26 multiple-choice questions with ‘yes or no’ answers combined with open questions and was from Leuven University. The questionnaire [listed in Appendix I (English version) and III (Dutch version)], was used in a study of Flemish students, but has not been validated nor published.

This questionnaire was developed based on a non-systematic literature review, on pain symptoms associated with and risk factors for endometriosis and on the recommendation of experts (the co-authors CM and TD) This questionnaire sounds to the menstrual pattern and the possible pain complaints and contains 12 questions focused on menstruation, menstrual cycle length and other characteristics, menstrual cycle related pain, methods of pain relief, influence on school, social life and, for the young adults, influence on the sexual relationship. The questionnaire contained mainly closed questions with predefined answer categories (‘never’, ‘sometimes’, and ‘frequently’, ‘generally’, ‘always’) and used Visual Analogue Scales for the assessment of pain intensity. Filling in the questionnaire can be done electronically and takes 10 - 15 minutes. This questionnaire has not been validated but has been used in 2 studies with papers submitted for publication (Meuleman et al, 2011; Rijkers et al, 2011).

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Step III. Comparison of the 6 selected questionnaires (Tables I - II).

We compared the value of 3 internationally published questionnaires (selected in Step I) and 3 locally developed questionnaires (presented in Step II) in order to identify items of menstrual pattern that might be relevant for adolescents with possible endometriosis. The results of this analysis were used to develop a new questionnaire.

Data were independently extracted by the author. The selected questionnaires were compared on the following substantive items 1) content of the questionnaire and 2) description of the questionnaire (development and the user-friendliness) (Table I - II). Attention went out: (1) the target group, (2) what one wants to measure and with which aim (3) the Questionnaires content and format, (4) the presence of an accompanying letter and (5) methodology (Beurskens et al., 2008) (Table II).

Description of selected questionnaires

Target group

Four questionnaires were developed specifically for adolescent girls (Groenen et al., 1970; Degroote et al., 1996; Parker et al., 2010; Meuleman et al., 2011) whereas 2 other questionnaires focused on women in the age group 18 - 45 years (Nnoaha et al., 2009) or on all women with endometriosis regardless their age (EHP-30 and EHP-5; Jones et al., 2001; Jones et al., 2004, Jenkinson et al., 2008). The sample size in the selected studies varied between 27 and up to 1300 female adolescents or women. Four questionnaires were developed in the context of mono-centric studies: (Groenen et al., 1970; Degroote et al., 1996; Parker et al., 2010; Meuleman et al., 2011) whereas 2 other questionnaires were developed for multi-centric (Nnoaham et al., 2009) or global use (Jones et al., 2001, Jones et al., 2004, Jenkinson et al., 2008). All questionnaires were developed in the original mother language with exception of The Global Study on Women Health (Nnoaham et al., 2009) and The Endometriosis Health Profile Questionnaire - 30 (Jones et al., 2001, Jones et al., 2004, Jenkinson et al., 2008) that have been translated in multiple languages.

Target topic

In 5 questionnaires (Groenen et al., 1970; Degroote et al., 1996; Parker et al., 2010; Meuleman et al., 2011; Nnoaham et al., 2009) the target of the questionnaires was the documentation of menstrual cycle characteristics, pain problems, and their influence on school and social life.
**Questionnaires content and format**

All 6 questionnaires addressed menstrual cycle characteristics and pain. Other items included: control, emotional well-being, social support, self-image, medication-use, school absence and doctor visits. Questionnaires contained only closed questions (Groenen et al., 1970; Meuleman et al., 2011; Nnoaham et al., 2009; Jones et al., 2001; Jones et al., 2004; Jenkinson et al., 2008), or a combination of closed and open questions (Degroote et al., 1996; Parker et al., 2010).

The questionnaires included a minimum of 7 and a maximum of 67 questions. The type of questions or propositions allowed simple or plural answers with the option to choose the most conformable answer (multiple-choice, judgments) or required nominal (i.e. Ethnic context), dichotomous (i.e. yes, no), ordinal (i.e. frequently, sometimes, almost never, never) or continuous answers (scale between 0-10, i.e. 0 = no pain; the 10 = most terrible possible pain).

Questionnaires were based on short senses using simple language with synoptic elaboration: (Groenen et al., 1970; Degroote et al., 1996; Jones et al., 2001; Jones et al., 2004; Jenkinson et al., 2008; Parker et al., 2010; Meuleman et al., 2011) or included long sentences with multiple answer possibilities (Nnoaham et al., 2009).

**Accompanying letter**

An accompanying letter was used for all questionnaires, except one (Groenen et al., 1970).

**Methodology and Validation**

The Endometriosis Health Profile Questionnaire - 30 (Jones et al., 2001, Jones et al., 2004, Jenkinson et al., 2008) was developed in 3 steps: (1) an open interview with patients to assess the items of the questionnaire, (2) development of a questionnaire with 87 items in order to address the dimensions which reflect best health-related life quality and (3) evaluation of reliability and validity of the questionnaire.

The Prevalence or Menstrual Disorder or Teenagers-questionnaire (Parker et al., 2010) was tested twice as a pilot study. A first pilot study (n = 8) resulted in adaptations of the structure and order of the questions, a second one (n = 20) in change of a question and the layout to improve legibility. The questionnaire has not been validated yet.
The Global Study on Women Health (Nnoaham et al., 2009) was conducted as a pre-pilot study in voluntary healthy women in Oxford, from April to June 2008. This pre-pilot study resulted in several small adaptations of the questionnaire to improve layout and face-validity. After woods a pilot study, among women (n = 27), who were planned for a laparoscopy, was followed to assess the feasibility of the study. This resulted in small changes to questionnaire. This epidemiologic prospective study is worldwide carried out, collects data to get insight in the overall impact of endometriosis and is focused on developing a diagnostic measuring instrument based on symptoms.

The questionnaire menstrual complaints (Groenen et al., 1970) was used for a study in nulliparae girl students aged 18-25 years at Leuven University the K.U.Leuven but more details about methodology or validation are absent.

The dysmenorrhea questionnaire (Degroote et al., 1996) is a questionnaire of a preventive medical examination in female students from Leuven institutions for higher learning. There were three subgroups: (1) first-year students at the K.U.Leuven University (n = 884); (2) first, second or third year students from the Rega Institute [education for dietician or medical secretary (n = 213)] and (3) boarding school students in the St Elisabeth School for Nursing (n = 203). This last group contains especially first-year students. The questionnaires were completed on a different location and at a different time in the 3 subgroups (1) first-year students completed this questionnaire during a preventive medical examination (2) students from the Rega Institute filled out this questionnaire during the school hours and (3) the nurses received the questionnaires e in their personal mailbox on the boarding school.

The Leuven-questionnaire about menstrual complaints in female adolescents and young women (Meuleman et al., 2011) was used in 2 clinical studies (2008 and 2010) submitted for publication (Meuleman et al., 2011)

Step IV. Development of the Rijkers Questionnaire.

The Rijkers questionnaire was developed based on the previous 3 steps and on related discussions amongst the coauthors of this paper. In the Results section, we present the Rijkers questionnaire and justify its content. More specifically, the Rijkers questionnaire was developed on the method published by Beurskens et al., 2008. This method is a roadmap especially for using and developing questionnaires in healthcare. Topics as the target group,
what one wants to measure and with which aim, the questionnaires content and format, the presence of an accompanying letter and (5) the methodology were earlier described (Beurskens et al., 2008) (Table II).

Results
In Appendix V, the Rijkers questionnaire is presented and includes questions about menarche, menstrual cycle, menstruation duration, abundance of menstrual flow, acyclic and cyclic pelvic pain, chronic pelvic pain, associated pain symptoms, onset of dysmenorrhea or painful menstruation, medication use, first line relative with endometriosis, doctor’s visit, social life, fatigue and sexual life. Justification for the inclusion of these items is presented.

Menarche
The importance of this question was based on a strong and an inverse association between endometriosis and menarche after an age of 14 years (odds ratio, 0.3; 95% confidence interval, 0.1 – 0.6) (Treloar et al., 2009) and on the observation that early dysmenorrhea may also be a risk factor for the development of DIE with colorectal extension (Chapron, 2010).

Menstrual cycle, menstruation duration, abundance of menstrual flow
Questions related to menstrual cycle, menstruation duration and abundance of menstrual flow are incorporated in the questionnaire as the risk for endometriosis may be related to menstrual factors that predispose to greater pelvic contamination with menstrual products (Cramer, 1986; Klein et al., 1981; Burnett et al., 2005; Andersch, 1982; French, 2008; Vercellini, 1997), like heavy menstrual bleeding, long duration of menstruation and short cycle length.

Acyclic and cyclic pelvic pain, chronic pelvic pain
Questioning is particularly helpful for delineating the different types of pelvic pain symptoms (dysmenorrhea, deep dyspareunia, none cyclic chronic pelvic pain, gastrointestinal and lower urinary tract symptoms) that are related to the anatomic location of DIE lesions (Chapron, 2010). The pattern of pelvic pain in adolescents with endometriosis differs from that in adults. Whereas adults mention rather an increasing pain during the menstruation, adolescents indicate the pain rather as cyclic (menstruation-related) and acyclic (not menstruation-related). In one study 9.4% of adolescents had the adult pattern of cyclic pain with menses, whereas 65.5% had both acyclic and cyclic pain and only 28.1% had acyclic pain (Laufer, 2003). In another study (Roman et al., 2010) pelvic pain not related to periods was described
as the chief complaint in 20% (n = 4/20) of the adolescent with endometriosis. In other series (Bai et al., 2002), cyclic pelvic pain was commonly reported in teenagers with endometriosis.

Pelvic pain can occur unpredictably and intermittently or continuously throughout the menstrual, and can be dull, throbbing, or sharp, and exacerbated by physical activity (Giudice, 2010; Broach et al., 2009; Cramer and Missmer, 2002; Goldstein et al., 1980; Song and Advincula, 2005; Laufer et al., 1997; Farquhar et al., 2009). Chronic pelvic pain is described as non-cyclic pain during at least 3 months or as cyclic pain during 6 months, which has an impact on the normal daily activities (Sanfilippo and Erb, 2008). Some studies have suggested that endometriosis is the most common diagnosis among teenagers reporting chronic pelvic pain (Vercellini et al., 1989; Kontoravdis et al., 1999). In a recent systematic review based on 15 selected studies (Rijkers et al., 2011), the overall prevalence of endometriosis in adolescents was 62% (557/893; range 24 - 100%) and was significantly higher (p < 0.001) in girls with CPP resistant to treatment with OCPs (76%; 238/314) and in girls with dysmenorrhea (72%; 115/159) than in those with CPP only (49%; n = 204/420).

Associated pain symptoms

Associated pain symptoms are symptoms/changes/problems during menstruation, like bowel pain or bladder symptoms, and have been found to be present and important for adolescents (Chatman and Ward, 1982; Davis et al., 1993; Laufer et al., 1997; Laufer et al., 2003; Ballweg, 2003). It has been stressed that a properly conducted and thorough clinical interview is highly predictive of bladder detrusor endometriosis or posterior DIE (Chapron et al., 2004).

Onset of dysmenorrhea or painful menstruation

Primary dysmenorrhea has been reported to occur most frequently in subjects whose age at menarche was younger than 12 (88% of total sample) and less in subjects whose age at menarche was older than 12 (81% of total sample) (Balbi et al. 2000). A positive association between earlier menarche age and greater intensity of menstrual pain (p < 0.05) was reported by Chinese researchers (Du et al., 2003). A Correlation between earlier menarche and increased intensity of menstrual pain (r = -0.16, p = 0.011) has been described (Zhu et al., 2010). Finally, a strong and an inverse association with endometriosis has been observed in girls with a menarche after age of 14 years (odds ratio, 0.3; 95% confidence interval, 0.1 – 0.6), suggesting that girls with later menarche have a smaller risk to develop endometriosis.
(Treloar et al., 2009). The same investigators also concluded that early dysmenorrhea is a risk factor for endometriosis (Treloar et al., 2009).

**Medication use**
Adolescents with dysmenorrhea with or without impact on daily- or school activities will receive medical treatment first before surgery. Sometimes, NSAID only can already be enough to control the pain. For adolescents who, after a period of 3 months with only NSAID, still mention persistent pelvic pain, cyclic use of OAC in combination with NSAID will be recommended (Harel, 2006; Laufer, 2010). If this cyclic use of OAC is not effective, a continuous use of the pill is recommended to prevent the menstrual related pain complaints (Attaran, et al., 2002). This item is important to identify those adolescents who, in spite of a combination therapy of NSAID/OAC during 3 up to 6 months, still mention persisting pelvic pain, most likely adolescents who have an increased risk for endometriosis (Harel, 2006; Harel, 2008; Parker et al., 2010; Laufer, 2010).

**Sister(s) and mother**
The question about pelvic pain and/or endometriosis in sister(s) and/or mother is asked since there is evidence that the presence of a first line relative with endometriosis is a risk factor for endometriosis, probably because of a genetic predisposition (Barlow and Kennedy, 2005; Laufer et al., 2003; Parker et al., 2010; Zhu et al., 2010; French, 2005; Laufer, 2010). Women who have a sister or mother with endometriosis are more at risk than those without family history of endometriosis. (Vigano et al., 2004; Fraser, 2008). First degree relatives of women with endometriosis have been reported to have endometriosis 4 to 8 times that of the general population. One study showed an 11.6-fold increasing the risk of endometriosis among sisters and 8-fold increase among mothers of those diagnosed with endometriosis (Simpson et al., 1980; Matalliotakis et al., 2008). A previous family history of endometriosis is significantly associated with DIE (Chapron, 2010).

**Doctor’s visit**
Only a limited number of adolescents visit a doctor to get advice are limited in spite of the high prevalence of pelvic pain complaints. It is important to know if earlier examination and/or interventions have taken place and to know the results, and to find out if the possible therapy and/or the intervention was effective.
This information can provide healthcare workers with additional information to evaluate the need to care, to start clinical management, or to refer the patient to a gynaecologist with expertise in endometriosis.

**Social life**
Dysmenorrhea has a negative influence on social- and school activities (Parker *et al.*, 2010)

**Fatigue**
Research indicates that, after pain, fatigue is the second most important symptom in adolescents with endometriosis (Ballweg, 2003).

**Sexual relations**
Pain during or after sexual intercourse becomes more significant at women who have their first pelvic pain complaints below the age of 25 years whereas this is lower at women who got symptoms after the age of 24 years (Ballweg, 2003).

**Discussion**
The review of selected questionnaires showed that the 2 validated questionnaires (Nnoaham *et al.*, 2009: EHP-30 and EHP-5 questionnaire) were not developed specifically for adolescents with menstrual cycle associated pain symptoms, but for women with established (EHP-30, EHP-5) or possible endometriosis. The 4 questionnaires developed specifically for adolescents were either only used locally without validation or publication (Groenen *et al.*, 1970; Degroote *et al.*, 1996) or were used locally and published internationally without validation (Parker *et al.*, 2009; Meuleman *et al.*, 2011). None of these questionnaires has had as primary outcome the detection of serious pelvic pain as primary outcome. However, all selected questionnaires included the following important domains: pain, menstrual pattern, medication use, doctor’s visit and social activities were present in all questionnaires. Furthermore, they have been developed based on available scientific literature and/or by people with expertise in topic youth healthcare or endometriosis.

The Rijkers questionnaire has been developed specifically for the detection of significant menstrual and non menstrual pain in female adolescents and young women. This questionnaire now needs to be validated, pilot tested and used during preventive medical examinations at appropriate places like high schools and higher education institutions, in
order to test the hypothesis that this screening tool can identify girls affected by endometriosis and guide their referral to a gynaecologist specialized in endometriosis care.

The user friendliness of this questionnaire for both adolescents and scientists needs to be tested in future research. In that context, it is important to have a short questionnaire with easy words which is likely to be completed fully by most participants. In our experience (Meuleman et al, 2011; Rijkers et al, 2011) patients in generally have no problem with filling in questionnaires as long as these are not too long. We also took into account that questions concerning menstrual-related complaints have an intimate and personal character what can result in uncomfortable feelings in adolescents.

Subsequently, this questionnaire could be integrated into routine developmental surveillance practices of healthcare workers who take care for adolescent girls. Nurses, midwives and school doctors are often the first health professionals patients encounter in settings such as community health clinics, schools, emergency rooms and surgery units. With increased information, they can educate patients about menstrual pattern, help them cope emotionally and physically with the chronic symptoms and use this questionnaire to identify possible risk factors for endometriosis. This way an early diagnosis of endometriosis can be made, adolescents can be referred to an expert centre and an appropriate treatment can be established.
Reference List


Denny E (2009) I never know from one day to another how I will feel: pain and uncertainty in women with endometriosis. Qual Health Res, 19, 985-995.


Book references


Non-published sources


Figure 1. The process of literature identification and selection.
<table>
<thead>
<tr>
<th>Questionnaire Title</th>
<th>Age of respondents (year, average, range)</th>
<th>Objective</th>
<th>Research topic</th>
<th>Questions pertaining to specific time period</th>
<th>Questionnaire development, format and type of questions</th>
<th>Type of domains addressed</th>
<th>Informed Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Endometriosis Health Profile Questionnaire – 30 (2001; 2004; 2008)</td>
<td>32.5 ± 7.2 (17 - 58) 32.5 ± 5.8 (21.5 - 44) 30.5 ± 6.57 (19.2 - 48)</td>
<td>Evaluation Inventory Prognostic</td>
<td>Quality of life in the presence of endometriosis</td>
<td>Last 4 weeks</td>
<td>Five domains 30 item Scales</td>
<td>Control and powerlessness</td>
<td>Unknown</td>
</tr>
<tr>
<td>The Global Study of women's Health (2009)</td>
<td>18 - 45</td>
<td>Evaluation Inventory</td>
<td>Health Impact and risk factors of endometriosis</td>
<td>Preoperative period</td>
<td>67 questions Multiple-choice Scales</td>
<td>Pain (pelvic pain, coitus) Health and welfare Medical and family history Menstrual pattern Contraception Pregnancy</td>
<td>Yes</td>
</tr>
<tr>
<td>The Prevalence or Menstrual Disorder or Teenagers (2010)</td>
<td>15 - 19</td>
<td>Evaluation Inventory</td>
<td>Pre-menstrual pattern Prevalence Menstruation disorder</td>
<td>Last 12 months</td>
<td>7 questions (Closed/Open) items/propositions Scales Free text</td>
<td>Medication use (pain and OAC) and effectiveness Psychological well-being Medical and family history Menstrual pattern - pain Social activities School absenteeism</td>
<td>Yes</td>
</tr>
<tr>
<td>Leuven questionnaire menstrual complaints among adolescents (2011)</td>
<td>18 (young adults) 15.2 ± 6.88 (adolescents)</td>
<td>Evaluation Inventory</td>
<td>Menstrual cycle Dysmenorhea</td>
<td>Last 3 months</td>
<td>12 closed questions with sub items Multiple-choice Scales</td>
<td>General well-being; Doctor visit Medication use (analgesics-OAC) Menstrual pattern – pain Social activity School absenteeism</td>
<td>Yes</td>
</tr>
<tr>
<td>Questionnaire menstrual complaints, University Health Center (1970)</td>
<td>18 - 25</td>
<td>Evaluation</td>
<td>Dysmenorrhea</td>
<td>Not described</td>
<td>7 questions (closed) Multiple choice</td>
<td>Doctor visit Medication use (painkiller) Menstrual pattern - pain</td>
<td>No</td>
</tr>
<tr>
<td>Dysmenorrhea-questionnaire, University Health Center (1996)</td>
<td>19 ± 1.2 (17.9 - 30.4)</td>
<td>Evaluation Inventory</td>
<td>Dysmenorrhea</td>
<td>Not described</td>
<td>26 questions (closed/open) Multiple-choice</td>
<td>Information Source Attitude/coping family data Medication use (Painkiller-OAC) Menstrual pattern – pain Social activities School absenteeism</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table II. Critical appraisals of selected questionnaires used as basis for development of the Rijkers Questionnaire

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Clear aim</th>
<th>Description of target group</th>
<th>Development of the questions</th>
<th>Pilot study</th>
<th>Validation</th>
<th>Readability</th>
<th>Accompanying letter</th>
<th>Nature of questions</th>
<th>Participation (how, where, when)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Endometriosis Health Profile Questionnaire – 30</td>
<td>n = 168 (2001)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>n = 66 (2004)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>n = 225 (2008)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Global Study of women's Health (2009)</td>
<td>n = 27**</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>The Prevalence or Menstrual Disorder or Teenagers (2010)</td>
<td>n = 1051</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leuven questionnaire menstrual complaints among adolescents (2011)</td>
<td>n = 542 (2008)*</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
<td>n = 658 (2010)*</td>
<td></td>
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<tr>
<td>The questionnaire menstrual complaints, University Health Centre (1970)</td>
<td>n = 682</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dysmenorrhoea-questionnaire, University Health Centre (1996)</td>
<td>n = 1300</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+ Clear description; - No clear description; ± Uncertain; * Both were queried in a Msc pilot study; ** Pilot study.
Appendix I. The dysmenorrhea - questionnaire (Degroote K. and Hoppenbrouwers K., Dept Youth Health Care K.U.Leuven, 1996)

1. When did you menstruate for the first time?
2. What is the average duration of your cycle?
3. How many menstruations have you had in the past 12 months?
4. On average, what has been the number of days of your menstrual flow?
5. If you menstruate, how many times must you use a new tampon on the day of maximal blood loss?
6. At present, do you experience pelvic pain during your periods?
7. Have you experienced pelvic pain during the first months when your periods started?
8. Do you experience pelvic pain outside the menstrual period?
9. At present, do you use painkillers for pelvic pain during the menstrual period?
10. How frequently do you use medication for pelvic pain during the menstrual period?
11. Do you use other resources then medication for pelvic pain during the menstrual period?
12. Do you experience headache during the menstrual period?
13. Do you experience headache outside the menstrual period?
14. Do you experience other complaints sometimes than mentioned during the menstrual period?
15. Do you use medication or alternatives for complaints during the menstrual period?
16. Do you use a contraceptive pill?
17. Did your mother have regularly pelvic pain or other complaints during the menstrual period?
18. When do experience pelvic pain?
19. Where do you experience pelvic pain?
20. Do you need to lie down because of your menstrual pain?
21. Do you sometimes miss school because of your menstrual pain?
22. Have you sometimes visited a doctor for pelvic pain?
23. Have you ever used painkillers for pelvic pain during the menstrual period?
24. According to you, are your complaints during the menstrual period natural?
25. Is there in your opinion enough information available concerning menstrual problems?
26. Do you like more attention for menstrual problems?
Appendix II. the questionnaire menstrual complaints, University Health Centre (Groenen G., Hoppenbrouwers K., K.U.Leuven, 1970)

1. Do you experience menstrual pain?
2. When do you feel pain?
3. To what extent do you feel that pain?
4. Where is the pain localized?
5. Is this pain accompanied by other symptoms?
6. Have you visited a doctor for menstrual pain
7. Do you use painkillers?
Appendix III. De dysmenorrhea - vragenlijst (Degroote K. en Hoppenbrouwers K., Jeugdgezondheidszorg K.U.Leuven, 1996)

<table>
<thead>
<tr>
<th>Q.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Op welke leeftijd menstrueerde U voor het eerst?</td>
<td></td>
</tr>
<tr>
<td>2. Wat is de gemiddelde duur van uw cyclus?</td>
<td></td>
</tr>
<tr>
<td>3. Hoeveel menstruaties hebt U de afgelopen 12 maanden gehad?</td>
<td></td>
</tr>
<tr>
<td>4. Hoelang duurt uw menstruatie gemiddeld?</td>
<td></td>
</tr>
<tr>
<td>5. Als U menstrueert, hoeveel keer moet U dan een nieuw maandverband of een nieuwe tampon gebruiken op de dag waarop het bloedverlies het hevigst is?</td>
<td></td>
</tr>
<tr>
<td>6. Hebt U momenteel buikpijn tijdens de maandstonden?</td>
<td></td>
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<tr>
<td>7. Had U de eerste maanden dat U menstrueerde buikpijn tijdens de maandstonden?</td>
<td></td>
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<tr>
<td>8. Hebt U buikpijn buiten de menstruatieperiode?</td>
<td></td>
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<tr>
<td>9. Gebruikt U momenteel medicatie tegen buikpijn tijdens de menstruatieperiode?</td>
<td></td>
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<tr>
<td>10. Hoe frequent gebruikt U geneesmiddelen tegen buikpijn tijdens de menstruatieperiode?</td>
<td></td>
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<tr>
<td>11. Gebruikt U andere middelen dan geneesmiddelen tegen buikpijn tijdens de menstruatie?</td>
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<tr>
<td>12. Hebt U tijdens de menstruatieperiode last van hoofdpijn?</td>
<td></td>
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<tr>
<td>13. Hebt U buiten de menstruatieperiode last van hoofdpijn?</td>
<td></td>
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<tr>
<td>14. Hebt U tijdens de menstruatieperiode wel eens last van onderstaande klachten?</td>
<td></td>
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<tr>
<td>15. Gebruikt U geneesmiddelen of andere middelen tegen de klachten tijdens de menstruatie?</td>
<td></td>
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<tr>
<td>16. Gebruikt U de pil?</td>
<td></td>
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<tr>
<td>17. Komen/kwamen er regelmatig buikpijn of andere klachten tijdens de menstruatie voor bij uw moeder?</td>
<td></td>
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<tr>
<td>18. Wanneer treedt uw buikpijn op?</td>
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<tr>
<td>19. Waar treedt uw buikpijn op?</td>
<td></td>
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<tr>
<td>20. Moet U wegens de pijn gaan liggen?</td>
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<tr>
<td>21. Moet U in verband met de menstruatiepijn wel eens de lessen verzuimen?</td>
<td></td>
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<tr>
<td>22. Bent U wel eens voor menstruatiepijn naar een dokter geweest?</td>
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<tr>
<td>23. Gebruikte U in het verleden geneesmiddelen tegen buikpijn tijdens de menstruatieperiode?</td>
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<tr>
<td>24. Zijn volgens U klachten bij menstruatie een natuurlijk gebeuren?</td>
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<tr>
<td>25. Is er volgens U genoeg informatie beschikbaar over menstruatieproblemen?</td>
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<tr>
<td>26. Vindt U dat er meer aandacht aan menstruatieproblemen besteed moet worden?</td>
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</tbody>
</table>
**Appendix IV. De Vragenlijst menstruele klachten Universitair Gezondheidscentrum (Groenen G., K.U.Leuven, 1970)**

1. Zijn de maandstonden pijnlijk?
2. Wanneer treedt de pijn op?
3. In welke mate voelt u die pijn?
4. Waar is de pijn gelokaliseerd?
5. Gaat deze pijn gepaard met andere tekens?
6. Raadpleegde u reeds een geneesheer voor pijnlijke maandstonden?
7. Gebruikte u pijnstillende geneesmiddelen?
Appendix V: Rijkers questionnaire for the detection of significant menstrual and non-menstrual pain problems

(All of the questions are related to the last 6 months!)

I. General information

1. What is your date of birth?

2. Have you had your first menstrual period yet?
   □ Yes
   □ No, then you go directly to question 8

II. On the basis of the following questions we would like to map out your menstrual pattern

3. At what age did you have your first menstrual period? (Fill in your age in years and months. If you cannot remember the number of the months you may only enter the years. Ex.13 years and 5 months).

<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
</tr>
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</table>

4. On average, what is the usual number of days of your menstrual cycle? (from the first day of your bleeding at one period till the first day of bleeding at your next period)
   □ Usually shorter than 25 days
   □ Usually between 25 and 32 days (25 days included)
   □ Between 32 and 40 days (32 days included)
   □ Usually 40 days or more
5. How many days of menstrual flow do you usually have? (count the number of days that you have actual red blood loss)
   □ ≤ 2 days
   □ 3 or 4 days,
   □ 5 or 6 days
   □ ≥ 7 dagen

6. Do you experience an abundant or heavy menstrual flow?
   □ Yes
   □ No

7. Does your bleeding contain clots?
   □ Yes
   □ No

III. The following questions are about pelvic pain ( = abdominal pain)

8. Have you experienced pelvic pain over the past 6 months?
   □ Yes
   □ No, then here ends the questionnaire for you. Thank you very much for your cooperation.

9. When did you experience pelvic pain?
   □ During the menstrual period
   □ Outside the menstrual period
   □ During and outside the menstrual period
   □ I have never had a menstruation but I have pelvic pain.

10. How long have you experienced pelvic pain? Enter this question for every positive answer on the topic of question 9
   □ Less than 3 months
   □ Between 3 and 6 months
   □ Longer than 6 months
11. Has your pelvic pain worsened over the past 6 months?
   
   □ Yes
   □ No

12. Please rate on the following scale the pelvic pain you experience (0 = means no pelvic pain; 10 = means worst possible pelvic pain)
   
   □ During menstrual period:
     No pain  0-1-2-3-4-5-6-7-8-9-10  Worst possible pain
   □ Outside menstrual period:
     No pain  0-1-2-3-4-5-6-7-8-9-10  Worst possible pain

"IF YOU HAVE NEVER HAD A MENSTRUATION, YOU MAY GO DIRECTLY TO QUESTION 34,"

<table>
<thead>
<tr>
<th>IV. The following questions are about bladder and/or bowel problems during the menstrual period</th>
</tr>
</thead>
</table>

13. Have you noticed problems/ pain associated with the stool during the menstrual period? (ex. diarrhoea, constipation)
   
   □ Yes
   □ No

14. Have you noticed problems/ pain associated with urination during the menstrual period? (ex. pain, frequent urination, bladder infections)
   
   □ Yes
   □ No
15. a. Have these problems/pain with the stool worsened over the past 6 months?
   - [ ] Yes
   - [ ] No

b. Have these problems/pain with urination worsened over the past 6 months
   - [ ] Yes
   - [ ] No

16. a. Please rate on the following scale the problems/pain with the stool that you experience during your menstruation (0 = means no problems/pain; 10 = means most possible problems, pain)

   No problems/pain  0-1-2-3-4-5-6-7-8-9-10  Worst possible problem/pain

b. Please rate on the following scale the problems/pain with urination that you experience during your menstruation (0 = means no problems/pain; 10 = means most possible problems, pain)

   No problems/pain  0-1-2-3-4-5-6-7-8-9-10  Worst possible problem/pain

V. The following questions are about the use of medication during your menstrual period

17. Did you use painkillers for menstrual pain over the past 3 till 6 months
   - [ ] Yes
   - [ ] No

18. Have you ever used painkillers for menstrual pain in the past?
   - [ ] Yes
   - [ ] No, then you go directly to question 20
19. If you are/were using painkillers did your menstrual pain disappear/disappeared?
   - ☐ Yes
   - ☐ No

20. **Do/did you use** a contraceptive pill (vaginal ring/patch)?
   - ☐ Yes
   - ☐ No, then you go to question 25

21. Did the doctor prescribe a contraceptive pill (or vaginal ring/patch) because you had menstrual pain?
   - ☐ Yes
   - ☐ No, then you go to question 25

22. If you are/were using a contraceptive pill (or vaginal ring/patch) ‘without painkillers’ has your pain disappeared/did your pain disappear?
   - ☐ Yes
   - ☐ No

23. Do/did you use a contraceptive pill AND painkillers because you had/have menstrual pain?
   - ☐ Yes
   - ☐ No, then you go to question 25

24. If you are/were using a contraceptive pill AND painkillers has/did your pain disappeared/disappear?
   - ☐ Yes
   - ☐ No

25. Please rate on the following scale the (pelvic)pain you experience while you are using medication (Contraceptive pill and/or painkiller) (0 = means no pain; 10 = means most possible pain)
   - No pain 0-1-2-3-4-5-6-7-8-9-10 Worst possible pain
VI. The following questions are about your social life during your menstrual period

26. Do you sometimes miss school or work because of your menstrual pain?
   □ Yes,
   □ No, then go to question 28,

27. How often do you miss school or work every time when you have your menstrual period?
   □ Always
   □ Often (more than 50% of the times)
   □ Sometimes (about 20-50% of the times)
   □ Rarely (less than 20% of the times)

28. Are you limited in the kind of school- or work activities because of menstrual pain?
   □ Yes
   □ No

29. Are you limited in performing hobbies/ sport activities because of menstrual pain?
   □ Yes
   □ No

30. Are you limited in going out with friends because of menstrual pain?
   □ Yes
   □ No

31. Are you tired or exhausted during your menstrual period?
   □ Yes
   □ No

VII. The following questions are about pain during or after sexual intercourse

32. Are you sexually active?
   □ Yes
   □ No, then go to question 34
33. Are you limited in having sexual intercourse because of (pelvic) pain?
   □ Yes
   □ No

VIII. The following questions are related to your mother and/or sisters

34. Does/did your mother have regularly pelvic pain or other complaints during menstruation?
   □ Yes
   □ No
   □ I do not know

35. Does/did your sister(s) have regularly pelvic pain or other complaints during menstruation?
   □ Yes
   □ No
   □ I don't have a sister
   □ I do not know

IX. The following questions are about a doctor’s visit

36. Have you visited a doctor about (pelvic) pain?
   □ Yes
   □ No, then stops the questionnaire for you here. Thank you very much for your cooperation.

37. Has the doctor done some examination?
   □ Yes, namely
     ○ A vaginal examination
     ○ Blood sample
     ○ Ultrasound
     ○ Others (fill in): … …
   □ No
38. Has the doctor proposed a treatment?
   □ Yes, namely
     o Painkillers
     o Regularly use of the contraceptive pill (= three continuous weeks then
       a one week break)
     o Continuous use of the contraceptive pill (= to take the pill without
       stopping for a “period”
     o Operation (vb. laparoscopic surgery )
     o Other treatment (fill in):
   □ No, then please go to question 40

39. When you went into a treatment, did your menstrual pain disappear?
   □ Yes
   □ No

40. Did the doctor refer you to another healthcare worker? (vb. gynaecologist, internal
    specialists, urologist)
   □ Yes
   □ No

Here ends the questionnaire
Thank you very much for your cooperation!
Chapter 4

General Discussion
**General Discussion**

This PhD project focuses on endometriosis, a gynaecologic disease causing pain and fertility problems in women of reproductive age.

**Adults**

How to handle this enigmatic disease, considered to be chronic, to realize an optimal QOL, a high pregnancy rate, and a low complication and recurrence rate after surgical approach is the subject of hot discussions in literature since many years.

Medical management, based on suppression of the symptoms, is not curative and is often associated with significant side effects. Moreover, as suppression of symptoms is based on suppression of ovarian function, medical management prevents pregnancy. In addition, being not curative, discontinuation of this therapy commonly results in recurrence. Moreover, as the most severe form of this disease, DIE with intestinal involvement, often undergoes fibrotic changes, it can be resistant to hormonal therapy, which makes surgical therapy the only option for treatment of the more extensive forms of this disorder.

Different surgical strategies have been proposed for the different clinical presentations of endometriosis, more specifically for DIE with colorectal involvement. Very few long term follow-up data are available to determine which surgical approach is to prefer, and if there is only one surgical approach ‘to prefer’, in view of the end-points that should be reached, as they are: optimal QOL, high pregnancy rate, low complication and recurrence rate (Chapter 2.3) (Kennedy et al., 2005).

In this PhD thesis a clinical outcome assessment of a CO₂ laser laparoscopic radical but fertility sparing multidisciplinary surgical approach of DIE with colorectal involvement is discussed.

First of all the population at need for surgical diagnosis and treatment of endometriosis had to be identified. Therefore a retrospective case series was performed to determine the prevalence of histologically proven endometriosis in a subset of infertile women with a regular cycle (21 – 35 days), whose partner has normal semen analysis (Chapter 2.2). Without endoscopic evaluation of the female reproductive system, these couples are catalogued as having
‘unexplained infertility’ and are at risk of quickly entering an IVF program to realize a pregnancy, which is a time consuming and costly treatment.

As we found out in the selected patient population, firstly, that the prevalence of endometriosis was 47% (104/221), including stage I (39%, 41/104), stage II (24%, 25/104), stage III (14%, 15/104), and stage IV (23%, 23/104) endometriosis, and was comparable in patients with (54%, 61/113) and without (40%, 43/108) pelvic pain and secondly, that the prevalence of fertility reducing non-endometriotic tubal and/or uterine pathology was 29% in all patients (15% in women with and 40% in women without endometriosis) and thirdly, that a multivariate logistic regression model including pain, ultrasound data, age, duration of infertility and type of fertility was not or not sufficiently reliable for the prediction of endometriosis rAFS I - II and endometriosis rAFS III - IV, respectively, we concluded that reproductive surgery is indicated in infertile women belonging to the study population, regardless of pain symptoms or trans vaginal ultrasound results, since half of them have endometriosis and 40% of those without endometriosis have fertility reducing pelvic pathology.

As DIE with colorectal involvement is surgically challenging (Kennedy et al., 2005) due to the extent of the disease to organ systems beyond the scope of a gynaecologist, a systematic review (Chapter 2.7) was performed to asses clinical outcome of surgical treatment of DIE with colorectal involvement.

Our review included 49 studies and a total of 3894 patients with advanced endometriosis and colorectal extension. Remarkably, a large majority of these patients had been treated by bowel resection and reanastomosis (n = 2776, 71.2%), and only a minority had been treated by full-thickness disc excision (n = 383, 9.8%), or shaving/superficial excision (n = 679, 17.4%). The majority of studies (n = 32) included data related to surgical treatment with only bowel resection and reanastomosis. Other studies (n = 16) included data related to a combination of mixed surgical techniques in different patients, mostly either resection and reanastomosis or disc excision. Only 1 study included data related to full-thickness disc excision only. The bowel resection and reanastomosis group included the highest number of patients, was fairly homogenous, and allowed a meaningful analysis. It was impossible to meaningfully analyze the mixed surgical group since outcome was very often not specified according to surgical technique used (bowel resection and reanastomosis, disc excision or another surgical technique).
technique). The group of patients with discoid excision only was described in only 1 study with limited outcome data. In general, data were reported in such a way that comparison of different surgical techniques was not possible.

In this review, both the total recurrence rate and the visually and/or histologically proven recurrence rate appeared to be lower in the bowel resection and reanastomosis group (5.8% and 2.5%, respectively) than in the mixed study group (17.6% and 5.7%, respectively). On the other hand, most of the severe complications of this radical type of surgery are related to bowel surgery.

We agree with the statement of the President of the World Endometriosis Foundation, Hans Evers, that not all laparoscopies are equal, and that we need to include patient perception and patient preferences (Harvey and Warwick, 2010) into our clinical management and in our follow-up studies in order to answer the question: how can we be aggressive enough to remove all destructive endometriosis and prevent recurrence, but at the same time be not too aggressive that QOL is affected by bladder dysfunction, digestive problems, intestinal complaints and sexual pain (Evers, 2010).

In a complex population with recurrent endometriosis – from patient perspective – we have shown, in two retrospective cohort studies and in one prospective follow-up study (Chapters 2.4, 2.6, 2.8), that our surgical approach results in a better outcome when compared with those reported in our systematic review of clinical outcome after bowel resection and reanastomosis for bowel endometriosis (Chapter 2.7) (Meuleman, Tomassetti et al., 2011) with respect to complications requiring surgical intervention [3% versus 4.5% (Meuleman et al., 2011)], pregnancy rate [50% versus 39% (Meuleman et al., 2011)], and endometriosis recurrence rate [5% versus 10% (Meuleman et al., 2011)]. Additionally, we report fertility outcome and recurrence data using life table analysis [used before in only 1 other study (Coronado et al., 1990) and used as first ever, respectively]. This is surprising in view of the fact that it is generally accepted for more than 20 years (Olive, 2003) that life table analysis is the best way to calculate fertility outcome while controlling for the duration of follow-up and drop-out rate for each patient and should, for the same reasons, perhaps also be used to calculate recurrence rate.
Furthermore, we used patient-based VAS to assess the major pain complaints [used in less than 20% of studies covered in our review (Meuleman et al., 2011)]. According to current consensus (Vincent et al., 2010), a patient-based 11-point Numerical Rating Score, in which the pre-operative and post-operative symptoms are given by the patient, allows a better evaluation of the postoperative pain situation as well as the evaluation of de novo pain symptoms possibly associated with a specific type of surgery, when compared to the rating of symptom prevalence and severity by others (physicians, nurses) who may be biased themselves or may introduce bias among patients. Additionally, we also reported data on the Quality of Live after treatment for extensive DIE with colorectal extension [reported in only 10% of studies covered in our review (Meuleman et al., 2011)].

The type and success of our strategic measures to prevent lower limb compartment syndrome, a complication that occurred during complex multidisciplinary laparoscopic surgery, was reported (Chapter 2.5).

Overall, we can conclude that the multidisciplinary surgical team that was build up over the past 15 years, to perform a radical but fertility sparing resection of extensive endometriosis with involvement of surrounding organ systems, realizes a good clinical outcome with low complication and recurrence rate, a very good improvement of QOL and a high pregnancy rate.

**Future issues regarding design of clinical outcome studies in surgical treatment of endometriosis**

The time has come to seek international agreement on terms and definitions in clinical outcome studies after endometriosis surgery in order to achieve standardized reporting of presenting symptoms, preoperative tests, inclusion criteria, pre-, per- and postoperative care, complications, follow-up, patient centred assessment of pain and QOL, fertility and recurrence corrected for postoperative use of hormonal suppression or infertility treatment, and we have made a first proposal in that direction (Meuleman et al., 2011).

With regard to the comparison of clinical outcome of different surgical managements of extensive forms of endometriosis the major problem is that in fact the quality of the different surgeons is compared (and not the quality of the different techniques) as every study reports the best results a surgeon can realize. On the other hand, it is very hard to have a control
group with no treatment as this is unethical in view of the pain suffered by patients and the results achieved in cohort studies (Meuleman et al., 2011).

Moreover it is also impossible to have a control group with another treatment by the same group of surgeons (i.e. a randomized controlled trial comparing a more conservative approach with a more radical approach) as surgeons have their own skills and preferences (Fan et al., 2010).

It is also difficult to set up a randomized controlled trial in the same hospital centre comparing 2 groups of surgeons as, due to historical and psychological issues, in most of the centres where this would be eventually possible, their risk to be a lack of agreement on essential outcome variables. However, it would be possible to compare complication rate and recurrence rate by clinical audit performing retrospective assessment of patient records (i.e. all patients with transmural invasion protocollled at bowel barium enema and treated with bowel resection and reanastomosis versus discoid excision and suturing).

Due to all those arguments, the best solution seems to reach agreement on study design and reporting of clinical outcome data after endometriosis surgery (international consensus meeting planned in 2012) and to set up a multicenter study with clear patient identification and outcome parameters, based on the checklist proposed in our systematic review (Meuleman et al., 2011).

We would like to propose to organize a multicenter study with for instance 5 centres specialized in surgical treatment of bowel endometriosis as defined by Chapron (Chapron et al., 2003). The respective surgeons should agree on patient inclusion criteria (i.e. based on a mutually agreed aspect of the bowel wall at bowel barium enema). Each surgeon could use his own surgical technique as this aims at realizing the best possible results for each centre. Patient centred VAS of endometriosis associated pain symptoms and a disease specific Quality of Live questionnaire [i.e. EHP30, (Jones et al., 2001)] should be used, preoperatively and during a follow-up period of at least 2 years after surgery. As such, a Before-After Study is realized in each centre, assuming that the observed differences in the outcomes of respective interventions will be attributable to the type and quality of the interventions in each centre, allowing the comparison of different surgical techniques for a well defined patient population (Fan et al., 2010). Life table analysis, controlling for the duration of follow-up and drop-out rate for each patient, should be used to calculate recurrence rates and pregnancy
rates. Postoperative hormonal treatment and fertility treatment/pregnancy should be registered. For such a multicenter study, evaluating different surgical approaches, eventually funding could be seek from the World Endometriosis Society or the European Union. The final aim should be that every surgical team tries to ameliorate his own technique to realize the lowest complication and recurrence rate, the highest pregnancy rate as well as an optimal level of QOL for the local patient population as every surgical approach which realizes this outcome measurements is per definition a good surgical approach.

Focusing on the problem which surgical approach is to prefer for extensive endometriosis, a possible research framework is the complex intervention framework (developed by the Medical Research Council, UK - www.mrc.ac.uk/complexinterventionsguidance). This framework is describing 5 phases (in line with the phases of clinical trials): theory (developing an intervention), modelling (piloting and feasibility), exploration (evaluating the intervention), testing (reporting) and follow-up (implementation).

The surgical approach of extensive endometriosis can be considered as a ‘complex intervention’ as flexibility or tailoring of the intervention is inevitable, making the intervention ‘complex’. The implications for development and evaluation of a certain surgical approach of extensive endometriosis are that strict fidelity to a protocol is inappropriate, even not possible, as adaptation to a local setting and to the skills and the preferences of the surgeon are inevitable.

The outcome measures formulated through this PhD project are: complication rate, recurrence rate, pain, QOL and pregnancy rate. One has to be aware of the fact that not the reproducibility of the intervention ‘as such’ is important, as well that every surgeon adapts his/her surgical management of extensive endometriosis in order to achieve the best possible results of the end-points formulated.

According to the above mentioned research framework, the evaluation of the ESHRE guidelines (Chapter 2.3) and the systematic review focusing on the surgical treatment of DIE with colorectal involvement (Chapter 2.7) can be considered as the base of the ‘theory’ phase. It results in the conclusion that for these extensive forms of endometriosis, surgery is the preferred treatment. There are no data reported that allow comparison of different surgical techniques.
Endometriosis is considered a chronic disease with a high recurrence rate after surgical treatment. As extensive endometriosis has logically started as minimal/mild disease and as it is clear that radical resection of minimal/mild disease has a positive effect upon pain and fertility problems (Kennedy, 2005), also moderate/severe forms of endometriosis have to be resected radically otherwise moderate/severe forms are only reduced to minimal/mild forms which logically results in quick recurrence of symptoms as not all endometriosis has been removed. On the other hand, radical resection of moderate/severe forms guides the gynaecologic surgeon to work upon surrounding organ systems as there are: the bowel, the ureters, the bladder. To avoid complications due to the fact that working upon the surrounding organ systems is in principle beyond the scope of a gynaecologist, probably a multidisciplinary surgical team is the way to afford low recurrence rates thanks to the combined possibility of being radical but being able to restore the impact of radical excision surgery on surrounding organ systems with the best possible results.

The retrospective studies of Chapters 2.4 and 2.6 can be considered as the ‘modelling phase’ of the abovementioned framework. Both retrospective case studies underline the feasibility of the technique (radical/multidisciplinary). According to a logic line of thought radical surgery seems necessary due to the presence of ‘remaining endometriosis’ in bowel resection specimens after apparently ‘complete’ removal of all macroscopically visible endometriosis by the gynaecologic surgeon. Moreover, as we wanted to evaluate our surgical technique as good as possible, the items suggested in the CONSORT inspired checklist, suggested in our systematic review (Chapter 2.7), have been reported.

To deal with recall bias of the retrospective design and to ensure that the validity of the statement that radical surgery provides no supplementary risk for complications in case it is performed in a multidisciplinary setting and, moreover, results in lower recurrence rate, optimal QOL and good pregnancy rate, a prospective follow-up of all patients operated at the LUFc was organized (Chapter 2.8). The advantage of the prospective follow-up was that the whole group of patients with moderate/severe endometriosis could be selected, taking into account the ‘complexity of the intervention’. Indeed, the ‘surgical treatment for extensive endometriosis’ does not follow a strict protocol about which patient undergoes a bowel resection. However, the level of multidisciplinarity depends on the situation during laparoscopy at the moment of intervention. As such, bias due to retrospective selection of a
cohort of patients, is overcome. This prospective study can be considered as a part of the ‘exploration phase’ of the abovementioned framework.

The results of this technique can stand the comparison with the results mentioned in our systematic review (they are even better than the results mentioned in literature) as part of the ‘testing phase’. But, to be sure about the added value of working radical and therefore multidisciplinary, and taking into account the limited possibility to compare the results published of different surgical techniques, due to incomplete reporting in literature, a more thorough ‘testing phase’ of the above mentioned research framework needs to be developed, possibly by a multicenter cluster randomized trial.

First of all, in a consensus meeting, a group of centres focusing on surgical treatment of extensive endometriosis, need to agree about the patients to include and the items to report about those patients. Further on, one has to be aware of the fact that each surgeon can only operate according to his/her own skills, conviction and the local possibilities. As such, the different surgical techniques can be compared according to the endpoints that should be reached: the lowest possible complication rate and recurrence rate, together with the highest possible pregnancy rate and QOL possible.

As such, in the ‘follow-up’ phase, the endpoint results can be compared so that every surgeon, by consulting/watching (teleconference, life surgery etc.) the surgical technique of the colleagues with better endpoint results. This allows each surgeon to become aware of those elements that can be added to his/her own technique in order to improve it and to reach a better level of endpoint results. As such, based on a comparison of surgical techniques and an evaluation of results of the end-points formulated (considered as decision making elements), a change in individual behaviour can perhaps be reached. In this context, there is no ‘best surgeon’, but every surgeon is stimulated to improve his/her own technique in order to reach the best endpoint results.

Finally, in a first ever Health Economic assessment in a prospective follow-up study (Chapter 2.9), a significant difference was demonstrated between the total non-health care costs of patients with a rAFS I, II and III classification and the total non-health care costs of patients in stage rAFS IV. The cost data (health care and non-health care) can be fed into economic evaluations, so that decision makers can ascertain the cost-effectiveness of various
approaches to diagnose and treat endometriosis by examining their effectiveness in relation to their costs.

Moreover, this stage of the disease should be prevented by an earlier diagnosis. Years of pain and disability as well as a lot of money could be saved when patients, at risk of developing (extensive forms of) endometriosis could be diagnosed during adolescence.

**Adolescents**

The clinical symptoms of endometriosis are variable with, moreover, a considerable overlap with other conditions. As a result, there is often a delay of up to 12 years between symptom onset and a definitive diagnosis (Arruda *et al.*, 2003; Hadfield *et al.*, 1996; Husby *et al.*, 2003).

Recent evidence suggests that absenteism from school, and both the incidence and duration of oral contraceptive use for severe primary dysmenorrhea during adolescence is higher in women who later develop DIE than in women without DIE (Chapron *et al.*, 2010). Moreover, an early history of dysmenorrhea contains a high risk, and, on the contrary, a late age at menarche (> 14 years) contains a low risk for a later diagnosis of endometriosis (Treloar *et al.*, 2010).

In a systematic review (*Chapter 3.3*) about the prevalence of endometriosis diagnosed by laparoscopy in adolescents the overall prevalence was 62% (n = 557/893), with a prevalence of 49% in adolescents with chronic pelvic pain resistant to treatment with oral contraceptives/NSAIDs and 72% in adolescents with dysmenorrhea.

However, the papers withheld in the systematic review, report about adolescents referred to a gynaecologist, mostly one with expertise in diagnosis and (surgical) treatment of endometriosis. The percentage of girls with severe menstrual pain, who are not referred to a gynaecologist, remains unknown. Taking into account the association between menstrual pain during adolescence and endometriosis at later age, there is a need to determine the prevalence of severe menstrual cycle associated pain complaints during adolescence.
In a subset of children, born in 1996 (Chapter 3.4), the prevalence of painful menstruation was 40%, in a subset of third year high-school adolescents and of first year university young women the prevalence of pelvic pain during menstruation was 40 and 52% respectively (Chapter 3.5).

Our data (Chapters 3.4, 3.5) indicate that a significant proportion of adolescents and young adults have frequently occurring and severe pelvic pain and lower back pain during menstruation, often resistant to medical treatment with hormonal contraception and/or analgesics. We observed a rising number of complaints together with increasing age, especially in the menstrual phase. Therefore, we assume that girls already start suffering in adolescence and that the number and severity of complaints increase during adulthood. Unfortunately, dysmenorrhea is still too often considered as a physiological condition. Consequently, many physicians fail to recognize dysmenorrhea in the younger population as a possible expression of an underlying condition. Therefore, many of the young patients receive an inadequate treatment for their complaints and are often not correctly redirected to a specialist. Considering our data and the literature, it seems appropriate to assume that endometriosis is a disease affecting the younger female population. Properly administered NSAIDs, whether or not in combination with oral contraceptives, often alleviate the symptoms. When this treatment appears insufficient in order to relieve complaints, these girls should be referred to an endometriosis specialist, as they deserve additional counselling, medical treatment, and, possibly, laparoscopic investigation with surgical removal of implants at the time of diagnosis, followed by continuous administration of low-dose combination oral contraceptives to prevent recurrence. Based on a literature review, a flow chart is proposed for the management of diagnosis and treatment in adolescents with chronic pelvic pain suggestive for the presence of endometriosis (Chapter 3.2).

Based on a selection of national and international questionnaires focused on menstrual cycle related pain complaints in adolescent girls, we determined common domains and questions and developed a new screening questionnaire as a case finding instrument for adolescents at risk of endometriosis (Chapter 3.6).
Future issues regarding detection of endometriosis in adolescents and young adults and as such eventually prevent development of cases of DIE

The proposed questionnaire/screening tool can be a basis for early detection of a possible endometriosis but has to be validated multi-centrically and will be used in a pilot project to identify adolescents/young women at risk for endometriosis in the Leuven area.

Future research should focus on determining optimal approaches to identify adolescent girls with increased risk to develop endometriosis. These approaches should be integrated into routine developmental surveillance practices of clinicians who take care for adolescent girls. Formal clinical pathways should be established to refer these adolescent girls at risk for endometriosis for additional evaluations and possibly surgical interventions by gynaecologists with expertise in the diagnosis and (medical and surgical) treatment of endometriosis.

Here again the complex intervention framework can be used as a general research framework. Although the positive impact of radical excision of endometriosis on pain and fertility problems is known (Kennedy, 2005), nobody knows if radical excision of endometriosis during adolescence prevents the development of more extensive forms of endometriosis at later age. On the one hand, in a preference trial, patients not willing to undergo surgical resection of endometriosis can be compared with patients demanding an operative laparoscopy for radical solution of their pain problem. On the other hand different surgical techniques used in different centres (electrosurgery, laser surgery, excision, vaporization, coagulation, etc.) could be compared in a cluster-randomized trial.
Reference List


Chapter 5

Summary
5.1 Scientific Summary

The PhD project, entitled ‘Deeply Infiltrative Endometriosis: Clinical Outcome after Surgery in Adults and Pathways to Potential Prevention in Adolescent’ has two aims.

The first aim was to provide a clinical outcome assessment of CO2 laser laparoscopic radical excision of DIE with extension to bowel and/or bladder, in order to monitor the quality of care of the multidisciplinary surgical team developed at the LUFc over the last 15 years.

The second aim was to address ways of preventing the development of DIE by documenting the need for early diagnosis and treatment of endometriosis in adolescents and young women with significant menstruation-associated pelvic pain.

In a retrospective case series (Chapter 2.2) we reported that in a subset of infertile women with a regular cycle, whose partner has normal semen analysis the prevalence of endometriosis was 47% and was comparable in patients with (54%) and without (40%) pelvic pain. The prevalence of fertility reducing non-endometriotic tubal and/or uterine pathology was 15% in women with and 40% in women without endometriosis. A multivariate logistic regression model including pain, ultrasound data, age, duration of infertility and type of fertility was not or not sufficiently reliable for the prediction of endometriosis rAFS I - II and endometriosis rAFS III - IV, respectively. Therefore we concluded that reproductive surgery is indicated in infertile women belonging to the study population, regardless of pain symptoms or transvaginal ultrasound results, since half of them have endometriosis and 40% of those without endometriosis have fertility reducing pelvic pathology.

A systematic review (Chapter 2.7) performed to assess clinical outcome of surgical treatment of DIE with colorectal involvement included 49 studies and a total of 3894 patients with advanced endometriosis and colorectal extension. A large majority of these patients had been treated by bowel resection and reanastomosis (n = 2832, 72.7%), and only a minority had been treated by full-thickness disc excision (n = 383, 9.8%), or shaving/superficial excision (n = 679, 17.4%). Both the total recurrence rate and the visually and/or histologically proven recurrence rate appeared to be lower in the bowel resection anastomosis group (5.8% and 2.5%, respectively) than in the mixed study group (17.6% and 5.7%, respectively). On the other hand, most of the severe complications of this radical type of surgery were related to
bowel surgery. In general, data were reported in such a way that comparison of different surgical techniques was not possible.

Therefore, we made a first proposal (checklist) in the direction of an international agreement on terms and definitions in clinical outcome studies after endometriosis surgery in order to achieve standardized reporting. This checklist was applied in two retrospective cohort studies (Chapters 2.4, 2.6) and in one prospective follow-up study (Chapter 2.8) in a complex population with predominantly recurrent endometriosis. In these studies, our surgical approach results in a better outcome than reported in our systematic review of clinical outcome after bowel resection and reanastomosis for bowel endometriosis with respect to: complications requiring surgical intervention (3% versus 4.5%), pregnancy rate (50% versus 39%) and endometriosis recurrence rate (5% versus 10%). Additionally, we were the first group to report recurrence data and the second group to report fertility outcome data using life table analysis, generally considered as the best way to calculate reproductive outcome. Furthermore, we used patient-based VAS to assess complaints, an approach used in less than 20% of studies covered in our review, but considered to be superior to physician-based assessment of pain symptoms. Finally, our 3 studies measured patient perception of QOL using validated questionnaires, which has been reported in only 10% of studies covered in our review on surgical treatment for extensive DIE with colorectal involvement.

The type and success of our strategic measures to prevent lower limb compartment syndrome, a complication that occurred during complex multidisciplinary laparoscopic surgery before 2004, was reported (Chapter 2.5).

Overall, we can conclude that the multidisciplinary surgical team that was built up over the past 15 years, to perform a radical but fertility sparing resection of extensive endometriosis with involvement of surrounding organ systems, realizes a good clinical outcome with low complication and recurrence rate, a very good improvement of QOL and a high pregnancy rate.

Moreover, in a first ever Health Economic assessment in a prospective follow-up study a significant difference was demonstrated between the total non-health care costs of patients with a rAFS I, II and III classification and of patients in stage rAFS IV (Chapter 2.9). These cost data (health care and non-health care) can be fed into economic evaluations, so that
decision makers can ascertain the cost-effectiveness of various approaches to diagnose and treat endometriosis by examining their effectiveness in relation to their costs.

For future research evaluating surgical treatment of extensive endometriosis, it is important to reach agreement on study design and on reporting clinical outcome data. A multicenter study with clear patient identification and well defined outcome parameters, based on the checklist proposed in our systematic review needs to be set up.

Moreover, it is important to prevent DIE with colorectal extension, ideally by early identification and management of girls and women at risk. Years of pain and disability as well as a lot of money could be saved when patients, at risk of developing (extensive forms of) endometriosis could be diagnosed during adolescence.

In a literature search the prevalence, the pathogenesis and the clinical manifestations of endometriosis in adolescents are reported (Chapter 3.2). The importance of a thorough history taking, a vaginal examination and technical investigations to diagnose endometriosis in adolescents is discussed as well as different options to treat the complaints of the adolescent. A flow chart is proposed for the management of diagnosis and treatment in adolescents with chronic pelvic pain suggestive for the presence of endometriosis.

In a systematic review, the prevalence of laparoscopically diagnosed endometriosis in adolescents was 62% (n = 557/893), with a prevalence of 49% in adolescents with chronic pelvic pain, 76% in adolescents with chronic pelvic pain resistant to treatment with oral contraceptives/Non-Steroidal anti-inflammatory drugs and 72% in adolescents with dysmenorrhea (Chapter 3.3).

In a subset of children, born in 1996, the prevalence of painful menstruation was 40% (Chapter 3.4), whereas in a sample of third year high-school adolescents and of first year university young women the prevalence of painful menstruation was 40% and 52% respectively (Chapter 3.5). These data suggest that the prevalence of pain increases with increasing age, especially in the menstrual phase. Properly administered NSAIDs, whether or not in combination with oral contraceptives, often alleviate the symptoms. When this treatment appears insufficient in order to relieve pain complaints, the girls should be referred
to an endometriosis specialist and offered laparoscopy, which remains the gold standard in the diagnosis of endometriosis.

Based on a selection of national and international questionnaires focused on menstrual cycle related pain complaints in adolescent girls, we determined common domains and questions and developed a new screening questionnaire as a case finding instrument for adolescents at risk of endometriosis (Chapter 3.6). Studies that evaluate the effectiveness of this screening instrument including risk factors could lead to a more standardized approach, to define gold standards and acceptable referral criteria.
5.2 Wetenschappelijke Samenvatting

Het doctoraatsproject met als titel ‘Deeply Infiltrative Endometriosis: Clinical Outcome after Surgery in Adults and Pathways to Potential Prevention in Adolescents’ bestaat uit twee delen.

In het eerste deel van dit project werd het klinisch resultaat onderzocht van radicale excisie van diep infiltrerende endometriose (DIE) met uitbreiding naar darm en/of blaas door middel van CO₂ laser laparoscopie, teneinde de zorgkwaliteit van het multidisciplinair chirurgisch team ontwikkeld binnen het Leuvens Universitair Fertiliteitcentrum (LUFc) gedurende de laatste 15 jaar, te evalueren.

In het tweede deel van dit project werd de focus gelegd op manieren om de ontwikkeling van DIE bij adolescenten en jong volwassen vrouwen te voorkomen. Een vroege diagnose en behandeling van endometriose bij adolescenten en jong volwassen vrouwen met uitgesproken, aan de menstruatie gerelateerde, onderbuikpijn is het belangrijkste element in deze preventie.

In een retrospectieve casus studie (Hoofdstuk 2.2) uitgevoerd in een groep vrouwen met vruchtbaarheidsproblemen gekenmerkt door een regelmatige cyclus en waarvan de sperma-analyse van de partner normaal was, was de prevalentie van endometriose 47%. De prevalentie van endometriose was bovendien vergelijkbaar in patiënten met (54%) en zonder (40%) onderbuikpijn. De prevalentie van vruchtbaarheidsverminderende pathologie ter hoogte van eileiders en/of baarmoeder was 15% in patiënten met en 40% in patiënten zonder endometriose. Een multivariaat logistisch regressiemodel waarin pijn, gegevens van de transvaginale echografie, leeftijd, duur en soort van vruchtbaarheidsproblemen werden opgenomen, bleek niet of onvoldoende de aanwezigheid van minimale/milde en van matige/ernstige endometriose te kunnen voorspellen. Deze studie leidde tot het besluit dat reproductieve chirurgie aangewezen is bij patiënten met vruchtbaarheidsproblemen die deel uitmaken van de studiepopulatie, onafhankelijk van pijnklachten of van de resultaten van een transvaginale echografie, aangezien de helft van hen endometriose heeft en van diegenen bij wie geen endometriose kan worden vastgesteld, 40% andere vruchtbaarheidsreducerende bekkenpathologie vertoont.

In een systematische review van de literatuur (Hoofdstuk 2.7), uitgevoerd om het klinisch resultaat van de chirurgische behandeling van DIE met uitbreiding naar de darm te evalueren,
werden 49 studies weerhouden. In totaal betrof het 3894 patiënten met ernstige endometriose, uitbreidend naar de darm. De overgrote meerderheid van deze patiënten was behandeld door middel van resectie van het aangetaste darmsegment (n = 2832; 72,7%), een minderheid was behandeld door middel van resectie van de darm endometriose waarbij het aangetaste deel van de wand werd verwijderd (n = 383; 9,8%) of door middel van oppervlakkig afschaven (n = 679; 17,4%). Zowel de totale ratio van het opnieuw optreden van endometriose, als de ratio van de visueel en/of histologisch bewezen opnieuw opgetreden endometriose scheen lager in de groep met darm resectie (5,8% en 2,5%, respectievelijk) dan in de groep waarbij verschillende operatietechnieken werden gehanteerd (17,6% en 5,7%, respectievelijk). Anderzijds bleken de meest ernstige complicaties van deze radicale chirurgie gerelateerd aan de darmchirurgie. In het algemeen was er evenwel zo weinig eenvormigheid in het rapporteren van resultaten dat een vergelijking tussen de verschillende chirurgische technieken niet mogelijk was.

Om gelijkvormigheid te bekomen in het rapporteren van klinische uitkomst van endometriose chirurgie werd een controlelijst opgesteld met termen en definities. Deze controlelijst werd toegepast in twee retrospectieve cohortstudies (Hoofdstukken 2.4, 2.6) en in een prospectieve opvolgstudie (Hoofdstuk 2.8) in een populatie van patiënten met in hoofdzaak recidiverende endometriose. Uit deze studies blijkt dat de chirurgische benadering van uitgebreide endometriose, zoals ontwikkeld in het LUFc, resulteert in betere resultaten dan waargenomen in het systematische literatuuronderzoek aangaande de klinische uitkomst na darmresectie voor darmendometriose betreffende complicaties die een interventie vereisen (3% versus 4,5%), zwangerschapsratio (50% versus 39%) en het opnieuw optreden van endometriose (5% versus 10%). Bovendien waren wij de eerste onderzoeksgroep die gebruik maakte van ‘life table’ analyse om gegevens rond het opnieuw optreden van endometriose te rapporteren en de tweede groep die op die manier resultaten met betrekking tot vruchtbaarheid rapporteerde. Bovendien vroegen we aan de patiënten om aan hun pijn een visuele score toe te kennen op een pijnschaal. Ondanks het feit dat deze methode om pijnklachten te evalueren betrouwbaarder is dan indien de klachten door een arts worden genoteerd, werd deze benadering gebruikt in slechts 20% van de studies behandeld in onze systematische review. Tot slot werd de perceptie van de levenskwaliteit van de patiënt geëvalueerd met gevalideerde vragenlijsten.
Tijdens langdurige, complexe multidisciplinaire chirurgie bestaat het risico op compartimentsyndroom van de kuit indien de patiënte in de voor gynaecologen vertrouwde lithotomie positie wordt geïnstalleerd. Een aangepaste installatietechniek werd ontwikkeld en deze techniek alsmede de gunstige resultaten werdengerapporteerd (Hoofdstuk 2.5).

Samenvattend kan besloten worden dat het multidisciplinair chirurgisch team dat gevormd werd gedurende de voorbije 15 jaar met als doel om endometriose met uitbreiding naar de omgevende orgaansystemen te verwijderen op een radikale doch vruchtbaarheidssparende/-herstellende manier, een goed klinisch resultaat neerzet met een lage complicatieratio en een lage kans op opnieuw optreden van endometriose, een goede verbetering van de levenskwaliteit en een hoog zwangerschapsceijfer.

Bovendien werd tijdens de prospectieve opvolgstudie eveneens een gezondheidseconomische evaluatie verricht waarbij een significant verschil werd vastgesteld tussen de totale niet-gezondheidskost voor patiënten met minimale, milde en matige vormen van de ziekte enerzijds en ernstige vormen van de ziekte anderzijds (Hoofdstuk 2.9). Zowel de gezondheids- als de niet-gezondheidskosten kunnen het onderwerp uitmaken van economische evaluaties van de verschillende benaderingen in de diagnose en behandeling van endometriose. Zo kan een kosten-baten analyse gemaakt worden van diagnostische/therapeutische methoden.

Voor verder onderzoek naar de beste chirurgische benadering van uitgebreide endometriose dient een consensus bereikt te worden over hoe studies dienen te worden opgezet en hoe de klinische uitkomst dient te worden gerapporteerd.

Bovendien lijkt het evident dat een poging dient ondernomen te worden om DIE met uitbreiding naar de darm te voorkomen, bij voorkeur door vroegtijdige identificatie en behandeling van adolescenten en jong-volwassenen die het risico lopen deze aandoening te ontwikkelen. Jaren van ongemak en pijn zouden kunnen voorkomen worden en een hele hoop geld zou kunnen bespaard worden indien patiënten die het risico lopen om een uitgebreide vorm van endometriose te ontwikkelen, zouden kunnen gediagnosticeerd worden tijdens de adolescentie.
In een literatuuronderzoek werd de prevalentie, de pathogenese en de klinische verschijningsvormen van endometriose bij adolescenten gerapporteerd (Hoofdstuk 3.2). Het belang van een grondige anamnese, een vaginaal onderzoek en technische onderzoeken om endometriose bij adolescenten te diagnosticeren, wordt geschat alsook de verschillende behandelingsopties om klachten bij adolescenten te behandelen. Een stroomdiagram werd voorgesteld om de diagnose en behandeling te begeleiden van adolescenten met chronische pijn in de onderbuik die een indicatie voor endometriose zou kunnen zijn.

Uit een systematisch literatuuronderzoek blijkt dat de prevalentie van laparoscopisch vastgestelde endometriose bij adolescenten 62% (n = 557/893) was, waarbij de prevalentie 49% bedroeg bij adolescenten met chronische onderbuikpijn, 76% bij adolescenten met chronische onderbuikpijn resistent aan een behandeling met orale anticonceptiva/niet-steroidale anti-inflammatoire medicatie en 72% bij adolescenten met dysmenorrée (Hoofdstuk 3.3). De prevalentie van pijnlijke menstruatie in een groep kinderen geboren in 1996 was 40% (Hoofdstuk 3.4). De prevalentie van pijnlijke menstruatie bij een cohorte adolescenten uit het derde middelbaar en een cohorte eerstejaarsstudenten aan de universiteit was respectievelijk 40% en 52% (Hoofdstuk 3.5). Deze gegevens suggereren dat de prevalentie van menstruatie gebonden pijn toeneemt met de leeftijd. Toediening van niet-steroidale anti-inflammatoire middelen, al dan niet in combinatie met orale anticonceptiva, verlichten vaak de symptomen. Indien deze medicamenteuze benadering niet volstaat, zouden de adolescenten en jongvolwassen vrouwen doorverwezen moeten worden naar een endometriosespecialist voor een laparoscopie. Dit laatste onderzoek is immers de gouden standaard voor de diagnose van endometriose.

Op basis van een selectie van nationale en internationale vragenlijsten die zich richten op pijnklachten gerelateerd aan de menstruele cyclus, definieerden we gemeenschappelijke domeinen en vragen en ontwikkelden we een nieuwe vragenlijst om adolescenten op te sporen die het risico lopen om op latere leeftijd ernstige vormen van endometriose te ontwikkelen (Hoofdstuk 3.6). Onderzoek dat de doeltreffendheid van dit opsporingsinstrument evalueert, inclusief de verschillende risicofactoren, zou kunnen leiden tot een meer gestandardizeerde aanpak en tot het vinden van gouden standaarden en aanvaardbare doorverwijscriteria.
5.3 Lay Summary

Endometriosis is named from the word "endometrium", which is the lining of the uterus. When the endometrial stroma and glands (which should be located only inside the uterus) are also found outside the uterus, we talk about endometriosis. The precise origin of endometriosis remains unknown. This disease predominantly affects women of reproductive age and is associated with pelvic pain and infertility. The prevalence of endometriosis in the general female population has been estimated to be 10%. DIE is a form of endometriosis in which organs such as the bowel and the bladder are affected with endometriotic tissue.

In a first part of this study, we investigated the clinical outcome of radical excision of DIE with extension to bowel and/or bladder. First, we noted that reproductive surgery is indicated in infertile women with a regular cycle whose partner has normal semen analysis. Half of these women seem to have endometriosis and 40% of those without endometriosis have fertility reducing pelvic pathology.

Secondly, we performed a systematic review to assess the clinical outcome of surgical treatment of DIE with colorectal involvement. Unfortunately, the way results are reported in literature made a comparison of the different surgical techniques impossible. In order to report data in a standardized manner, we proposed to apply a checklist. This checklist contains terms and definitions in clinical outcome studies after endometriosis surgery. We used this checklist in 3 of our studies. In these studies, our surgical approach showed better results than those reported in literature with respect to complications requiring surgical intervention, pregnancy rate and endometriosis recurrence rate. Additionally, we reported recurrence data and fertility outcome data using life table analysis. Furthermore, we asked patients to visually score their pain on a scale. Finally, we measured patient perception of QOL using validated questionnaires.

In this PhD project we also compared the total non-health care cost of patients with a mild to moderate endometriosis and of patients with severe endometriosis.

Overall, we can conclude from this first part that the multidisciplinary surgical team that was built up over the past 15 years delivers high quality work. We have obtained low complication and recurrence rates, a very good improvement of QOL and a high pregnancy rate. For future
research on this topic, it is important to reach agreement on how to perform the study and how to report the study results. A multicenter study with clear patient identification and well defined outcome parameters, based on the checklist proposed in our systematic review needs to be set up.

In a second part of this PhD project, we addressed ways of preventing the development of DIE in adolescents and young women. Early identification and management of girls and women at risk plays an important role in this prevention. Years of pain and disability as well as a lot of money could be saved when patients, at risk of developing (extensive forms of) endometriosis could be diagnosed during adolescence.

We reported the prevalence, the pathogenesis and the clinical manifestations of endometriosis in adolescents. A flow chart is proposed for the management of diagnosis and treatment in adolescents with chronic pelvic pain suggestive for the presence of endometriosis. Additionally, our data suggest that the prevalence of pain increases with age, especially in the menstrual phase. Properly administered pain killers, whether or not in combination with oral contraceptives, often alleviate the symptoms. When this treatment does not relieve pain complaints, the girls should be referred to an endometriosis specialist.

Finally, we developed a new screening questionnaire as an instrument for identifying adolescents at risk of endometriosis. Studies that evaluate the effectiveness of this screening instrument including risk factors could lead to a more standardized approach, to define gold standards and acceptable referral criteria.
5.4 Samenvatting voor leken

De benaming endometriose is afgeleid van het woord “endometrium”, de slijmvlieslaag van de baarmoeder. Normaal bevindt dit slijmvlies zich enkel in de baarmoeder, maar wanneer we dit weefsel buiten de baarmoeder terugvinden, spreken we van endometriose. De exacte oorsprong van endometriose is tot op heden niet gekend. Deze ziekte treft hoofdzakelijk vrouwen van vruchtbare leeftijd. De belangrijkste symptomen zijn pijn in de onderbuik en onvruchtbaarheid. Naar schatting komt endometriose voor bij 10% van de vrouwen. Diep infiltrerende endometriose (DIE) is een vorm van endometriose waarbij verschillende organen zoals de darmen en de blaas aangetast zijn door de wildgroei van de slijmvlieslaag.

In een eerste deel van deze studie hebben we de klinische uitkomst onderzocht van het radicaal weghalen van DIE met een extensie naar de darmen en/of blaas. In eerste instantie hebben we gevonden dat chirurgie aangewezen is bij onvruchtbare vrouwen met een regelmatige menstruele cyclus die een partner met een normale spermakwaliteit hebben. De helft van deze vrouwen heeft endometriose en van diegenen die geen endometrioses hebben, lijdt 40% aan een aandoening ter hoogte van het bekken die de vruchtbaarheid vermindert.

Ten tweede voerden we een systematische review uit om de klinische uitkomst van een chirurgische behandeling van DIE met colorectale uitzetting te bekijken. Jammer genoeg laat de manier waarop de resultaten in de literatuur gemeld worden geen vergelijking toe van de verschillende chirurgische technieken. Om ervoor te zorgen dat resultaten op dezelfde wijze worden gerapporteerd, hebben we een controlelijst opgesteld. Deze controlelijst bevat termen en definities voor het rapporteren van de klinische uitkomst na endometriose chirurgie. We hebben deze controlelijst ook toegepast in 3 van onze studies. Uit deze studies blijkt dat onze chirurgische aanpak leidt tot betere resultaten dan die gemeld worden in de literatuur, vooral op het vlak van complicaties, zwangerschapsceiijer en terugkeer van endometriose. Daarenboven hebben we de gegevens over de terugkeer van endometriose en vruchtbaarheid berekend met ‘life table analysis’. Bovendien hebben we aan de patiënten gevraagd om aan hun pijn een visuele score toe te kennen op een pijnschaal. Tenslotte hebben we de perceptie van de levenskwaliteit van de patiënt geëvalueerd met gevalideerde vragenlijsten.
In dit doctoraatsproject vergeleken we ook de totale niet-gezondheidskost van patiënten met een milde tot matige vorm van endometriose en van patiënten met een ernstige vorm van de ziekte.

Globaal kunnen we besluiten uit dit eerste deel dat het multidisciplinaire chirurgisch team dat we de voorbije 15 jaar hebben opgebouwd werk van hoge kwaliteit levert. We bekwamen een laag aantal complicaties, een grote verbetering van de levenskwaliteit en een hoog zwangerschapscliënt en de terugkeer van endometriose was ook laag. Voor verder onderzoek naar dit onderwerp is het belangrijk dat er een akkoord kan gevonden worden over hoe het onderzoek moet gevoerd worden en hoe de resultaten moeten gerapporteerd worden. Het is nodig om een multicentrisch onderzoek op te zetten met een duidelijke identificatie van de patiënt en goed gedefinieerde uitkomstfactoren gebaseerd op de controlelijst die we hebben voorgesteld in onze review.

In een tweede deel van dit doctoraatsproject hebben we ons gericht op verschillende manieren om de ontwikkeling van DIE bij adolescenten en jonge vrouwen te voorkomen. Een vroege vaststelling en begeleiding van meisjes en vrouwen die risico lopen speelt een belangrijke rol in deze preventie. De patiënten die risico lopen op de ontwikkeling van (zware) endometriose zouden jaren van pijn en belemmeringen en ook veel geld bespaard kunnen worden indien deze ziekte zou kunnen opgespoord worden tijdens de adolescentie.

We hebben de prevalentie, de pathogenese en de klinische manifestaties van endometriose in adolescenten beschreven. Er werd een stroomdiagram voorgesteld om de diagnose en behandeling te begeleiden van adolescenten met chronische pijn in de onderbuik, wat een indicatie voor endometriose kan zijn. Daarenboven suggereren onze resultaten dat de prevalentie van pijn stijgt in functie van de leeftijd, zeker in de menstruele fase. Juiste toediening van pijnstillers, al dan niet in combinatie met orale contraceptiva, verzacht vaak de symptomen. Als deze behandeling niet volstaat om de pijnklachten te verminderen zouden deze meisjes moeten doorverwezen worden naar een endometriosespecialist.

Tenslotte hebben we een nieuwe vragenlijst ontwikkeld die kan dienen als een instrument om adolescenten op te sporen die risico lopen op endometriose. Onderzoek dat de doeltreffendheid van dit opsporingsinstrument nagaat, inclusief de verschillende
risicofactoren, zou ons kunnen brengen tot een meer gestandaardizeerde aanpak en tot het vinden van gouden standaarden en aanvaardbare doorverwijscriteria.
Curriculum Vitae

Christel Louis Colette Meuleman was born on November 11th 1959 in Leuven, Belgium.

After completing her secondary education (Latin-Mathematics) at the Mater-Dei Lyceum, Sint-Pieters Woluwe, Belgium (1971 - 1977) she started her university studies at the Faculty of Medicine of the Katholieke Universiteit Leuven, Belgium (1977 - 1984), where she graduated with great honours. She performed her training in Obstetrics and Gynaecology, from 1984 till 1986 under the supervision of Dr. R. Mingeot in the Sint-Michiels Kliniek, Brussels and, from 1986 till 1989 under the supervision of Prof. Dr. A. Van Assche at the University Hospital, Leuven.

After finishing her specialization, she became a staff-member of the department of Obstetrics and Gynaecology, with special interest in reproductive medicine. She focused on ‘fertility exploration and treatment’ and was instructed in reproductive surgery (by means of CO₂ laser laparoscopy) by Prof. Dr. P. Koninckx.

Since the establishment, in 1996, of the LUFc under the coordination of Prof. Dr. T. D’Hooghe, she first performed the whole range of fertility exploration, medical assisted procreation and fertility surgery. Progressively, being confronted with women in reproductive age suffering from fertility problems and pain due to severe endometriosis, she set up a multidisciplinary surgical collaboration with Prof. Dr. A. D’Hoore (colorectal surgeon) and Dr. B. Van Cleynenbreugel (urologist) to treat laparoscopically advanced endometriosis with colorectal wall invasion and/or invasion of the wall of the bladder and the ureters.

The first results of multidisciplinary CO₂ laser laparoscopic radical resection of DIE were presented at the IX World Congress on Endometriosis, in September 2005, Maastricht, The Netherlands. As part of a quality control program related to the ISO 9001 - 2000 certification of the LUFc for the management of reproductive problems, a continuous clinical outcome assessment of CO₂ laser laparoscopic radical excision of deeply infiltrative endometriosis with extension to bowel and/or bladder, in order to monitor the quality of care of the multidisciplinary surgical team developed at the LUFc since 1996, was set up. Moreover, since there are indications that adults with deeply infiltrative endometriosis were adolescents with severe pelvic pain, the idea rose of addressing ways of preventing the development of
DIE by documenting the need for early diagnosis and treatment of endometriosis in adolescents and young women with significant menstruation-associated pelvic pain.

Clinical outcome after surgery in adults and pathways to potential prevention in adolescents became the two parts of a PhD project (2006 - 2011), in which the insights Dr. Meuleman, gained during 20 years of clinical practice, were laid down. Her research was supported by the Clinical Research Fund of the University Hospital Leuven, Belgium and results of this research appeared in a series of internationally peer-reviewed publications.

Dr. Meuleman followed courses of Assisted Reproductive Technologies (Bourn Hall, Cambridge, UK, 1995) and Microsurgery (Centre of Surgical Technologies, Leuven, 2001), as well as Biomedical Statistics (K.U. Leuven, 1990, V.U. Brussels, 2006), Good Clinical Practice (Leuven, 2004) and ‘Evidence-Based Medicine’ (CEBAM, Leuven, 2006). ‘Academic Writing and Presentation Skills for Doctoral Students’ were courses followed as part of her doctoral training. To gain insights in how to make a success of a multidisciplinary team, she followed courses in Negotiation Techniques (ProCom, Leuven, 2003), as well as a course about general and financial management in a hospital setting at the Vlerick School of Leuven (2006). Since 2001, Dr. Meuleman is herself responsible for the course ‘Fertility Exploration and Treatment’ in the 3th bachelor of midwifery at the K.H. Leuven.

Dr. Meuleman is a member of the Flemish Society of Obstetrics and Gynaecology (VVOG), the Belgian Society for Reproductive Medicine (BSRM), the Society for Fertility Study, The European Society of Human Reproduction and Embryology (ESHRE), the American Society of Reproductive Medicine (ASRM), the European Society for Gynaecologic Endoscopy (ESGE), the American Association of Gynaecologic Laparoscopists (AAGL), The International Society for Gynaecologic Endoscopy (ISGE) and the World Endometriosis Society (WES).

Christel Meuleman is married to Prof. Dr. Paul Vanderschot and together they have two daughters: Daniëlle and Louise. She is the stepmother of Bernadette and Pieter, the mother in law of Koen and Sarah and the grandmother of Simon.
Publications related to this PhD


Meuleman C, Tomassetti C, Timmerman D, D’Hooghe T (2010) Reply of the Authors to two letters to the Editor. Fertil Steril, 93, 3,


Meuleman C, D’Hoore A, Van Cleynenbreugel B, Tomassetti C, D’Hooghe T (2011) Letter to the Editor: Why we need international agreement on terms and definitions to assess clinical outcome after endometriosis surgery, Human Reproduction, accepted for publication

Laparoscopic Segmental Bowel Resection and Reanastomosis, Human Reproduction, resubmitted after review


Simoens S, Meuleman C, D’Hooghe T (2011) Non-health care costs associated with endometriosis, Human Reproduction, prepared for submission


Full Publication List (PUBMED)

Koninckx PR, **Meuleman C**, Demeyere S, Lesaffre E, Cornillie FJ (1991) Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril, 55, 759-765.


Koninckx PR, Oosterlynck D, D'Hooghe T, **Meuleman C** (1994) Deeply infiltrating endometriosis is a disease whereas mild endometriosis could be considered a non-disease. Ann N Y Acad Sci, 734, 333-341.


Werbrouck E, Spiessens C, **Meuleman C**, D'Hooghe TM (2006) No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertil Steril, 86, 566-571.


ACTA BIOMEDICA LOVANIENSIA

483. M. THOMEER, Epidemiology and Diagnostic Assessment of Interstitial Lung Diseases. 2009
484. F. CLAERHOUT, The Introduction of Laparoscopy and Novel Biomatrices for Surgical Repair of Vaginal Vault Prolapse by Sacral Colpopexy. 2010
485. J. VANDERHAEGEN, The Effect of Physiological and Pathophysiological Changes on the Neonatal Cerebral Oxygenation, as Measured by Near-Infrared Spectroscopy. 2010
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