Minimally invasive surgery of the uterine cavity: resectoscope in use without hormonal preoperative treatment

Reproductive Health Ph.D. programme

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Ph.D. thesis

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1. List of publications

List of publications directly related to the subject of the Thesis

I. Kormányos Zs, Molnár GB, Pál A Remove residual portion of a uterine septum in women of advanced reproductive age: obstetric outcome Hum Reprod. 2006; 21(4):1047-51 **(IF: 3,769)**

II. Molnár GB, Kormányos Zs, Kovács L, Pál A Long-term efficacy of transcervical endometrial resection with no preoperative hormonal preparation European J Obstet Gynacol & Repr Biol, 2006 ; 127:115-122 **(IF: 1,141)**

III. Molnár GB, Kormányos Zs, Kovács L, Pál A Long-term efficacy of transcervical endometrial resection Magy. Nőorv. L. 2001; 64: 139-145. (in Hungarian)

List of abstracts directly related to the subjects of the Thesis

I. Kormányos Zs, Molnár GB, Pál A The role of diagnostic hysteroscopy in examination of infertility Hungarian Congress of Obstetrics and Gynaecology, 2000; Okt 13-14. Szeged, Hungary **The lecture won the first prize award of the congress**

II. Molnár GB, Kormányos Zs, Kovács L, Pál A. Long term follow-up of 112 TCRE patients. 10th Annual Congress of International Society for Gynaecologic Endoscopy (ISGE), March 28-31, 2001 Chicago, USA

III. Molnár, GB, Kormányos Zs. The role of TCRE in avoiding hysterectomy.World Congress on Gynecological endoscopy, 1st Croatian Congress on Gynecological Endoscopy Dubrovnik, Croatia, May 15-18. 2002

IV. Molnár GB, Kormányos Zs., Pál A, Kovács L. Long-term follow-up of patients who underwent transcervical resection of the endometrium. Congress of Gynecological Endoscopy and Innovative Surgery, 11th Annual Congress of International Society for Gynecological endoscopy (ISGE), Berlin, Germany, April 25-28. 2002.

V. Kormányos Zs, Molnár GB, Pál A Intrauterine abnormality = infertility ?- Hungarian Congress of Gynaecologic Endoscopy, 2003; May., Kaposvár, Hungary

VI. Molnár GB., Kormányos Zs: The effect of endoscopic myomectomy on success of in vitro fertilization. 12th Annual Congress of the European Society for Gynaecological Endoscopy, Luxemburg, 2003. november 26-29.

VII. Molnár GB., Kormányos, Zs, Pál, A: Who should follow-up the patients after special endoscopic operations? 13th Annual Congress of the European Society for Gynaecological Endoscopy, Cagliari, Sardinia, Italy, 14-17, October 2004

VIII. Kormányos Zs, Molnár GB, Pál A Treatment of the intrauterine malformations Hungarian Congress of Gynaecologic Endoscopy, 2004; May., Karcag Hungary

IX. Molnár GB, Kormányos Zs., Pál A.,Congenital uterine abnormalities – How and when to operate - 6.Tagung für Gynakologische Chirurgie auf Burg Lockenhaus 2004 Lockenhaus Burgenland Austria May 20-22. 2004

X. Kormányos Zs, Molnár GB, Pál A Does it need a regular uterine cavity for the succesfull pregnancy – septumresection?! Hungarian Congress of Gynaecologic Endoscopy, 2005; May., Sopron, Hungary **The lecture won the first prize award of the congress**

XI. Molnár GB, Kormányos Zs. Remnant uterine septum in women of advenced reproductive age: obstetrical outcome 14th Congress of the European Society for Gynaecological Endoscopy Athens, Greek, 2005. october 6-8.

XII. Kormányos Zs., Németh G., Zádori J., Pál A. Recurrent ectopic pregnancies after in vitro fertilization and embryo transfer Hungarian Congress of Obstetrics and Gynaecology, 2005; Oct. Békéscsaba, Hungary **The lecture won the II. prize award of the congress**

Papers, abstracts and book part not related to the subject of Thesis

I. Kormányos Zs., Novák T., Németh G., Daru J., Pál A., Changes in the management of ectopic pregnancy during the last seven years in our department Magy Nőorv L 2002; 65: 175-180. (in Hungarian)

II. Kormányos Zs., Németh G., Daru J., Vajda Gy., Pál A., Treatment of adnexal hemorrhage during vaginal hysterectomy without conversion Hungarian Congress of Obstetrics and Gynaecology, 2002; Okt. Szolnok, Hungary

III. Kormányos Zs. Malformation of vagina in Encyclopaedia of illness editor Kornya L, - Springer - Budapest 2002; 1001-1002. (in Hungarian)

IV. Kormányos Zs., Németh G., Daru J., Vajda Gy., Pál A., Treatment of adnexal hemorrhage during vaginal hysterectomy without conversion Magy Nőorv L 2004; 67: 163-165. (in hungarian)

V. Kormányos Zs., Németh G., Zádori J., Pál A. Recurrent ectopic pregnancies after in vitro fertilization and embryo transfer Magy. Nőorv. L. 2005; 68, 337-339. (in hungarian)

VI. Ducza E, Kormányos Zs, Resch BE, Falkay G Correlation between the alterations in the expression of the estrogen and alpha1-adrenergic subtypes mRNA in the pregnant human uterus and cervix Eur J Pharmacol. 2005, 28;528(1-3):183-7. **(IF: 2,477)**

2. Abbreviations

AUB:	Abnormal Uterine Bleeding
CI:	Confidence Interval
D&C:	Dilatation and Curettage
DUB:	Dysfunctional Uterine Bleeding
FGEAT:	First Generation Endometrium Ablation Techniques
FSH:	Follicle-Stimulating Hormone
HMB:	Heavy Menstrual Bleeding
IVF:	In Vitro Fertilisation
LH:	Luteinizing Hormone
MEA:	Microwave Endometrial Ablation
OR:	Odds Ratio
RB:	Roller Ball technique
SD:	Standard Deviation
SE:	Standard Error
SEAT:	Second Generation Endometrial Ablation Techniques
SPSS:	Statistical Package for the Social Sciences for Windows program
TAH:	Total Abdominal Hysterectomy
TCRE:	Transcervical Resection of Endometrium

3. Index of Contents

4. Introduction

Hysteroscopy was one of the very earliest approaches to the direct study of the uterine cavity. The hysteroscope is a telescope attached to a light source, which is passed into the uterine cavity by way of the endocervical canal. Pantaleoni initially described hysteroscopy in 1869, but it did not achieve routine gynecologic use due to its poor optic system. Hence that advances in hysteroscopy had to wait for technical innovations in other endoscopic fields before the technique became feasible in ordinary clinical practice. A number of specific problems throttled the scientific progress in the field of hysteroscopy for several decades. The earliest attempts were made with a simple tube inserted into the uterus through the cervix. Lighting was provided from an external source, and there was no lens system. Not the least of these was the difficulty in distending the uterine cavity, the friable nature of the uterine mucosa, and the frequent need for dilatation of the cervical canal leading to the need for adequate anesthesia.

The hysteroscope consists of 3 parts: the eyepiece, the barrel, and the objective lens. All of these scopes require an outer sheath for introduction and removal of media, as well as for accommodating instruments.

Since the early 1980s, hysteroscopy has opened up new diagnostic vistas for the evaluation of the cervical canal and uterine cavity, revealing the limits of dilatation and curettage. A few years later, surgical interventions carried out through the hysteroscope have demonstrated equivalent or better results than traditional laparotomic surgery of the uterus. This is not just because of its postoperative results, which are comparable to those achieved with the abdominal approach, but mainly because of several post-operative benefits (reduced morbidity, convalescence and costs, and no scar tissue on the abdominal and uterine walls), improved reproductive performance (no reduction in uterine volume, shorter interval to conception after operation) and the mode of delivery (avoiding Caesarean section). However the two procedures, diagnostic and operative, have long been considered separate entities, as they required different instruments and a different approach to the patient.

Obviously, the indications for the hysteroscopic examination have increased considerably. All those cases which in theory require direct visualization of the cervical canal and uterine cavity are now considered indications for hysteroscopic approach. Diagnostic and surgical hysteroscopic interventions have become "gold standards" in the

gynecological practice and are regarded as the latest important step forward in the gynecologic practice. The possibility of visual examination of the uterine cavity and contextual operative facilities has provided endoscopists with the perfect "diagnostic" tool: they can examine the cavity and take targeted operations thanks to visualisation of the suspected areas. Some indications, such as uterine malformations, intrauterine adhesions, submucous and intramural myomas, unimpressionable recurrent menorrhagia, which formerly were limited to conventional surgery, have now become a domain of the hysteroscopic techniques. This has been defined as a "See and Treat" procedure (Bettocchi S et al., 2002), there is no longer a distinction between a diagnostic and an operative procedure, but a single procedure in which the operative part is perfectly integrated in the diagnostic work-up. Also, management of abnormal uterine bleeding by means of hysterectomy has been largely replaced by endometrial ablation or resection through the hysteroscope, which is considered to more extensively preserve the integrity of the urogynecological tract. Hysterectomy was for a long time the only surgical alternative; however, more conservative surgical approaches became available during the 1980s.

The resectoscope is a specialized hysteroscope with a built in monopolar double-armed wire loop (Fig 1) or other shape electrode with a trigger device that causes an electrosurgical effect by contact desiccation through resistive heating uses high-frequency electrical current. The depth of thermal damage is based on multiple factors, including degree of endometrial thinning; speed, pressure, and duration of contact during motion; and power setting.

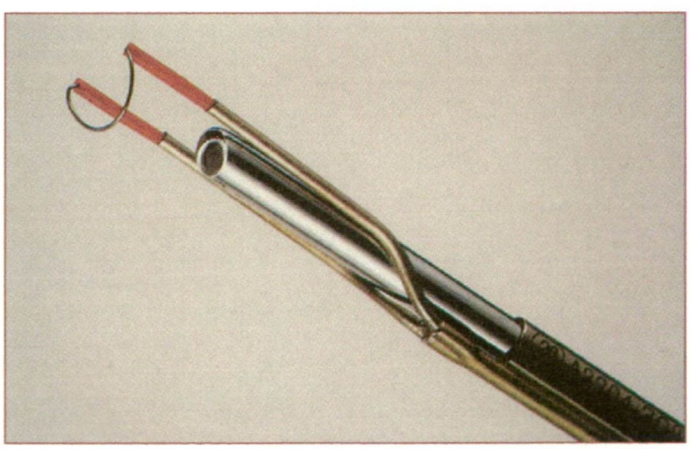

Figure 1. Resectoscope with a built in wire loop

The resectoscope is available with a 5- to 7-mm cutting loop. A thin electrode can cut tissue, whereas a larger surface area, such as a ball or barrel, is more suited for coagulation .When using the blend waveform, as opposed to the cut option, hemostasis can be better achieved at the cut edges, allowing for improved visibility during operative procedures such as submucosal myomectomy and endomyometrial resection . When used with a 30-degree scope angled toward the electrode, clear visualization can be achieved during manipulation.

The resectoscope was originally developed for surgery of the bladder and the male prostate over fifty years ago to allow surgery inside an organ without having to make an incision, since the beginning of the '80s, it has provided to be a powerful operative tool in the gynecology.

5. Conceptual background

The follow up studies are the most effective statistical procedures to evaluate benefits of the medical or the surgical interventions. The longer observational method is the better for the increase of the merits of cases. The follow up periods in most of report are short, often averaging less than one year, and the important issue of whether resectoscopic procedures would be more advisable with time has not been carefully studied.

5.1. Studies on transcervical resection of endometrium

Many women suffer from bleeding abnormalities, especially from the age of 40 until menopause. The reason is often fibroids, hyperplasia of the endometrium, or dysfunctional bleeding due to abnormal function of the ovary. Previously, hysterectomy was the only surgical alternative to nonsurgical treatments such as hormones, antifibrinolytic treatment, or no treatment.

Destruction of the endometrium under endolumenal endoscopic guidance was originally described using the neodymium:yttrium aluminum garnet (Nd:YAG) laser (Goldrath et al., 1981), but the modified urological resectoscope later became overwhelmingly the most commonly used instrument with resection using loop electrodes. The procedure of transcervical endometrial resection (TCRE) was introduced in the late 1980s and markedly changed the treatment of dysfunctional uterine bleeding (Goldrath et

al., 1981; DeCherney et al., 1983; Vancaillie et al., 1989; Magos et al., 1990). This technique was easier to perform and required less complex and less costly surgical equipment. These are called "First Generation Endometrium Ablation Techniques (FGEAT)". It is "minimal invasive" approach which retains the structurally normal and healthy uterus and removes only the bleeding endometrium. Many local destructive agents and modalities had been used unsuccessfully until Goldrath described the hysteroscopic ablative technique. Later this same modality has been shown to be effective in treating uterine polyps, submucous fibroids and intrauterine septa.

The early attempts at treatment were unsuccessful because the endometrium has amazing powers of regeneration. It is shed at the end of each menstrual cycle and rapidly replaces itself. The endometrium is repaired from the glands situated in the pars basalis deep in the zone of the endometrium retained when the more superficial layers are shed at menstruation (Fig 2).

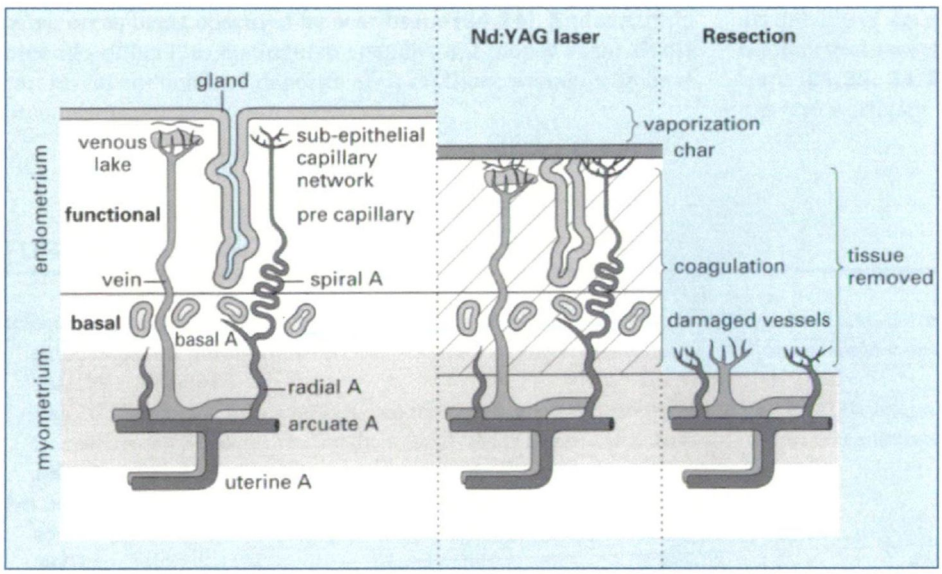

Figure 2. A diagrammatic representation of the endometrium. This shows the location of the basal glands and how they can be removed either by ablative or excisional techniques.

Any successful attempt to prevent the rapid regrowth of endometrium after trauma must effectively and completely remove these basal glands (Fig 3). Techniques which simply remove the superficial endometrium are certain to fail.

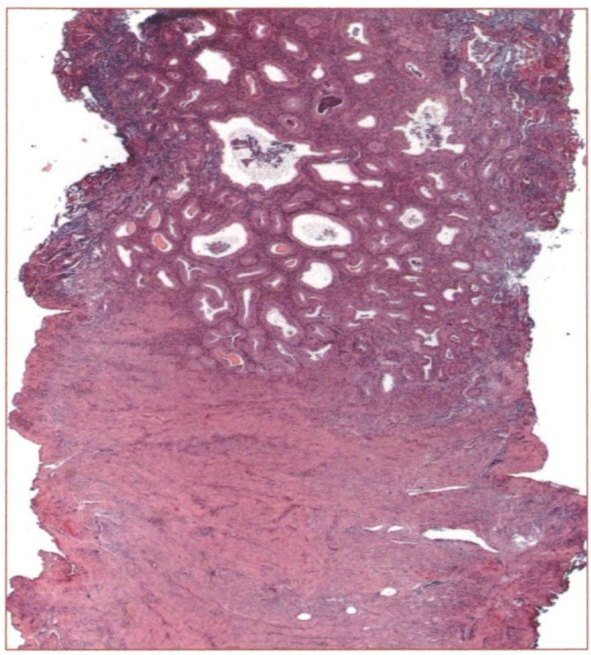

Figure 3. Section of the endometrium with adjacent upper myometrium after TCRE (hematoxyllin and eosin stain, original magnification x25).

The ''dysfunctional uterine bleeding'' (DUB) may occur either in the context of ovulatory cycles, when it may be more appropriately called „heavy menstrual bleeding" (HMB), or in association with an anovulatory or mostly anovulatory state characterized by bleeding that is usually unpredictable in timing and volume (anovulatory DUB). It is important to note that such „abnormal uterine bleeding" (AUB) may exist in the presence of asymptomatic structural anomalies such as polyps or leiomyomas.

Dysfunctional uterine bleeding affects 20-30% of women, most of them undergoing hysterectomy (Crosignani et al., 1996). The prospective, epidemiological study carried out by the Oxford Family Planning Association between 1968 and 1974 on 17032 women suggested that a minimum of 20% of women undergo hysterectomy by the age of 55 (Vessey et al., 1992).

Hysterectomy rates increased to 670 per 100.000 women in 1975, then declined and stabilized since the 1980s at approximately 568 per 100.000 in the USA. This decrease

may be due to in part to the increase in alternative approaches to managing problems that might otherwise result in hysterectomy (Wilcox et al., 1994; Carlson et al., 1994). Although hysterectomy is effective therapy for dysfunctional uterine bleeding, it is associated with serious morbidity in up to 40% of surgical patients (Marjoribanks et al., 2006). Complications include intraoperative and postoperative bleeding, infection, thromboembolism, and damage to adjacent viscera. The incidence and severity of the complications assume a heightened importance in women with coexisting morbidities (such as extragenital malignancies, diabetes mellitus, and morbid obesity) that pose additional anesthetic and surgical risks.

Numerous papers have been published on the short-term effects of the transcervical endometrium resection, but only a few discuss the long-term consequences or the findings of the long-term follow-up of patients who undergo TCRE (Derman et al., 1991; Magos et al., 1991; O'Connor et al., 1996; Mints et al., 1998; Cooper et al., 2001). The experience to date is that the efficacy of the operation cannot be assessed correctly merely a few years after the surgery, as further surgical treatment might be necessary even after a very long time if either the patient or her doctor feels that the TCRE did not lead to the expected result.

The technique was introduced in Hungary in 1992 (Molnár et al., 1993, 1998; Bacskó Gy. 1997). The aim of the present study was to examine the long-term effects of TCRE performed without any hormonal pretreatment for thinning the endometrium on the menstrual period and dysmenorrhoea. We wanted to establish how satisfied our patients are with the long-term results of the operation, and how many of them are able to avoid hysterectomy.

5.2. Studies on septum resection

In the USA and Western Europe, there has recently been a major shift in reproductive behaviour towards delayed childbearing. In many instances, couples are postponing childbearing; hence, infertility specialists have witnessed a dramatic shift in the age of infertile women undergoing examination during the past decade. Among couples of advanced reproductive age, there is a strong trend toward uterine factor infertility becoming more common (Menken et al.,1986; Hollander et al., 1990; Death et al., 1999).

Congenital uterine anomalies have been estimated to affect 0.06% to 10% of women, depending on the method of patient selection, the criteria for diagnosis, and the types of diagnostic tests used (Buttram, 1983; Rock et al., 1985; Acién, 1997; Campo et al., 1999). A septate or partial septate uterus accounts for approximately 80% to 90% of these abnormalities (Fayez, 1986; Simon et al., 1991), (Fig 4, 5.).

Most Müllerian defects are never diagnosed because they do not cause complications. The ones that do come to medical attention are those that cause a gynaecological or obstetric dysfunction. Many such anomalies are therefore recognized among women in their thirties (Golan et al., 1989).

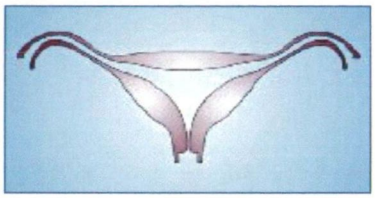

Figure 4. Normal uterine cavity

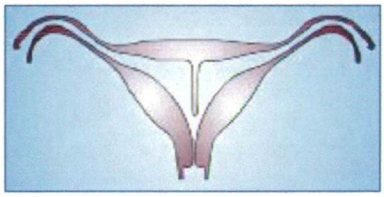

Figure 5. Partial septate uterus

Congenital uterine malformations have been associated with a poor reproductive outcome. The pregnancy loss in patients with uterine septa has been reported to be as high as 90% after other causes for miscarriage have been excluded (Daly et al., 1989; Acién, 1993; Goldenberg et al., 1995; Acién, 1996).

Endsröm described the first hysteroscopic division of the uterine septum in two cases in 1974 and used biopsy forceps to resect the septum piecemeal (Edstrom , 1974). After '80s this approach became popular (Chervenak et al., 1981; Daly et al., 1983; Candiani et al., 1990). In 1997 we performed our first operative hysteroscopy for septate uterus.

After initial hysteroscopic metroplasty, a residual septum or adhesions are more frequent than normally anticipated (Fedele et al., 1991; Fedele et al., 1993; Parsanezhad et al., 2000; Porcu et al., 2000; Saygili-Yilmaz et al., 2002). In contrast with the numerous studies on the outcome of initial hysteroscopic metroplasties (Homer et al., 2000), there has been only one report (Fedele et al.,1996) on the reproductive performance after hysteroscopic remnant uterine septum resection in women of advanced reproductive age. There is still insufficient evidence that a remnant intrauterine abnormality definitely has an effect on the reproductive outcome. It is reasonable to suppose that a septal

endometrium is unsuitable for implantation of the blastocyst, independent of the extent of the uterine abnormality (Fedele et al., 1996).

6. The aims of the studies

- to examine the long-term effects of TCRE performed without any hormonal pre-treatment for thinning the endometrium on the menstrual period.
- to establish how satisfied are our patients with the long-term results of the operation, and how many of them are able to avoid hysterectomy.
- to evaluate the influence of the elimination of a residual septum on the reproductive performance of women of advanced reproductive age with recurrent miscarriage.

7. Materials and Methods

7.1. Instrument

The surgical procedure was performed under general anaesthesia after dilatation of the cervix up to Hegar size 10, with a 10-mm passive resectoscope fitted with a monopolar knife, loop and ball electrode and with a 30-degree fore-oblique hysteroscope. To eliminate any bias in results from operators of differing experience, all endometrial resections were performed by the same surgeon (B.G.M.). The uterine cavity was distended with 4% sorbitol as medium for dilatation irrigation. A Hamou Hysteromat was used to ensure an intrauterine pressure of 100-120 mm Hg with a flow rate of 150 ml/min. (All equipment was manufactured by Karl Storz GmbH, Tuttlingen, Germany.) Surgery was scheduled early in the follicular phase to obtain the best conditions of visibility in the reproductive age population.

7.2. Patients

7.2.1. Studies on transcervical resection of endometrium

One hundred and thirty-one patients were treated with TCRE in our Department between November 1992 and November 1996. All of the patients were enrolled with the indication for the operation was intractable uterine bleeding with no response to hormonal treatment. A negative histology of endometrial biopsy (D&C) within one year was mandatory, but diagnostic hysteroscopy was not routinely performed. Each patient had to have a complete family with no desire for further pregnancy, and the uterus had to be smaller than a 12-week uterus. Furthermore, no preoperative hormonal treatment was applied to thin the endometrium and no perioperative antibiotic medication with the exception of the two cases where the cardiac status of the patients made this necessary. The fundal endometrium was ablated with the roller-ball electrode in a majority of the cases, while the rest of the cavity was treated with the loop electrode. The overwhelming of the cases, the operation was performed under general anaesthesia, but an appreciable number were sedated with local anaesthetics accomplished with intravenous sedation. For the current study participants who were postprocedure were sent a questionnaire - containing open- and closed-type questions - concerning satisfaction with and acceptability of their treatment method, menstrual status, changes in health-related quality of life, and any further surgery received (Annex 1). Additional patient comments were also requested. Satisfaction rate was assessed with the following question regarding the surgical procedure performed: „What is your opinion about the effect of the operation in general?" Women had to choose between five different assessments of satisfaction: very satisfied, satisfied, unsure, dissatisfied, very dissatisfied. With responses the patients were dichotomized to "satisfied" and "dissatisfied" group demonstrated statistically substantial differences in ratings of postoperative contenting thoroughness. The „satisfied" group contained very satisfied and satisfied subjects; the dissatisfied group enclosed unsure, dissatisfied and very dissatisfied patients.

7.2.2. Studies on septum resection

The reproductive efficiency in patients with septate uteri who underwent uterine septum resection in our Department of Obstetrics and Gynaecology between July 1997 and June 2002 was analysed in a prospective self-control observational study. We enrolled patients with a subseptate uterus who had had two or more spontaneous miscarriages. Before surgery, all patients underwent a standardized examination. Women with associated

genital or pelvic diseases (myomas, endometriosis, adhesions and sequelae of pelvic inflammatory disease) were excluded, and other causes of infertility were eliminated by work-up procedures such as sperm analysis, hormonal profiles that included thyroid, LH, FSH and midluteal progesterone assay, karyotyping, transvaginal ultrasound scan and hysterosalpingography. Traditionally, hysterosalpingography has been used to screen for anatomic abnormalities and tubal patency in patients with a history of infertility. Laparoscopy was used for a clear differentiation of a bicornuate from a septate uterus. The septum length was measured by ultrasound (Kretztechnik AG, Combison C530). The measurement was accepted if the hysteroscopic verification was < 5 mm. The structural points of the resectoscope were applied to consider the length of the septum in the uterine cavity. The intrauterine anomalies were classified according to the American Society for Reproductive Medicine guidelines (American Fertility Society, 1988). The exclusion criteria included a bicornuate and a complete septate uterus. After visualization of the tubal ostia, the section was carried cephalad with progressive horizontal cuts equidistant from the anterior and the posterior walls extended up to the fundus. The incision was considered complete when the uterine architecture had been normalized and vertically-running blood vessels of the myometrium appeared. The same author performed all of the hysteroscopies, including the initial and (if required) the consecutive procedures. All enrolled patients were found to have normal external uterine fusion by laparoscopy within a month. (Not all of the patients underwent laparoscopy in our department.) All patients were scheduled for follow-up ultrasound and diagnostic hysteroscopy 2 months after the initial resection in order to assess the uterine cavity. If the resection was judged to be adequate (no residual septum, or a residual septum $\leq$ 1 cm), patients were allowed to attempt to conceive in subsequent cycles. After the first operative hysteroscopy, we examined the outcome of pregnancy without regard to the residual septum ($\leq$1 cm). However, if there was no successful pregnancy during the next 24-month follow-up period, the remnant ($\leq$1 cm) was removed during a second hysteroscopy with the aim of increasing the frequency of term pregnancy. The reproductive outcome was monitored in the 24 months after the first hysteroscopy and in the 24 months after removal of the remnant. Preoperatively, all patients received a detailed explanation of the operative hysteroscopic and laparoscopic procedures, including the risks and benefits involved. They also signed a general surgical informed consent for the procedure. This is part of our routine surgical protocol; special approval from the Human Investigational Board was

therefore not needed. Patient confidentiality was maintained at all times. No preoperative hormonal treatment was applied to thin the endometrium. All patients received postoperative combined oestrogen-progestogen hormonal therapy (30 ug of ethinyloestradiol and 150 ug levonorgestrel; Richter Gmbh, Hungary) over 1 month.

7.3 Statistical analyses

Analyses of the differences in the opinions of patients in the TCRE study, following various operative techniques were performed Chi square tests. Yates-corrigation was also applied due to low number of entries. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated for categorical variables. In the septum resection study because of the low numbers of cases in the study groups and the lack of statistical normality of the samples, non-parametric statistical tests were applied for comparisons with the Wilcoxon-test for continuous variables. Univariate comparisons for categorical variables were assessed by means of Fisher's exact test. The cumulative delivery rate was assessed after the initial (with and without remnant groups) and the second (septum $\leq$ 1 cm) hysteroscopy with Kaplan-Meyer analysis. All data are presented as mean $\pm$ SD. The results relating to studies were computed and analysed with the Statistical Package for the Social Sciences for Windows program (SPSS 11.0, Inc. Chicago, IL, USA). We considered differences with a probability level of less than 0.05 to be statistically significant.

8. Results

8.1. Studies on transcervical resection of endometrium

The completed postal questionnaires were returned by 82 of the 131 patients. Answers were collected by telephone interview from another 15 women, and all the details of the gynaecological data on one more patient were available from her clinical notes. Thirty-three cases were lost to follow up; thus, the data on 98 of the 131 patients (74.8%) were analysed in this long-term follow-up study (Fig. 6). Sixty-nine of the 98 women underwent TCRE alone, while 29 were treated with TCRE supplemented with myomectomy in the same session. The follow-up period was five years in five cases

(5.1%), six years in 14 cases (14.3%), seven years in 22 cases (22.4%), eight years in 23 cases (23.5%), nine years in 14 cases (14.3%), ten years in nine cases (9.2%) and 11 years in 11 cases (11.2%). The average follow-up period was 94.8 months (range: 60-132 months).

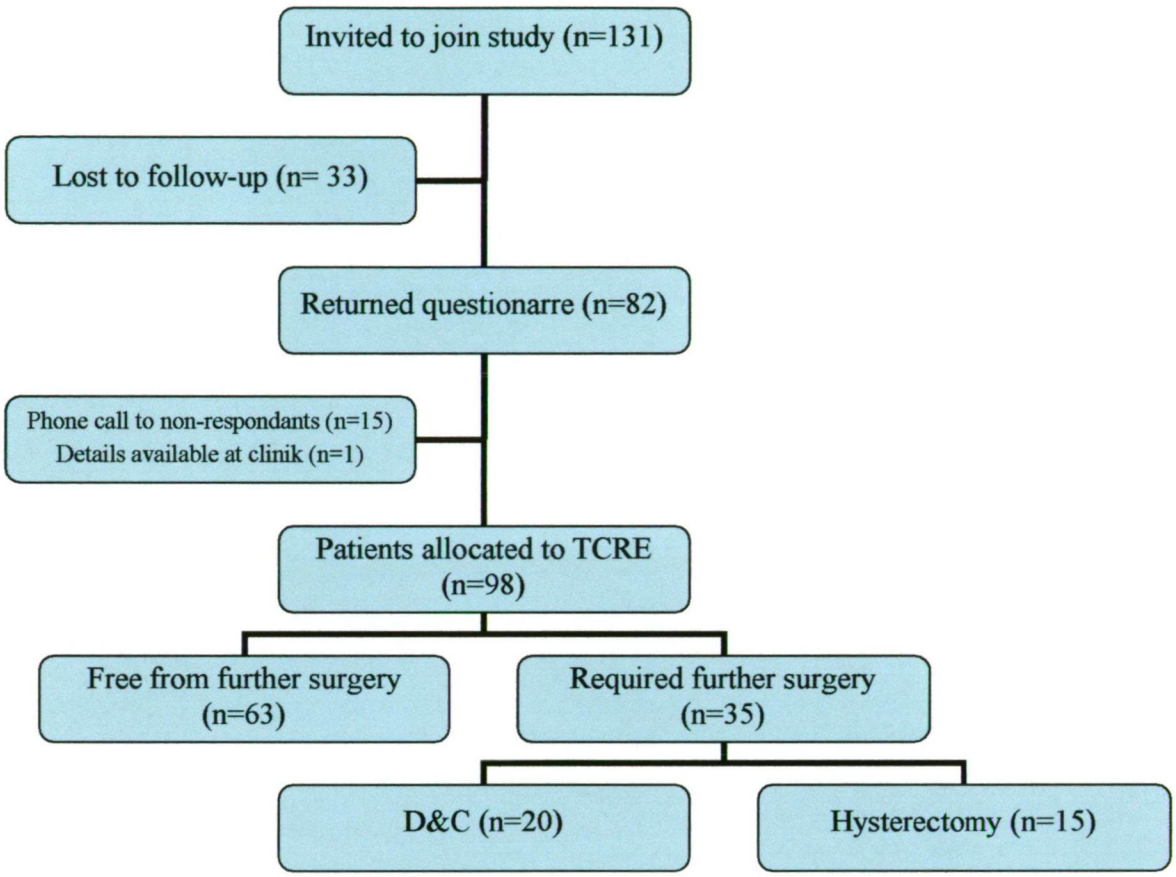

Figure 6. Flowchart of patient progress through the study

The average age of the patients at the time of the surgery was 43.5 years (range: 26-70 years). The length of the menstrual period was on average 26.9 days (range: 14-35 days), while the duration of the menstrual bleeding was on average 6 days (range: 3-19 days). Ninety of the patients were multiparous, and eight were nulliparous. The main complaint was the irregular and heavy bleeding by 46 recruited patients, whereas 44 observed subjects suffered from regular but heavy menstruation. In eight cases, the bleeding period lasted for more than 10 days; one patient complained of postmenopausal bleeding. Dysmenorrhoea was accompanied by bleeding disturbances in 9 patients. The complaints started on average 11.3 months before surgical intervention. D&C was resorted to at least two times before TCRE in an effort to eliminate the symptoms; and

hormonal treatment was administered to 45 patients, as a most common regime providing progesterone endometrium preparing therapy.

The average size of the uterus was equivalent to that of a 5.5-week pregnant uterus (range: 4-10 weeks). The uterine cavity length was on average 8.4 cm (range: 6-10 cm). The diameters of the submucosal fibroids varied in the range 0.5-6 cm (average 2.6 cm). Eight patients had fibroids larger than 4 cm in diameter for removal. All of the fibroids, even those with diameter >4 cm were removed totally during the endometrial resection procedure. According to the classification of the European Society of Hysteroscopy, the distribution of the fibroids was five of type 0, eight of type I, 12 of type II, and four of mixed type.

In 77 patients, we applied a roller-ball electrode to treat the endometrium in the top of the cavity and around the tubal ostia, and a loop electrode for removing the endometrium from the rest of the cavity. In 21 cases, a loop electrode was used to resect the endometrium even from the fundal area.

The average amount of irrigant fluid utilised for one procedure was 4527 ml (min: 2000, max.: 16000). The absorption did not exceed the 1500 ml limit and the average absorption was only 374 ml (min: 0, max.: 1200). All but one patient absorbed less than 1000 ml of irrigating fluid. On that one patient with 1200 ml of absorption we monitorised serum electrolytes and cardiovascular and respiratory function postoperatively. All of these values were within the normal range. TCRE was performed under general anaesthesia in 91 cases (92.8%), and under local anaesthesia accompanied with intravenous sedation in the remainder. All the seven patients who had the procedure under local anaesthesia with intravenous sedation were satisfied (three patients) or very satisfied (four patients) with the result of the operation. The duration of the procedure varied between 10 and 60 min, with an average of 30.7 min. No uterine perforation, fluid overload, hemorrhage or postoperative fever occurred. It was no necessary to interrupt the procedure because of intraoperative complications or technical problems. There were no postoperative complications either. At the time of the introduction of the procedure we suggested four days of hospitalisation to the patients, but our good experience led us later to discharge them on the day following surgery.

Postoperatively weak bleeding or spotting was observed by most of the patients, for a maximum of 7 days which turned to a watery discharge for another six days. Lower abdominal pain was present for an average of five days. The patients were ready for

normal home activities after six days, some of them immediately after going home, but others only after three weeks. Return to work required on average 16 days (min.: 0, max.: 48).

Altogether 35 of the 98 women (35.7%) required further surgery after the initial TCRE. Among these women, 20 (20.4%) underwent D&C and 15 (15.3%) needed hysterectomy. No patients underwent hysterectomy after D&C. There were no cases of repeated TCRE either.

Continuing dysfunctional bleeding was the indication for hysterectomy in seven of the 15 cases (46.7%); in the remaining eight cases (53.3%), organic abnormalities were in the lately verified pathologic reasons, such as fibroid in six cases, a suspicion of an ovarian mass in one case, and endometrial adenocarcinoma of the endometrium was diagnosed on endometrial resection in one case. We must emphasise that this patient also had a negative histological result of D&C one year prior to the TCRE. The indication for her TCRE was postmenopausal bleeding. During the operation, we resected a 0.5 cm diameter fibroid too. After hysterectomy, the patient aged 70 years, participated in a postoperative irradiation treatment and survived the operation for more than five years. The histological identification of the 15 removed uterus revealed adenomyosis in eight cases, three of which had fibroid as well, while in two cases the only histological abnormality was the presence of fibroid, in one case an adenocarcinoma residuum in the superficial myometrium (this case was discussed above), in one case a corpus luteum cyst, and in one case chronic endocervicitis was the only pathology observation. There were two hysterectomies in which no histological histopathologic disorder was found, and the bleeding from the residual endometrium was the only indication for hysterectomy. Hysterectomy was performed within one year after the initial surgery in 7.1% of the cases, within three years in 12.2%, and after six years in 15.3%. There were no further operations during the 11 follow-up years. There were three cases who had hysterectomy within two months after the initial surgery. As this would be a very short postoperative follow up period these three cases were dropped out from the final evaluation of the long-term results. Survival analysis demonstrated that the chance of avoiding hysterectomy 41 months after TCRE is 81.9% (SE: 4.5%), up to 61 months it is 80.2% (SE: 4.8%) and up to 72 months it is 78.3% (SE: 4.8%). No D&C was performed within 36 months after TCRE. The chance of avoiding D&C up to 44 months is 83.9% (SE: 4.4%) and up to 88 months is 82.% (SE: 4.6%). There was no D&C done after 107 months (Fig. 7).

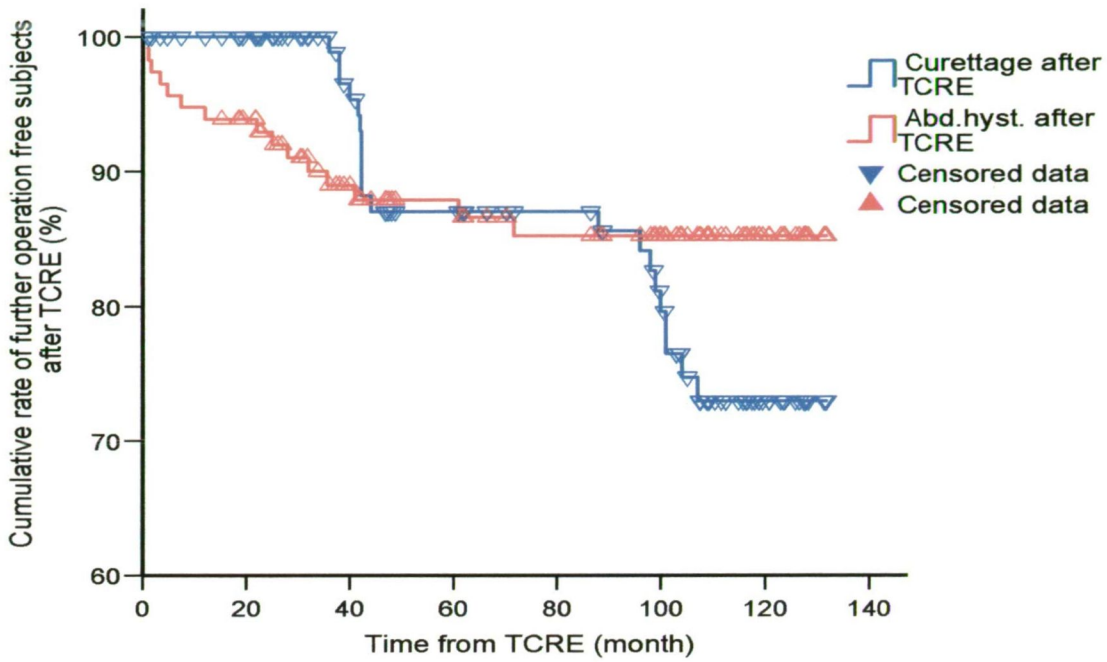

Figure 7. Survival analysis. Cumulative percentage of patients free from further surgery by the type of subsequent operation. Triangle marks on the plots are the censored observations.

On the same diagram the chance of the further two type of action (TAH and D&C) were illustrated and evaluated in the survival analysis. In the TAH and in the D&C curve the triangles which mean the censored items can be found nearly in the same position, because of the patients who were not in the need of further operation were used in each group when the survival analysis was made. Hormonal treatment was necessary in only seven cases: five of them received progesterone, one of them hormone replacement therapy and one of them a GnRH analogue for two months. Fifty-seven of the responding 98 patients (58.2%) were with amenorrhoea at the time of the survey. Discounting the 15 hysterectomy patients who had amenorrhoea, 42.8% (42/98) of the women with a preserved uterus were with amenorrhoea.

None of the patients experiences heavier period bleeding after the operation: no change was experienced in two cases, whereas all of the others reported less, much less or no bleeding at all (Fig. 8).

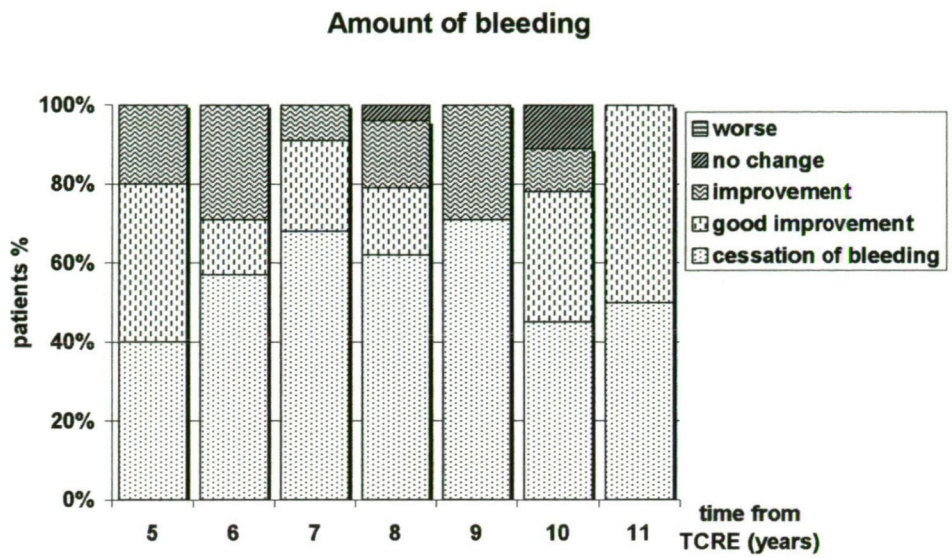

Figure 8. Outcome of TCRE: menstrual blood loss after TCRE.

The duration of the bleeding was unchanged in six cases, while 89 patients had a shorter bleeding period or no bleeding at all (Fig. 9).

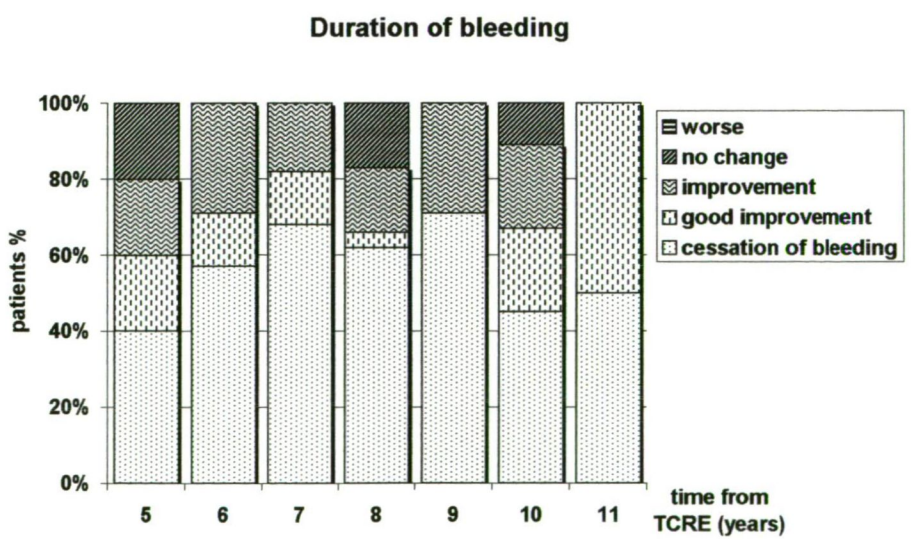

Figure 9. Outcome of TCRE: duration of bleeding.

Four women experienced more painful periods than before the endometrial resection, but all of the others had decreased dysmenorrhoea or no pain at all (Fig. 10).

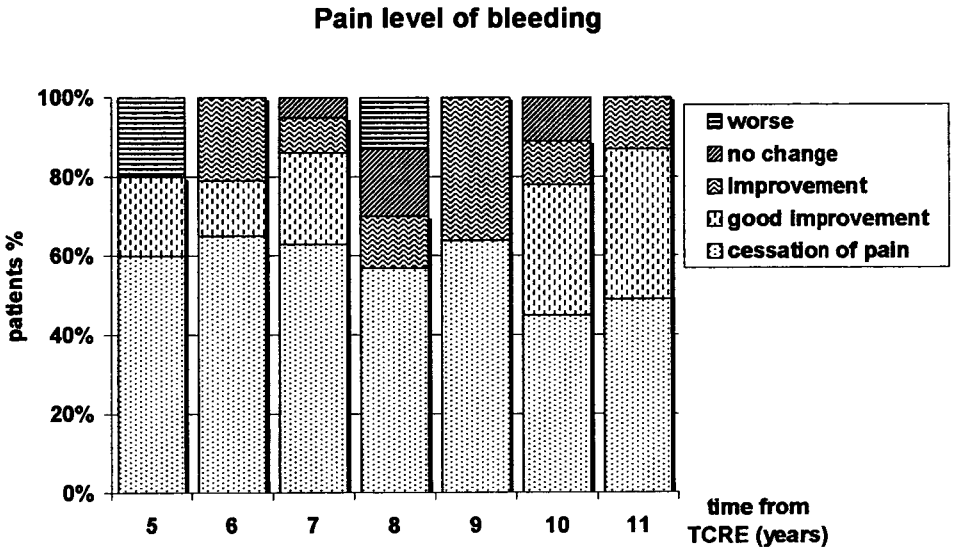

Figure 10. Outcome of TCRE: dysmenorrhoea.

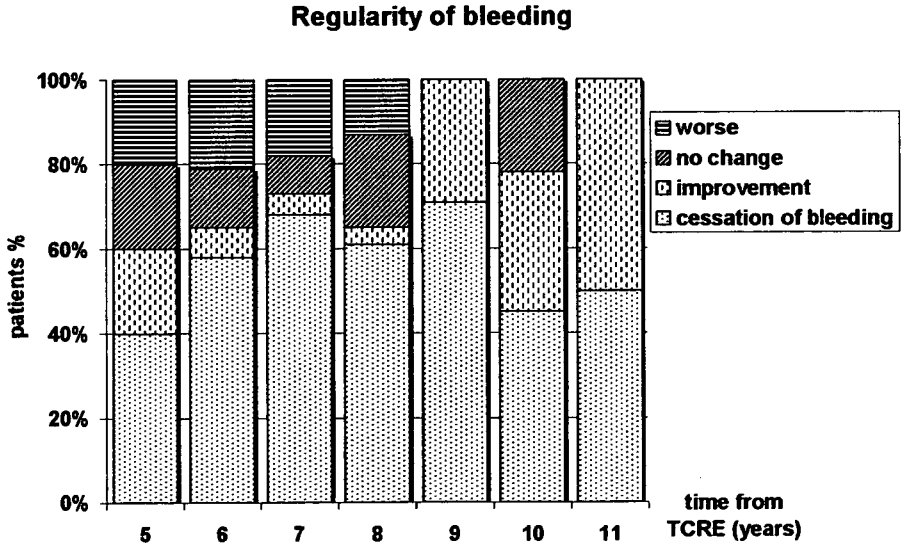

Figure 11. Outcome of TCRE: regularity of bleeding.

Twenty-seven patients had regular bleedings, with an average period length of 27.3 days (min.: 24, max.: 30). Duration of bleeding was 3.5 days on average (min.:1,

max.: 6). Fifteen patients had more regular periods, 12 experienced no change and eleven had more irregular bleedings at the time of the survey (Fig 11.).

Of the study group, eighty-six of the 98 patients (88%) were satisfied or very satisfied, seven women (7%) were dubious, three (3%) were dissatisfied and two (2%) was very dissatisfied with the outcome of the TCRE.

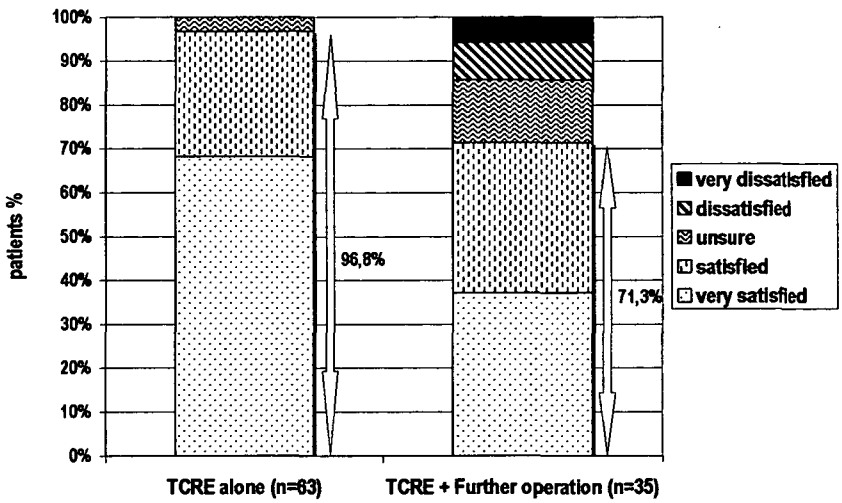

Figure 12. Outcome of TCRE: level of satisfaction of patients. (96.8% vs. 71.3% [P<0.001; OR: 12.2 (95% CI: 2.49 - 59.70)])

The main reasons for disappointment were worsening of dysmenorrhoea and pre-menstrual pain. Two of the dubious patients and all five women who expressed disappointment later underwent hysterectomy. The irregularity of the menstrual periods was the reason for uncertainty in the five cases which did not have hysterectomy, although the duration and volume of the menstruation were decreased in all of these women.

The TCRE was performed between 68 and 91 months before they were questioned. Seventy-one per cent of those who underwent operative treatment after the initial procedure were satisfied with the hysteroscopic surgery (96.8% vs. 71.3% [P<0.001; OR: 12.2 (95% CI: 2.49 - 59.70)]) (Fig. 12).

The reasons for hysterectomy were organic origin (8/98: 8,1%) and persistent DUB (7/98: 7,1%) with worsening of dysmenorrhoea and pre-menstrual pelvic pain.

The characteristic data on the patients operated on during the follow-up period are summarised in Table 1.

No. of patients with further surgery	**35/98 (35.7%)**
TAH	**15/98 (15.3%)**
Dysfunctional uterine bleeding	7/98 (7.1%)
Organic reason	8/98 (8.1%)
fibroid	6/98 (6.1%)
ovarian cyst	1/98 (1%)
adenocarcinoma	1/98 (1%)
D&C	**20/98 (20.4%)**

Table 1. Characteristics of the patients who needed further surgery after transcervical resection of the endometrium.

8.2. Studies on septum resection

After the exclusion of 52 patients in whom there were other reasons for the infertility, the remaining 94 women were enrolled in the study. Their mean age ± SD was 33.2 ± 4.9 years. The mean follow-up time was 26.4 ± 2.2 months. The mean septum length was 1.85 ± 0.9 cm. All of the remaining uteri were classified as American Society class Vb (partial septate uterus).

No hysteroscopic, laparoscopic (uterine perforation, fluid overload, haemorrhage or postoperative fever) or anaesthetic complication occurred. It was not necessary to interrupt the procedure because of intraoperative sequelae or technical problems.

The mean duration of infertility was 51.5 ± 27.5 months. After the first operative hysteroscopy, the results were similar to those reported in the literature: the follow-up diagnostic tools revealed a normal uterine architecture (complete removal of the septum) in 58 patients (62%), a residual fundal septum >1 cm in one patient (1%) and a residual fundal septum ≤1 cm in 35 patients (37%).

The 94 patients undergoing hysteroscopy were subsequently divided into two groups: those in whom complete septum resection was achieved (n=58) and those in whom there was a residual septum (n=36). All 94 patients were followed up for a minimum of 24 months postoperatively. During the 24-month postoperative period after the first operation, 48 patients (51.1%) became pregnant, 32 (55.2%) in the complete

resection group and 16 (44.4%) in the residual septum group. Of these pregnancies, a total of 15 (15.9%) (6 and 9, respectively) ended in miscarriage, 5 (5.3%) (2 and 3, respectively) ended in pre-term delivery; and 28 (29.7%) (24 and 4, respectively) ended in term delivery. The average length of gestation at the end of the pregnancy after the initial metroplasty was 33 ± 11 weeks, as compared with 18.1 ± 12.5 weeks prior to surgery. After an observation time of 24 months, 29 of the 36 patients with a residual septum and a history of pregnancy loss or continued infertility were reoperated. Because of these successful pregnancies, 7 patients were not scheduled for the remnant severing strategy. During the second follow-up period of 24 months after severing of the remnant, 23 patients (79.3%) achieved pregnancy: 5 (17.2%) of these pregnancies ended in miscarriage, 5 (17.2%) in pre-term delivery; and 13 (44.8%) in term delivery (Table 2). The average length of gestation at the end of pregnancy after the second operation was 33.7 ± 9.4 weeks.

Normal vaginal delivery was planned for all these patients, and the need for Caesarean section was based on obstetric indications rather than on the history of the metroplasty. Caesarean sections were more prevalent amongst the patients who underwent one hysteroscopy procedure (17/33: 51.5% versus 8/18: 44.4%).

The delivery in the group after the initial metroplasty where a remnant was observed ended with Caesarean section in a considerable proportion (71.4%). No systematic cervical cerclage was instituted in patients who underwent remnant severing.

The rates of pregnancy and delivery increased after the strategy of remnant severing (Table 2). The overall viable pregnancy rate (33/94; 35.1%) after the initial metroplasty improved to 54.2% of the total (51/94) after extirpation of the residue.

Although premature labour was more frequent as compared with the total number of deliveries after the remnant severing strategy (5/18, 27.8%, versus 5/33, 15.2%), the prematurity was associated with a longer gestation period (data not presented), reflected by a trend towards higher birth weight of the newborns in the second hysteroscopy group.

Significantly higher delivery (44.8% versus 19.4%; $P<0.05$) and term pregnancy frequencies (41.4% versus 11.1%; $P<0.05$) characterized the successful initial hysteroscopy group relative to those with a remnant. No significant difference was observed between the two groups as regards the pregnancy rate (55.2% versus 44.4%).

	Total number of patients undergoing first hysteroscopy (n=94)		Number of cases where the first hysteroscopy left no remnant (n=58)		Number of cases where the first hysteroscopy left a remnant (n=36)		Number of cases requiring remnant severing strategy (n=29)		P value***
	n	%	N	%	n	%	n	%	
Mean age (mean ± SD) (years)	33.2 ± 4.9		33.9 ± 5.1		32.7± 4.8		34.3 ± 5.0		**
Initial length of septum (mean ± SD) (cm)	1.85 ± 0.9		2.7 ± 0.9		1.7 ± 0.9		0.76 ± 0.3		**
Number of patients who become pregnant	48	51.1	32	55.2	16	44.4	23	79.3	NS*
Number of patients who delivered	33	35.1	26	44.8	7	19.4	18	62.1	P<0.05
Number of patients undergoing Caesarean section†	17	51.5	12	46.2	5	71.4	8	44.4	NS*
Number of patients achieving term pregnancies	28	29.7	24	41.4	4	11.1	13	44.8	P<0.05
Number of pre-term pregnancies	5	5.3	2	3.4	3	8.3	5	17.2	NS*
Number of miscarriages	15	15.9	6	10.3	9	25	5	17.2	NS*
Birth weight (mean ± SD) (g)	2952 ± 785.8		3138 ± 369.1		2937 ± 726.5		3136.0 ± 421.1		NS*

* Statistically not significant

** No statistical analysis was carried out

*** Statistical comparison was performed between the data after the first hysteroscopy without a remnant (n=58) and the data after first hysteroscopy with a remnant (n=36)

†: The number of Caesarean sections is compared with the total number of deliveries

Table 2. General characteristics of the patients in the study groups and characteristics of the patients after the first hysteroscopy and after the remnant severing strategy. Data are presented as mean ± SD.

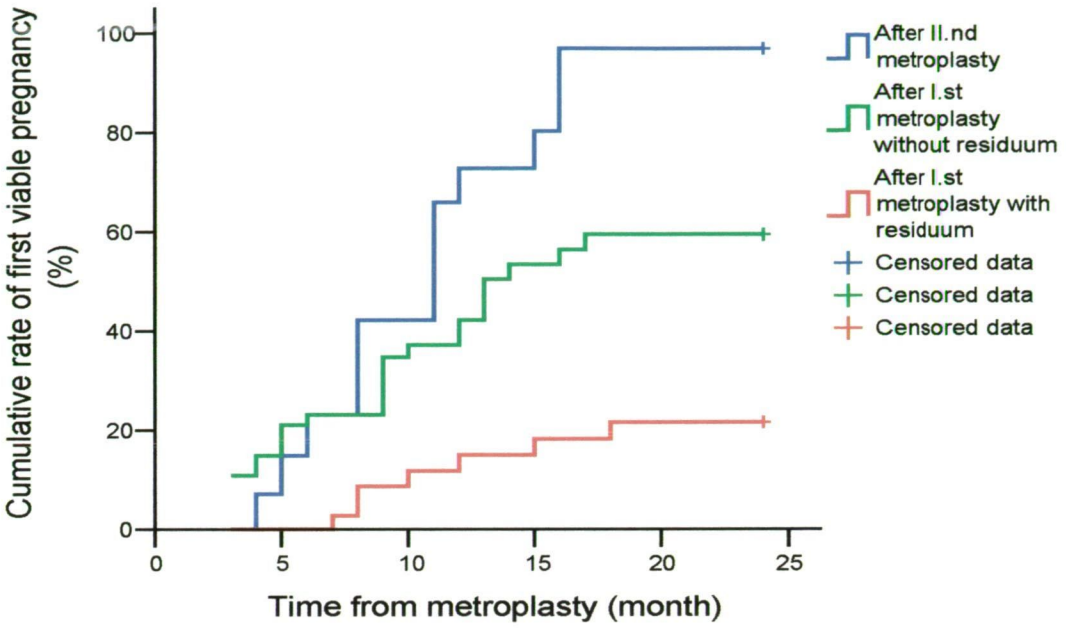

Figure 13. Cumulative 24-month probability of viable pregnancies after the first hysteroscopy in 58 women without a remnant (——), in 36 women with a remnant (——) and in 29 women after the remnant severing strategy (——). Vertical marks at the end of the plots are the censored observations.

A trend towards higher frequency of preterm birth (8.3% versus 3.4%; not significant) and an increased rate of miscarriage (25.0% versus 10.3%; not significant) were found in the remnant group. Severing of the remnant resulted in improvements in pregnancy rate (79.3%), delivery rate (62.1%), and term pregnancy rate (44.8%). The rates of Caesarean section and miscarriage (44.4% and 17.2%, respectively) were lower after the second metroplasty.

Figure 13. illustrates the distribution of the first viable pregnancies in time after the first and second hysteroscopies. The differences in the cumulative 24-month probability of viable pregnancies after the first operation between the 58 women without a remnant and the 36 women with a remnant, and between the 36 women with a remnant and the 29 women after the remnant severing strategy were significant when the log rank test was applied ($P<0.05$).

9. Discussion

9.1. Studies on transcervical resection of endometrium

The weakness of our study is the relatively high proportion of the patients lost for follow-up (33 (25.1%) patients were not analysed). The reason for high drop-out rate was the extensively long follow-up period. However, in our study, all of the TCRE procedures were performed by a single operator using a uniform technique confirming that the procedures can be done effectively despite relatively few cases being performed annually.

The "learning curve effect" influenced the operating time and consequently the amount of the fluid absorption. The average operation time of the first ten procedures was 40.1 min, than dropped to 26.0 , and after the 40'th operation it increased again to around 36 minutes for a few patients, and dropped again reaching a plateau at 27.2 minutes. As an explanation we can conclude that "having the technique in hands" the surgeon feels that he could perform endometrial resection even on an extremely obese patient (weight 150 kg) or on large uterine cavities which are responsible for the longer procedure time. After an adequate experience the selection of the patients become more exact and the time of surgery will reach a plateau. Our average operating time (30.7 min) is a little bit longer than others' reported in the literature, but we did not exclude from the study the patients with fibroids so the duration of this procedure time covers the length of an endometrial resection and in some cases a time of myomectomy as well.

For technical reasons most of the centres apply hormonal pre-treatment to narrow the endometrium for an easier performance of the operation. Istre et al. concluded that the preoperative endometrial thickness does have significant impact on the likelihood of achieving amenorrhoea after one year of surgery (Istre et al., 1996). On the other hand, no improvement in clinical outcome or patient satisfaction is conferred by the use of medical pre-treatments if TCRE is performed in the proliferative phase of the menstrual cycle. This avoids the need to treat patients pre-operatively with drugs that may be expensive and sometimes have unpleasant side-effects. Although no improvement in clinical outcome or patient satisfaction was observed, (Rai, et al., 2000). Thus it is important to emphasise that in our study there was no preoperative hormonal treatment used to thin the endometrium. On the other hand, it helped to cut down the cost of the operation as the hormonal pre-treatment especially with the GnRH analogues would be very expensive.

The only method was the timing of the operation within a two weeks period after a menstrual bleeding. In a few cases, when the endometrium was extremely thick the procedure was started with a D&C to remove approximately the upper two-third of the endometrium. Than TCRE was could be easily performed. Timing of the menstruation with a single dose of leuprolide acetate did not show any significant statistical difference in the effectiveness of endometrial thinning (Nathanson et al., 1997). Vercellini et al were able to find a good effect of two months goserelin depot therapy prior endometrial resection in their controlled clinical trial. Both, the mean distension medium deficit and the operating time were better in the treated group of patients. Although the differences statistically were significant it has no clinical importance whether the amount of the absorbed fluid is 511 ml or 647 ml since both of the values are well under the 1500 ml safety limit or whether the operating time is 14 min or 18 min (Vercellini et al., 1994). In our study the average absorption was 374 ml and there was only one case when we used 16000 ml irrigating fluid, because of leakage between the resectoscope and the cervical canal that we were not able to control even with the inserted cerclage. In spite of it the absorption was within the safety range. Because of our relatively short waiting list (less than two weeks) it was really easy for us to timing the operations for the proliferative phase of the endometrium, making the procedure much more cost effective.

Fifteen per cent of the patients needed hysterectomies during the 11 years follow up period. O'Connor et al. in a study with a two to five years follow-up period reported a 20% operative treatment rate, but a hysterectomy rate of only 10% after the initial operation (O'Connor et al., 1986). For a follow-up period of five years, in our study, the hysterectomy rate would be 13%. The explanation for this still high hysterectomy rate lies in the differences between the management of the patients who underwent hysteroscopic surgery (Table 3). Although all of the cases were operated on by one surgeon (BGM), the follow-up period were controlled by the referee doctors. If the patient did not become amenorrhoeic, hysterectomy was preferred as the method of treatment rather than hormonal treatment or repeated TCRE, as was the course of action in other studies. Hysterectomy is of course superior in attaining amenorrhea, and, although satisfaction with REA is high, there are greater patient satisfaction rates when the uterus is removed. It seems clear that women vary with respect to their desires with respect to amenorrhea – some see it as a primary goal whereas others would prefer to continue to menstruate, albeit with normal flow (Sculpher M., 1998).

Reference (TCRE±RB)	Patients (n)	Follow-up (years)	Amenorrhoea (%)	Satisfaction (%)	Further surgery (%)	Hysterectomy (%)
O'Conor and Magos (1996)	525	5	32	80	20	9
Crosignani et al.,(1997)	38	2	23	87	NR	10
Vilos et al., (1996)	800	1	60	NR	6	2
Bhattacharya et al., (1997)	372	1	47	90	18	10
Rauramo et al., (2004)	29	3	31	NR	17	NR
Our series	98	7,9 (5-11)	42,8	88	35,7	15,3

Table 3. Summary of published data for outcome following first generation endometrial ablation techniques (FGEAT)

NR= not reported; TCRE= transcervical resection of the endometrium; RB= roller ball technique

It is therefore important to emphasize that the aim of TCRE is not to attain amenorrhoea, but to normalise the amount of bleeding and the duration of the periods. In our study group, 79.6% of the patients (78/98) met this criterion.

The postoperative management of our patients did not involve D&C in the first 36 months; only hysterectomy was performed as an operative treatment for persistent symptoms. After this, D&C and hysterectomy were carried out in almost the same proportion up to 88 months. We had eight patients who underwent D&C between 88 and 105 months after the initial operation. The survival curve reached a final plateau after this period. These patients were at the age of menopause or post menopause and needed D&C for episodes of spotting. In a previous study on a population of similar size *de novo* dysmenorrhoea was not observed, whereas we did find such patients (Molnár et al., 1997).

For one of our patients the histological report on the endometrial chips came back as adenocarcinoma in spite of the negative histological result of D&C within one year prior to TCRE. By way of explanation, we can refer to literature data that the endometrial

abnormalities are unrecognisable in 10-35% of the cases (Gimpelson et al., 1988). The histological samples are sometimes simply not good enough or not sufficient for histological diagnosis.

Other literature reports revealed that techniques not involving hysteroscopic ablation can have a failure rate as high as 56% (Phipps et al., 1990; Singer et al., 1994). Speaking about transcervical endometrial resection especially in comparison with second generation ablative techniques it is always emphasized that the technique needs skilled surgeons. Hysterectomy, caesarean section and all of the "conventional operations" require experienced and able hands as well. So to mention the necessity of a practiced surgeon as a disadvantage is questionable. The other "disadvantage" of the gold standard techniques is that they require visualisation of the uterus with a hysteroscope, opposite with the newly developed techniques most of which can be performed blind. However visualisation of the entire surface of the uterus gives the possibility to discover previously not diagnosed intrauterine abnormalities, which can be treated during the endometrial resection. Certainly it is difficult to deny that second generation ablative techniques have the real advantages of less operating time and the similar effectiveness – at least within a few years of follow-up period - on curing dysfunctional uterine bleeding. Although the goal of our study was to evaluate the long term efficacy of TCRE and not a comparison between different type of techniques for final ablation of the endometrium we had to mention that recently a number of randomised controlled trials are available to compare the efficacy and satisfaction rate, the menstrual symptoms, quality of life, sexual activity and procedural satisfaction and acceptability and patients' satisfaction with and the acceptability of the treatment, operating time, postoperative stay and quality of life between the gold standard and the second generation ablation methods (Van Zon-Rabelink et al., 2004; Hawe et al., 2003; Cooper et al., 1999). None of these studies result comparable consequences with our study as the follow up period was 24, 12 and 12 months respectively. It means that larger studies with longer follow-up are required to determine the place of new ablative techniques in the modern treatment of dysfunctional uterine bleeding.

One important question is how inconvenient physically or mentally the chosen operative treatment is for the patients. It is generally agreed that vaginal hysterectomy is fewer problems than abdominal hysterectomy, though both procedures lead to loss of the uterus, so that the psychological effects of the procedures might be expected to be the

same. In our experience, the patients and particularly their husbands, especially if they are from lower social groups, are unable to accept the fact of hysterectomy. However, Rhodes et al. found that the sexual life was enhanced in every respect following hysterectomy (Rhodes et al., 1999). Specifically, a greater difference between pain experienced and pain expected was negatively associated with satisfaction. This finding has obvious clinical implications. First, we need to realistically council patients regarding the discomfort they may experience during the office procedure. Our study demonstrates that patients strongly associate aavoidance of further with satisfaction and a successful operation. The reason may be as simple as "something new is better" and may have been influenced by the media, internet, and social contacts. The surgeon must make the ultimate decision about the procedure, and if a further operation is needing it should be performed. The treatment team should be aware of a patient's treatment preferences and try to honor them if possible in the interest of better satisfaction. This is particularly true now that medical and surgical outcomes are assessed in terms of patient satisfaction. If a patient's surgical preference cannot be honored, additional time should be spent educating her regarding the reasons necessitating the surgeon's choice. A patient who feels part of medical decision-making will more than likely take responsibility for the outcome. Therefore, the importance of the type of the further operation on the outcome must be determined individually by the surgeon according to his or her skills, patient population. It is vital to educate all patients to the possibility of treatment failure to avoid unnecessary disappointment.

9.2. Studies on septum resection

The aetiology of reproductive failure in patients with uterine anomalies remains unclear. The mechanisms by which septate uteri cause early pregnancy loss and infertility have not been established. We do not know the minimal uterine cavity extent needed for a normal pregnancy. It has been demonstrated that the endometrial mucosa covering the septum is poorly responsive to oestrogen. The alterations indicate irregular differentiation and maturation of the septal endometrial mucosa. Accordingly, removal of the septum not only eliminates an unsuitable site for implantation, but also results in a better endometrial function, probably through revascularization of the connective tissue of the uterine fundus (Fedele et al., 1996).

The septum was discovered during infertility evaluation. All of our patients were referred with a diagnosis of septate or bicornuate uterus on hysterosalpingography. At the beginning of the study, diagnostic hysteroscopy was not widely used in the referral hospitals. We confirmed the diagnosis by using diagnostic hysteroscopy combined with diagnostic laparoscopy in one session. Only when the diagnosis in our department confirmed the presence of septum did we treat septate uterus in infertile patients at the time of diagnostic hysteroscopy without laparoscopic guidance. In our experience, laparoscopic guidance during hysteroscopic septum resection does not furnish any advantage. The septate uterus has been widely reported to be associated with miscarriage and other obstetrical complications (Goldenberg et al., 1995). As opposed to many previous studies, our investigation included only infertile women in whom no other cause of infertility was identified. In recurrent miscarriage, foetal chromosomal aberrations had not been excluded, although both parental karyotypes were normal. Accordingly, we concluded that the septum was the cause of pregnancy loss.

Very similar prevalences of residual septum occurrence were observed in previous publications (Fedele et al., 1991, Fedele et al., 1993, Parsanezhad et al., 2000, Porcu et al., 2000, Saygili-Yilmaz et al., 2002, Pabucu et al., 2004). The differences are probably due to the differences in the samples of women between the individual working-groups and to the hysteroscopic confirmation of the adequacy of the initial resection (Table 4). The most crucial part of the operation is the complete division of the septum, without causing uterine perforation or leaving a residual septum.

The occurrence of a remnant is greatly influenced by the location of the surgeon on his or her learning curve. In 2002, we observed a residual septum in only 2 cases, as opposed to 20 cases in the first 3 years.

From the beginning, we have applied exclusively the same method for resection of the septum. Previous studies agreed that the method of incision did not influence the reproductive outcome (Fedele et al., 1993).

Fedele et al. concluded that the preoperative endometrial thickness influences the operating conditions (Fedele et al., 1996). Thus, it is important to emphasize that in our study no preoperative hormonal treatment was used to thin the endometrium. The only method used was to time the operation within a 2-week period after menstrual bleeding.

	No. of patients	No. of patients with residual septum (n/%)
Fedele et al. (1991)	29	5/17.2
Fedele et al.(1993)	102	37/36.2
Parsanezhad et al.(2000)	14	3/21.4
Porcu et al (2000)	63	24/38.1
Saygili-Yilmaz et al (2002)	361	49/13.6
Pabucu et al. (2004)	61	54/88.5
Total	630	172/27.3
Our group	94	36/38

Table 4. Residual septum occurrence in selected series

On the second hysteroscopy, both the remnant and the myofibrous adhesions could be verified as whitish in colour and resistant to the touch. Some investigators claim that the adhesive process can be progressive and therefore advise early intervention. They postulate that adhesions limit the uterine muscular activity, thereby reducing the perfusion of sex steroids to the endometrium, with atrophy as a consequence (Edstrom et al., 1974). After 2 months, the uterine cavity is almost normal, with a minimal tendency to central fundal adhesion (Candiani et al., 1990). The control procedures to determine the adequacy of the metroplasty were therefore performed in that period.

Postoperative uterine rupture, one of the most serious life-threatening complications, did not occur in our series. It has been suggested that a residual septum may result in weakness during uterine enlargement in pregnancy (Angell et al., 2002).

Although the average gestation period is longer and the perinatal outcome is improved postmetroplasty, it remains unknown how much of this can be attributed to the metroplasty and how much to increased prenatal observation and intervention. Some authors have found that not all patients with unexplained infertility seem to be cured by hysteroscopic metroplasty, but it may prevent subsequent miscarriage or labour complications in patients considering conception and may improve the perinatal outcome (Daly et al., 1989;).

As opposed to previous investigations of patients with a ≤1 cm remnant septum, which tended only to consider the reproductive outcome in cases with this residual uterine anomaly (Fedele et al.,1996; Pabuccu et al., 2004), our study demonstrates the advantageous possibility of obstetric achievement after the remnant severing strategy. After the initial metroplasty, the pregnancy rate was 51.1%. This result is similar to a previous finding (Pabuccu et al., 2004).

Like every other report on this topic, this one is limited by its design. It compares a group of women examined because of failed reproduction with the same women after treatment. No clinical trial on uterine septa has been published in which the pregnancy rate is compared in a treated and an untreated group. A randomized prospective multicentre study should be undertaken, but it would not be ethical not to treat patients with infertility.

Our findings may fuel the controversy concerning the appropriate treatment of women with a remnant septum. There seems to be a general consensus, based on only a few reports, that a remnant septum ≤ 1 cm is supportable and there is no need for any further intervention to remove it. These results encourage a widening of the indications of hysteroscopic metroplasty in patients of advanced reproductive age with a residual septum so as to improve the ability for term child-bearing. Metroplasty seems to have one more potential benefit as to decrease the ability of fetal malpresentation and from this arising to decrease the cesarean section rate.

Our results may contribute to a better understanding and presumably to a better management of operative hysteroscopic procedures, as a minimal invasive technique for the solve the intrauterine anomaly in the advanced reproductive age.

10. Conclusions

The particular points of conclusion, derived from the above result, are the following:

- As outlined above, the first aim of the study was to examine the long-term effects of TCRE on the menstrual period. We described that in our study group, 79.6% of the patients (78/98) achieve to normalise the amount of bleeding and the duration of the periods. It is important to emphasise that the aim of TCRE in general is not to attain amenorrhoea.

- It is paramount of importance to conclude, that the vast majority of the patients were satisfied with the TCRE methods (61+25=86; 87.8%). Our data highlighted that 35.7% of the TCRE cases were unsuccessful and required further operative treatment. In spite of 35.7% long term unsuccessful rate 71.4% of the respondents were even satisfied with initial operation. Although 3.2% of the respondents were dubious with real usability of the endometrium resection. Despite of the experienced high effectiveness of TCRE, histological examination revealed an organic, untreatable disorder by TCRE in 8 cases. The endometrium resection study showed that eighty-eight percent of the patients were satisfied or very satisfied with the result of the endometrial resection. The need for a reoperation was strongly associated with dissatisfaction. This means that the majority of the patients set great value on the advantages of the operation, such as the like short period of hospitalisation and the quick recovery. Even those patients who later underwent hysterectomy included a few who would choose TCRE instead of hysterectomy if it was possible. Thirty-seven patients felt that they had to add a personal commentary at the end of the questionnaire; and these were all positive.
- Finally in the septum resection study, our Kaplan-Meyer analysis indicated a significantly favourable delivery rate after both the first and the second normalization of the uterine cavity as compared with the remnant group. Subsequent to the achievement of a normal uterine cavity, the pregnancy rate was relevantly higher (79.3%) than in the event of a remnant (44.4%). Our results point to prematurity not being significantly frequent after hysteroscopic septum resections (2/26 versus 5/18). On the other hand, the birth weight was more favourable after full normalization of the uterine cavity, reflecting that the gestational age in prematurity was higher and more deliveries occurred close to the term. The birth weight was lower and the prevalence of malposition as an indication of Caesarean section was higher after only one hysteroscopy when there was a remnant, highlighting the need for full normalization of the uterine cavity.

11. Summary of new findings of the thesis

- Our data proved that the TCRE is an efficacious endometrial ablative technique even in long term follow-up without any hormonal pre-treatment at the ever-growing SEAT milieu.
- We showed that the timing of the transcervical endometrial resection is a real alternative of hysterectomy for dysfunctional uterine bleeding and this advantage is remaining also after 11 years too.
- We conclude that it is naturally not meaningful to start any infertility treatment without clearing the uterine cavity up for the first time. Moreover, it would be incorrect to administer expensive In Vitro Fertlilsation (IVF) treatment on a patient whose uterine cavity has not been checked for normality in advance.
- However, our data reveal that women with a remnant have an increased and reasonable chance of successful pregnancy after normalization of the uterine cavity without serious sequalae.
- Finally, we demonstrated that the hysteroscopic metroplasty in patients of advanced reproductive age with a residual septum has advantageous possibility of obstetric achievement after the remnant severing strategy and improve the ability for term child-bearing.

12. Outlook

Recent technical innovations have revolutionized the diagnostic and operative hysteroscopic field – thinner version of hysteroscopes have been developed reducing the final diameter of the hysteroscope to 4.0 mm. The instruments feature two sheaths (one for the irrigation and another one for the suction) and 1,6mm operative canal. The hysteroscope is oval in shape ideal for atraumatic insertion of the scope into the cervix. It is now potentially possible to perform a comprehensive endoscopic examination of the uterine cavity in an office session without using any type of anaesthetic or dilating the cervical canal. This technical improvement is unstoppable. We think that in the near future the next question will be legitimate: - Do we still need to do hysteroscopy as an inpatient procedure for patient with infertility or

dysfunctional uterine bleeding? - realizing that the inpatient hysteroscopy are wastage of precious theatre time, resources and costs and increased anaesthetic complication when it is needed.

There are economic advantages with endometrial ablation because the number of days in the hospital is very few; and the necessary recuperation is only a few days. Regarding to our results we conclude that transcervical endometrial resection is a real alternative of hysterectomy for dysfunctional uterine bleeding.

The "Second Generation Endometrial Ablation devices", or "SEAT" for short, have now been developed and some of them are available in Hungary too. The advantage of these techniques may be in their ease of use and learn by physicians, have high success rates, and with some techniques requiring an average of 2 minutes treatment time. SEAT-s have been promoted as requiring less technical skill than FEAT. These second generation devices use various methods for ablating the endometium:

- electrical or electrocautery - electric current travels through a wire loop or rollerball that is applied to the endometrial lining to cauterize the tissue
- hydrothermal (HydroThermablator®)- heated fluid is pumped into the uterus and destroys the endometrial lining with high temperature
- laser - a beam of light radiation is used to destroy the endometrial lining
- balloon therapy (Thermachoice®)- a balloon at the end of a catheter is inserted into the uterus and filled with fluid, which is then heated to 85 °C that the endometrial tissues are eroded away
- electrode ablation (Novasure System®)- a triangular mesh electrode is expanded to fill the uterine cavity. A gentle suction brings the tissue into contact with the electrode which delivers electrical current and destroys the endometrial lining.
- cryoablation (Her Option®) - a probe uses extremely low temperatures to freeze and destroy the endometrial tissues
- Endometrial Ablation With Microwave (MEA®) - microwave ablation uses low-power microwaves to treat the uterine lining.

Most potential complications of EA involve use of the First Generation devices include risks of anesthesia, uterine perforation, and absorption of large volumes of fluid used during the ablation procedure (fluid overload). The SEATs have the

advantage of not using high volumes of fluids, requiring less anesthesia, requiring less time to complete, and in many cases, being able to perform these in your gynecologist's office rather than a hospital.

But don't forget that FGEAT's highest advantage of the hysteroscopy is that it can be used as a diagnostic and therapeutic tool in one session (see and treat) and with resectoscope we always obtain - not blindly - histological findings after the operation.

Hysteroscopic metroplasty has been shown to be safe, simple and expeditious method of treating the septate uterus. However the procedure requires significant hysteroscopic experience before it becomes simple and safe. Nowadays even in the era of operative hysteroscopy, transabdominal metroplasty remains the only approach in cases of bicornuate uterus.

11. Annex

Transcervical endometrial resection (TCRE)

Follow-up chart

Patient name:

Date of surgery:

How many days did you spend in the hospital? (Don't count the day of surgery!) ___

Bleeding after surgery (for how many days?): ___

Vaginal discharge after surgery (for how many days?): ___

Lower abdominal pain after surgery (for how many days?): ___

How many days did it take you to go back to normal home activity?: ___

How many days did it take you to go back to work?: ___

Did you need any drug treatment after surgery? 1 yes

(Please sign the appropriate!)

2 no

If "yes" what kind of medicine did you take?

.....

Did you have any other gynaecological operation since the TCRE?: 1 yes

(Please sign the appropriate!)

2 no

If "yes" what kind of operation? 1 D&C 2 anterior and posterior repair

(Please sign the appropriate!):

3 conisation 4 operation on the ovaries

5 hysterectomy

Date of surgery: _____year _____month _____day

In case of hysterectomy what was the indication?

(Please sign the appropriate!)

1 still irregular and heavy bleeding

2 less, but still irregular bleeding

3 regular, but heavy bleeding

4 small amount of bleeding and regular

5 other (Please give the details)

.....

Actual condition

Do you have regular bleeding? 1 yes 2 no

(Please sign the appropriate!)

If you have regular bleeding: How often? (day): ____

How many days does it last?:____

What is your opinion about the effect of the operation in general?

(Please sign the appropriate!)

1 very satisfied 2 satisfied 3 unsure 4 dissatisfied 5 very dissatisfied

How did your periods change after the surgery?

(Please sign the appropriate!)

1 no bleeding 2 irregular bleeding 3 regular bleeding

How did the duration of the bleeding change after the surgery?
(Please sign the appropriate!)

1 much shorter 2 shorter 3 no change 4 longer 5 much longer

How did the amount of bleeding changed after the surgery?
(Please sign the appropriate!)

1 much less 2 less 3 no change 4 more 5 much more

How did the menstrual pain change after the surgery?
(Please sign the appropriate!)

1 much less 2 less 3 no change 4 stronger 5 much stronger

What kind of operation would you choose in the event of necessity: endometrial resection or hysterectomy?
(Please sign the appropriate!)

1 repeated endometrial resection 2 hysterectomy

Any comment regarding to the operation:

.....
.....
.....
.....

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