Improving female fertility preservation through assisted reproductive technologies:

Strategies and promising outcomes

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List of original publications related to the PhD thesis

1. **Vesztergom D**, Téglás G, Nánássy L, Mátrai Z, Novák Z. A termékenység megőrzése daganatos betegségekben. Egy hazai felmérés tapasztalatai [Fertility preservation in cancer patients]. *Orv Hetil*. 2022;163(6):246-252. Published 2022 Feb 6. doi:10.1556/650.2022.32375, *D, Q Classification: **Q4***

2. **Vesztergom D**, Téglás G, Bahrehmand K, Torok A, Sipos M, Tandor Z, Zadori J, Balla L, Boga P, Forgacs V, Varnagy A, Manfai Z, Novák Z. Reducing radicality in fertility-sparing surgery is associated with improved in vitro fertilization outcome in early-stage cervical cancer: a national retrospective study. *Gynecologic Oncology.* 2024;186:35-41, doi.org/10.1016/j.ygyno.2024.03.024. *D, Q Classification: **D1***

3. **Vesztergom D**, Segers I, Mostinckx L, Blockeel C, De Vos M. Live births after in vitro maturation of oocytes in women who had suffered adnexal torsion and unilateral oophorectomy following conventional ovarian stimulation. *J Assist Reprod Genet*. 2021;38(6):1323-1329. doi:10.1007/s10815-021-02171-8 *D, Q Classification: **Q1***

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1. **Vesztergom D**, Székely B, Hegyi B, et al. Daganatos nőbetegek termékenységének megőrzése II. [Fertility preservation in female cancer patients. Possibilities beside current treatments in different types of cancer]. *Orv Hetil*. 2023;164(29):1134-1145. Published 2023 Jul 23. doi:10.1556/650.2023.32824 *D, Q Classification: **Q4***

2. **Vesztergom D**, Nánássy L, Polgár C, et al. Daganatos nőbetegek termékenységének megőrzése I. [Fertility preservation in female cancer patients. Gonadotoxicity of oncological therapies and possibilities of prevention]. *Orv Hetil*. 2023;164(28):1094-1101. Published 2023 Jul 16. doi:10.1556/650.2023.32823 *D, Q Classification: **Q4***

3. **Vesztergom D**, Takács T, Bíró K, et al. Gyermek- és felnőttkorú daganatos férfiak nemzőképességének megőrzése [Fertility preservation of adult and prepubertal male cancer patients]. *Orv Hetil*. 2023;164(51):2016-2023. doi:10.1556/650.2023.32953 *D, Q Classification: **Q4***

4. **Vesztergom D**, Téglás Gy, Fónyad G, et al. A hazai meddőségi ellátás fejlesztési koncepciója [The concept for the development of infertility care in Hungary] *Nőgyógyászati és szülészeti továbbképző szemle*. 2023; 25(2), 45-50 (6).

5. Sipos M, Polgár Cs, **Vesztergom D,** et al. A Belügyminisztérium egészségügyi szakmai irányelve a daganatos nőbetegek termékenységének megőrzéséről. [Ministry of the Interior's health professional guide on fertility preservation for women with cancer] *Egészségügyi Közlöny*. 2024;74(5): 869-891.

6. Szigeti F, J., Soltész K., Sipos M., Juhász A., Szöllősi K., **Vesztergom D**., Ujma P. P., & Purebl, G. A pszichológiai szűrés és ellátás helye az asszisztált reprodukcióban [The role of psychological screening and care in assisted reproduction]. *Orv. Hetil.* 2024; *165*(12), 455–463. https://doi.org/10.1556/650.2024.33007 *D, Q Classification: **Q4***

List of original publications directly not related to the PhD thesis

1. **Vesztergom D**, Vita E, Szekrényes Á, Krádi A, Szöllősi K. Miért fagyasszunk? A petesejtek krioprezervációjával kapcsolatos megfontolások [Why should we freeze? Considerations in oocyte cryopreservation] *Magyar Nőorvosok Lapja*, 2024, 87 : 2 pp. 70-74. , 5 p.

2. **Vesztergom D**, Sipos M, Illés A, et al. A mikrobiom és az infertilitás kérdései [The microbiome and infertility] *Magyar Nőorvosok Lapja*, 2021; 84(3), 128-135.

3. **Vesztergom D**, Szomszéd O, Nagy T, et al. A Magyar fiatalok termékenységtudatossága [Fertility awareness of Hungarian youth] *Kapocs.* 2021; 4:3-4, 3-20:17

Abbreviations

AFC   antral follicle count
AMH   Anti-Müllerian Hormone
ART   assisted reproductive technology
BMI   Body Mass Index
CLBR   cumulative live birth rate
COC   cumulus-oocyte complex
CPR   clinical pregnancy rate
DET   double embryo transfer
ET   embryo transfer
FET   frozen embryo transfer
FIGO   International Federation of Gynecology and Obstetrics
FP   fertility preservation
FSS   fertility-sparing surgery
HRT   hormone replacement therapy
ICSI   Intracytoplasmic sperm injection
IUI   intrauterine insemination
IVF   in vitro fertilization
IVM   in vitro maturation
MII   Metaphase II
NEAK   National Health Insurance Fund of Hungary
OHSS   Ovarian hyperstimulation syndrome
OS   ovarian stimulation
PCOM   polycystic ovarian morphology
PCOS   Polycystic ovary syndrome
PR   pregnancy rate
SET   single embryo transfer

I. Introduction

The incidence of cancer increases with age, and as family planning has been delayed over the last decade, there is an increasing number of cancer patients whose fertility may be affected by oncological treatments [1]. Recent advances in cancer treatment have greatly improved quality of life after treatment [2]. However, the potential loss of fertility is a significant emotional burden for many young people [3]. For women of reproductive age diagnosed with cancer, fertility preservation (FP) strategies have become an essential part of their treatment, offering hope for future motherhood.

The decision to use FP requires careful consideration, counselling and a comprehensive assessment of multiple factors. These strategies are primarily based on preserving the reproductive organs, cryopreserving reproductive cells and tissues, and selecting the most appropriate intervention based on the time available before cancer treatment.

The primary goal is to achieve oncological outcomes that are non-inferior to those without FP, while optimizing reproductive outcomes. Most FP techniques have been available to women of reproductive age for several decades.

International guidelines recommend that all cancer patients of reproductive age, including adolescents, should receive fertility preservation counselling. If indicated, fertility preservation procedures should be performed as part of their comprehensive cancer care [4].

In Hungary, approximately 2,066 women under the age of 40 are diagnosed with cancer each year, according to the National Cancer Registry [5]. Approximately two thirds of these patients require gonadotoxic treatment for their disease, which can potentially reduce their chances of conceiving and giving birth in the future. With an incidence of 16 cases per 100,000, there are approximately 230-250 new cases each year. This means that approximately 80 adolescents and young adults should be referred for FP treatment each year [3, 6].

As a result of our work, we have just published the Hungarian professional guideline on fertility preservation in women with cancer [7]. However, there is still no established oncofertility program in Hungary. This gap in resources and guidance poses a significant challenge for cancer patients of reproductive age who wish to preserve their fertility while undergoing essential treatment.

II. Aims and objectives

In oncofertility counselling, it is important to provide patients with accurate information to help them make informed decisions about their options for conceiving after cancer. However, there is limited knowledge about the effectiveness of assisted reproductive technology (ART) treatment in women who have undergone fertility-sparing surgery (FSS), and there are few reports of in vitro fertilization (IVF) outcomes following FSS. It is therefore essential to have comprehensive information on ART outcomes.

Our research efforts are focused on three main aims:

1. Evaluation of oncofertility practices in Hungary:

- To evaluate the knowledge, attitudes and existing clinical practices of Hungarian oncologists in the field of oncofertility.

- To identify factors that may prevent young women with cancer from accessing fertility preservation programs.

- To develop an educational program tailored for clinicians (oncologists and fertility specialists) with the aim of improving network accessibility for cancer patients.

2. IVF outcomes in early stage cervical cancer:

- To evaluate the results of in vitro fertilization (IVF) in patients with early-stage cervical cancer who have undergone fertility-sparing procedures.

- To compare outcomes between radical and non-radical approaches in specific cases of oncofertility.

3. To explore innovative approaches to fertility preservation:

- To investigate the feasibility of incorporating new methods, such as in vitro maturation (IVM), into a fertility preservation program.

By addressing these objectives, our research aims to fill critical gaps in the understanding of oncofertility, contribute to informed patient decision making, and pave the way for improved fertility preservation options and accessibility in Hungary.

III. Materials and Methods

1. Evaluation of oncofertility practices in Hungary:

Based on the existing literature [6, 8, 9], we designed a comprehensive questionnaire on fertility preservation, which was distributed twice to the members of the Hungarian Oncological Society via an online platform (SurveyMonkey). The distribution process was facilitated with the support of the Board of the Hungarian Oncological Society. A total of 154 oncologists initiated the survey and 94 physicians successfully completed the questionnaire. Our analysis was based on the data from these 94 fully completed responses, ensuring that each participant completed only one questionnaire. Participation was voluntary. The data collected were analyzed using R statistical software (version 4.1.0). Statistical significance was determined at a p-value of less than 0.05. Descriptive statistics were used to express the relative prevalence of each characteristic as a percentage of the total population surveyed.

2. IVF Outcomes in Early-Stage Cervical Cancer

This retrospective cohort study included all Hungarian patients who underwent fertility-sparing surgery (FSS) for early-stage cervical cancer performed by an experienced surgical team between 2004 and 2020, followed by IVF treatment between 2006 and 2022. Data were obtained from the database of the National Health Insurance Fund of Hungary (NEAK) [10].

The inclusion criteria were cervical cancer patients who desired to preserve their fertility; had histological confirmation of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma or other epithelial tumors; had stage IA1 to IB3 disease according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 revised staging of cervical cancer [11].

The exclusion criteria were previous neo-adjuvant chemotherapy, pelvic radiotherapy or total hysterectomy. We attempted to reduce the impact of maternal age by excluding patients over 40 years of age at the time of their first oocyte retrieval, as one of the major factors contributing to IVF treatment failure is advanced maternal age.

A team of six experienced gynecologic oncologists performed the FSS procedures at the designated centers. The team has extensive experience spanning two decades of performing FSS in patients diagnosed with early-stage cervical cancer. Patients were categorized into radical and non-radical surgical groups based on the type of their FSS procedure. Non-radical surgical procedures consistently preserved the uterine arteries. Patients in the non-radical group underwent simple trachelectomy or modified radical trachelectomy with preservation of the

uterine arteries [12]. In contrast, the radical group included patients who underwent classic abdominal radical trachelectomy with bilateral ligation of the uterine arteries. The latter procedure was previously detailed in the publication by Ungar et al [13]. Non-radical surgery was introduced after 2015, previously almost all patients underwent radical surgery.

Patients who underwent FSS and required fertility treatment were referred to assisted reproductive technology (ART) centers. Patients who underwent IVF treatment(s) between 2006 and 2022 following previous FSS performed between 2004 and 2020 for early-stage cervical cancer were included in the study. All Hungarian fertility clinics actively participated in this study, providing comprehensive data concerning patient characteristics and IVF outcomes. Patients were contacted and surgical/pathological reports were obtained to provide detailed clinical data. The National Central Ethical Committee approved the study: BMEÜ/2366- 1 /2022/EKU.

Outcome measures

The primary outcome of this study was live birth among women who underwent fertility treatment. This indicator was chosen to ensure the statistical independence of the sample elements and to estimate the odds, despite differing from the most commonly used outcome indicators in IVF treatments [14]. Both patient groups were analyzed for secondary outcomes including clinical pregnancy rate per transfer, cumulative live birth rate (CLBR) per oocyte retrieval, ovarian stimulation (OS) response, number of retrieved oocytes per cycle, fertilization rate, clinical pregnancy rate (PR) per embryo transfer cycle, miscarriage rate, cumulative live birth rate per aspiration, implantation rate, gestational age at birth and fetal birth weight.

Statistical analysis

For most variables, we calculated simple means, medians, or frequency values to describe the characteristics of the groups. The statistical analysis was performed using the RStudio program (R software version: 4.2.2). Student's t-test was used to compare group means, and Fisher's exact test was applied to assess independence and distributions between categorical variables, and to estimate odds.

3. Exploring Innovative Approaches in Fertility Preservation

We present two anovulatory patients with increased functional ovarian reserve who had previously experienced ovarian torsion after OS with gonadotropins.

Both patients had undergone unilateral oophorectomy despite the general recommendation of conservative surgical management of ovarian torsion. After self-referral to the Centre for Reproductive Medicine, Universitair Ziekenhuis Brussel, they were offered in vitro maturation (IVM) of oocytes as an alternative to IVF treatment, which resulted in a live birth in both patients. Data were obtained from chart review and reported without patient identifiers. Patients signed informed consent for publication of their data. Publication was approved by the local Ethics Committee (No B1432020000125).

IV. Results

1. Evaluation of oncofertility practices in Hungary

The majority of doctors surveyed (55%) were male and 96% had a specialist qualification. Approximately two-thirds of respondents worked in national or university centers, predominantly in the capital city (72%), and had 15-25 years of professional experience (30%). Figure 1 shows the demographic and professional characteristics of the participating oncologists.

Figure 1. Demographic and professional characteristics of oncologists participating in the study.
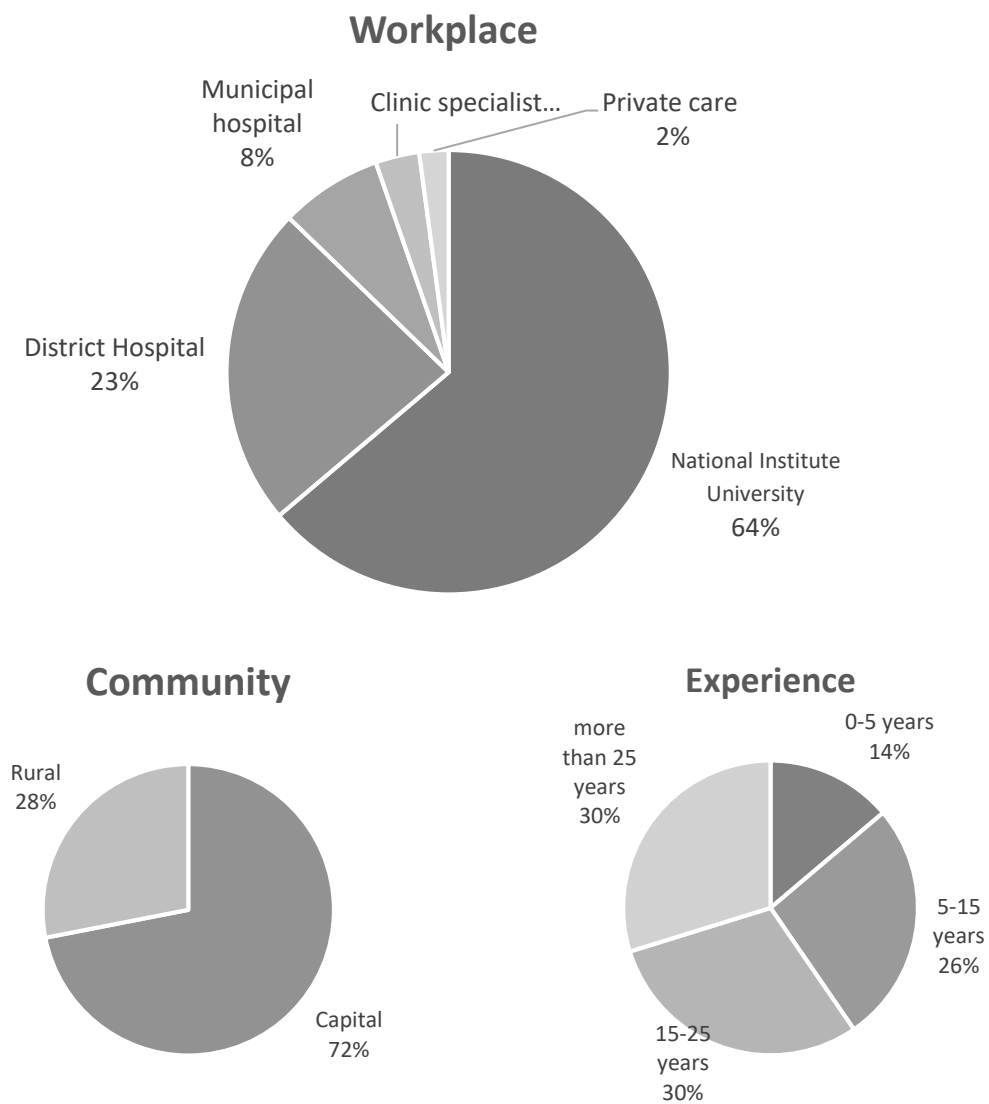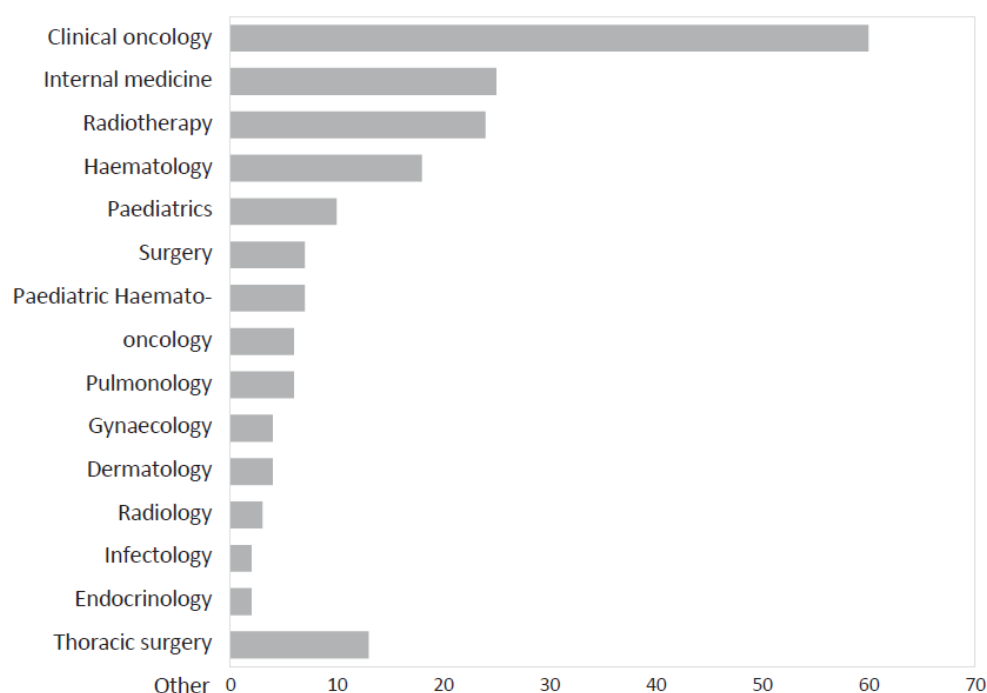

Figure 2. shows the distribution of participants by qualification, with the three most common specialties being clinical oncology, radiotherapy and internal medicine.

Figure 2. Distribution of participants by qualification

The three most common specialties were clinical oncology, radiotherapy and internal medicine. Seventy-five percent of participants reported a moderate or high level of knowledge about the gonadotoxic effects of radiotherapy and chemotherapy, whereas only nine respondents (9.5%) felt moderately or highly informed about the latest fertility-sparing techniques. Notably, professional experience correlated positively with awareness of gonadotoxic effects (Spearman's coefficient [ρ] = 0.4214, p<0.05). Regarding awareness of oncofertility centers, 48% of professionals were informed, 42% were unsure and 9.5% were not aware. Notably, 9.5% were unaware of a center offering fertility preservation for patients undergoing treatment. A significant majority (77%) of respondents routinely inquire about their patients' desire for more children, while 79% consistently consider the gonadotoxicity of treatments in patients of childbearing age, discussing these concerns with patients in 85% of cases.

However, despite these considerations, 45% of respondents rarely or never refer patients to fertility centers and 13% do not mention fertility preservation options during consultations.

Sperm and oocyte cryopreservation were the most commonly recognized and recommended fertility preservation methods, whereas embryo cryopreservation was less commonly recognized and recommended (see Table 1).

Table 1: Fertility preservation methods and respondents' perceptions of them

	Mentioning the method to the patient	Thinks the method is experimental	Thinks the method is available	Mention the method to the patient
Sperm cryopreservation (n)	88 % (82)	3 % (3)	90 % (85)	77 % (72)
Egg freezing (n)	80 % (74)	11 % (10)	77 % (72)	61 % (57)
Use of GnRH analogue (n)	65 % (60)	5 % (5)	51 % (48)	19 % (18)
Testicular tissue freezing (n)	58 % (54)	43 % (40)	25 % (23)	18 % (17)
Ovarian tissue freezing (n)	55 % (51)	37 % (35)	33 % (31)	34 % (32)
Ovarian transposition	46 % (43)	39 % (37)	28 % (26)	15 % (14)
Embryo cryopreservation (n)	44 % (41)	46 % (43)	26 % (24)	13 % (12)

Regarding referral practices, 86% of respondents felt that a multidisciplinary oncofertility guideline would be beneficial. Targeted education of professionals, an oncofertility network and accessible contacts (hotline) were identified as critical factors that would facilitate patient referral for fertility preservation, as shown in Figure 3.

Figure 3: Factors influencing referral for oncofertility treatment

What factors are helpful when referring patients for oncofertility counselling?
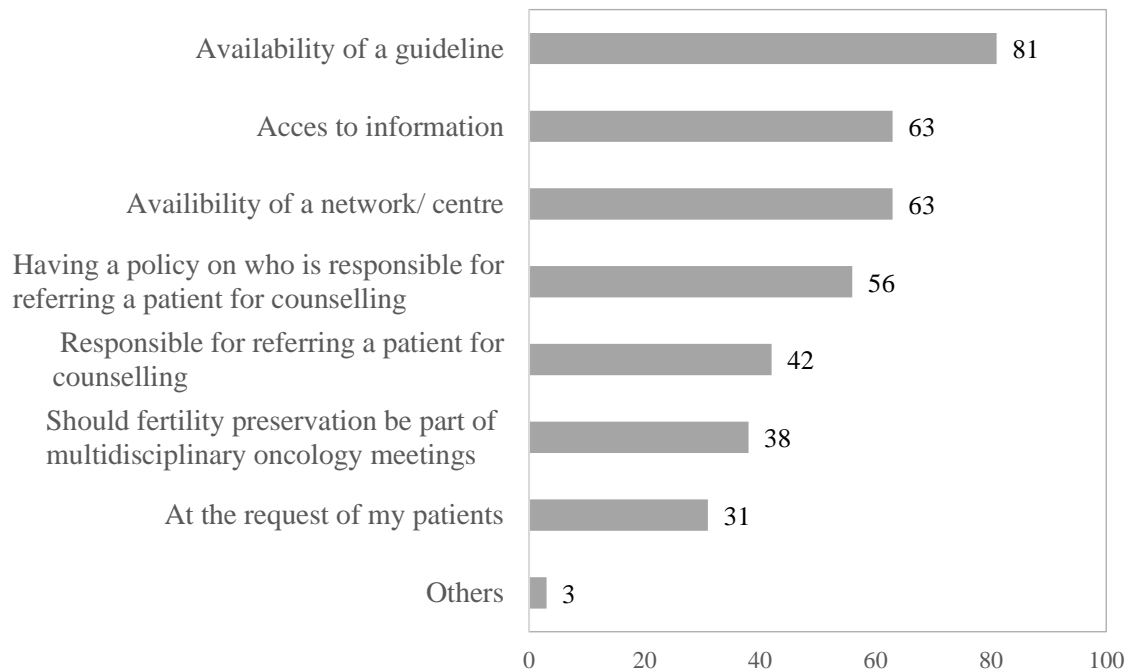
Barriers to patient referral for fertility preservation included inadequate cooperation between professionals, urgency of oncological treatment, lack of interest on the part of both patients and physicians, insufficient information and lack of a fertility preservation network (see Table 2). Free-text responses provided additional insights, revealing restrictions on accepting patients under 18 years of age in infertility clinics, limited fertility preservation methods in this age group, patient refusal of fertility preservation treatment, and instances where physicians deemed fertility preservation inappropriate. The concentration of assisted reproduction centers in the capital is likely to contribute to a more robust professional network.

Table 2: Factors leading to oncologists not referring patients for assisted reproduction

Main reasons for not referring a patient for fertility preservation treatment

Response	**(n)**
Insufficient collaboration between oncologist/fertility specialists.	64
There is no time for fertility preservation because the tumor needs urgent treatment.	58
Cancer treatment is more important than fertility preservation.	55
The information I have about fertility preservation is not up to date.	54
Lack of fertility preservation network.	53
Patients don't know that cancer treatment and fertility preservation can co-exist.	51
When a tumor is detected, the psychological burden of dealing with the loss of fertility is high.	35
Ovarian stimulation is considered dangerous in hormone receptor-positive gynaecological and breast cancers.	32
Short consultation time.	29
I don't think it's clear who has to tell the patient.	24
In the case of breast cancer, I am concerned about the oncological risk of subsequent pregnancies.	16
The patient is frightened by the prospect of fertility treatment.	8
I think the success rate of assisted reproduction is low.	2
Other	7

In terms of geographical differences, oncologists in the capital showed greater awareness of assisted reproduction centers (55%) than their rural counterparts (39%).

2. IVF Outcomes in Early-Stage Cervical Cancer

In the initial data retrieval process, we identified 148155 in vitro fertilization treatment cycles performed between 2006 and 2022 in the database of the National Health Insurance Fund of Hungary (NEAK). (Fig. 4).

Figure 4. Overview of the study course
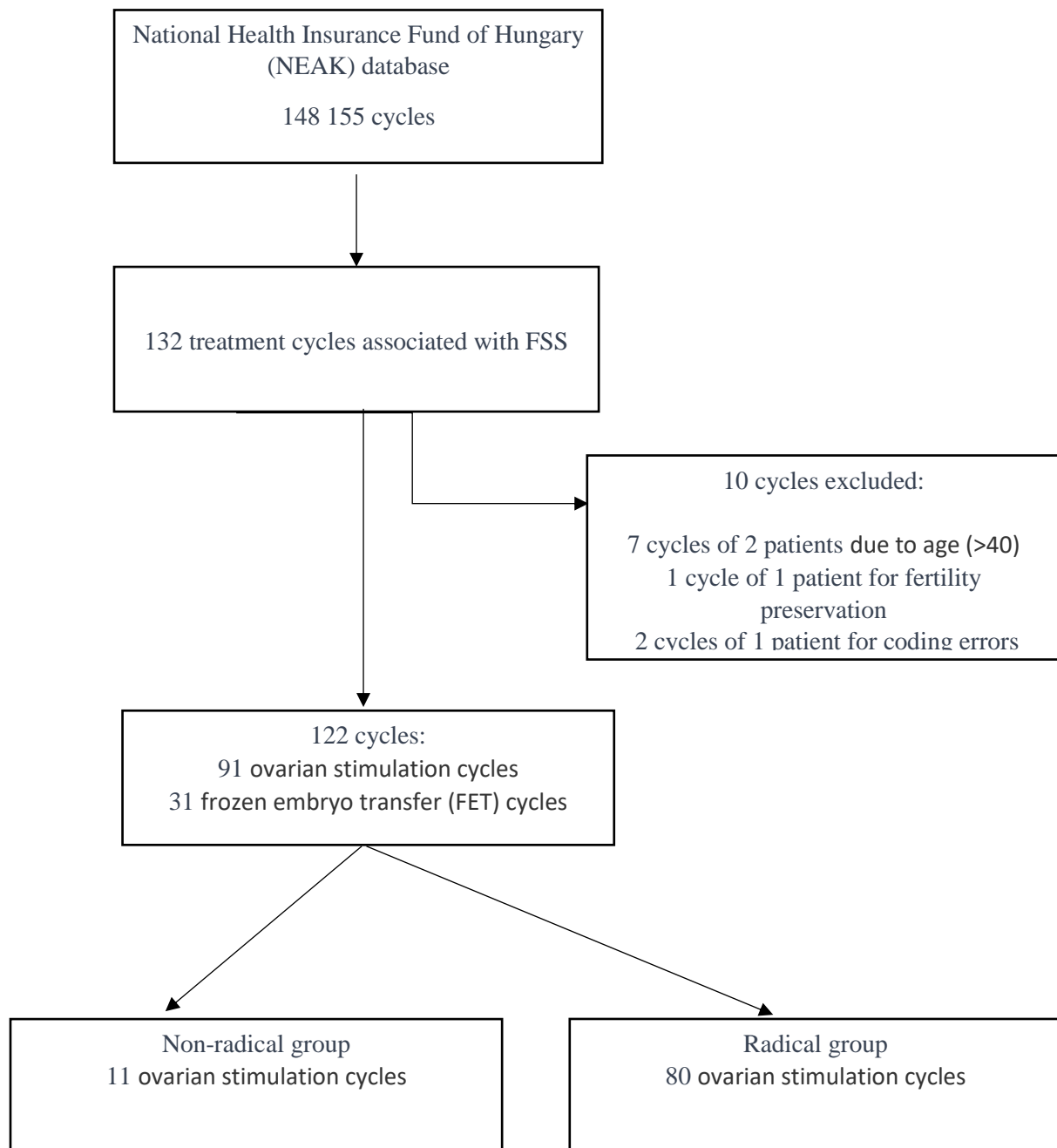
Of these cycles, 132 were performed in 40 patients who had previously undergone FSS for early-stage cervical cancer. After exclusion of four patients (with 10 cycles) - two due to

advanced age (>40), one who had undergone a fertility preservation cycle prior to FSS, and one due to coding error- the study included 36 patients representing 122 cycles. These cycles comprised 91 ovarian stimulation cycles and 31 frozen embryo transfer (FET) cycles. Out of the 91 ovarian stimulation cycles, 11 and 80 occurred in the non-radical group and radical group, respectively. An overview of the study course is presented in Fig. 4.

A total of 36 patients were included in the study, with 6 in the non-radical group and 30 in the radical group. Table 3 summarizes patient and tumor characteristics.

Table 3. Patient and tumor characteristics

| | Group | | | |
	All patients	**Non-radical group**	**Radical group**	*P* **value**
Number of patients, n	36	6	30	
Mean age at FSS, y (range)	31.7 (23-37)	31 (26-35)	30.2 (23-37)	
Nulliparous, n (%)	31 (86.1%)	5 (83.3%)	26 (86.7%)	
Stage distribution (FIGO 2018)				**<0.01**
IA1, n (%)	4 (11.1%)	4 (66.7%)	0 (0%)	
IA2, n (%)	3 (8.3%)	1 (16.7%)	2 (6.7%)	
IB1, n (%)	24 (66.7%)	1 (16.7%)	23 (76.7%)	
IB2, n (%)	3 (8.3%)	0 (0%)	3 (10%)	
IB3, n (%)	2 (5.6%)	0 (0%)	2 (6.7%)	
Histology				
Squamous cell carcinoma	20 (55.6%)	3 (50%)	17 (56.7%)	
Adenocarcinoma	12 (33.3%)	1 (16.7%)	11 (36.7%)	
Adenosquamous carcinoma	2 (5.6%)	2 (33.3%)	0 (0%)	
Other epithelial tumors	2 (5.6%)	0 (0%)	2 (6.7%)	
Type of FSS				
ART with bilateral ligation of uterine arteries, n (%)	30 (83.3%)	0 (0%)	30 (100%)	N/A
ART with preservation of uterine arteries non-radical, n (%)	1 (2.8%)	1 (16.7%)	0 (0%)	
Simple trachelectomy non-radical, n (%)	5 (13.9%)	5 (16.7%)	0 (0%)	
Cervical stenosis, n (%)	6 (16.7 %)	1 (16.7 %)	5 (16.7 %)	**1**
Median follow-up , y	13.6	16.4	13.2	
Note: FSS= Fertility-sparing surgery ; ART= Abdominal radical trachelectomy				

The mean age at the time of fertility-sparing surgery (FSS) was 31.7 years (range: 23-37 years) for all patients, with comparable ages of 31 and 30.2 years in the non-radical and radical groups, respectively. Most patients were nulliparous (86%), while 14% had one previous child

prior to the trachelectomy procedure. Most patients had FIGO stage IB1 tumors (66.7 %). The remainder had stage IA1 (11.1%), IA2 (8.3 %), IB2 (8.3 %), or IB3 (5.6%). All patients with tumors> 2cm underwent abdominal radical trachelectomy with bilateral ligation of uterine arteries. Patients were categorized into radical and non-radical surgical groups according to the type of their FSS procedure. The majority of the patients with stage IB1 tumors (95.8 %) underwent radical surgery; only one patient underwent modified abdominal radical trachelectomy with preservation of the uterine arteries. 71.4 % of the patients with stage IA had received non-radical surgery. No patients in our database received adjuvant treatment (XRT and/or chemotherapy) after fertility-sparing surgery (FSS). However, the radical and non-radical groups seemed unbalanced in terms of tumor stage. The Fisher exact test showed a statistically significant difference (p<0.01) in the tumor stage (IA vs. IB stadium) distribution between the non-radical and radical groups. Six patients (16.7%) have developed documented cervical stenosis after FSS: 1 out of 6 patients in the non-radical group, and 5/30 patients in the radical group. All had subsequent successful cervical dilatation under general anesthesia. Oncological outcomes were evaluated and showed 100% recurrence-free survival and overall survival in non-radical patients in our study with a median follow-up of 13.6 years. It's important to note that due to the limited number of patients in our study, we cannot comment in detail on oncological safety.

Reproductive Outcomes

Regarding ovulation stimulation outcomes (Table 4.), the mean time interval from FSS to the first oocyte retrieval for all patients, was 1681 days. The mean age at the first oocyte retrieval was 34.9 years for all patients, and there was no statistically significant difference between the two groups (p=0.4703). Furthermore, there was no significant difference between the two groups in terms of Body Mass Index (BMI) (22.9 kg/m2) and Anti-Müllerian Hormone (AMH) levels (2.5 ng/ml) (p=0.2264 and p=0.2878 respectively). The study also found that the radical group had four cases of male infertility, while the non-radical group had none. In addition, the radical group had ten cases of other causes of female infertility, compared to two cases in the non-radical group. On average, patients underwent 2.4 cycles of ovarian stimulation cycles. The radical group had more cycles (2.7) than the non-radical group (1.7). There was no significant difference in the mean number of retrieved oocytes between the non-radical and radical groups during the first cycle (p=0.46). The mean FSH dosage at the first cycle (IU) showed no significant difference between the two groups (p=0.9597). The

fertilization rates were also similar, with 55% and 53% in the non-radical and radical groups, respectively.

Table 4. Ovarian stimulation outcomes and patient characteristics

	Group			
	All patients	**Non-radical**	**Radical**	**P value**
Mean time interval from FSS to first oocyte retrieval, days	1681	1864	1644	**0.6938**
Mean age at the first oocyte retrieval, y	35.1	36.2	34.9	**0.4703**
BMI, mean (kg/m^2)	22.9	24.3	22.7	**0.2264**
AMH, mean (ng/ml)	2.5	4.1	2.3	**0.2878**
Male infertility	4 (11.1%)	0 (0%)	4 (13.3%)	
Other causes of infertility in women	12 (33.3%)	2 (33.3%)	10 (33.3%)	
Stimulation cycles	91	11	80	
Mean number of ovarian stimulation cycles (per patient)	2.4	1.7	2.7	
Mean number of retrieved oocytes in the first cycle	7.1	8.3	6.8	**0.4647**
Fertilization rate	53% (311/585)	55% (37/67)	53% (274/518)	
Mean FSH dosage at the 1. cycle (IU)	1811	1800	1815	**0.9597**
OS response (mean FSH dosage per matured oocyte at the 1. cycle) (IU)	282	243	303	
Note: OS= Ovarian stimulation; FSS=Fertility-sparing surgery				

Table 4 summarizes the IVF outcomes. Live births occurred in 10 patients (28%), with one woman having two deliveries, resulting in 11 babies. No multiple births were recorded. The live birth rate after fertility treatment was significantly higher in the non-radical group, with 83% of patients achieving a live birth compared to only 17% in the radical group (Fisher test, p=0.0035). In the non-radical group, the clinical pregnancy rate per embryo transfer (CPR) and the CLBR per oocyte retrieval were 64% and 55%, respectively. In contrast, the radical group had a CPR per embryo transfer of 12% and a CLBR per oocyte retrieval of 6%. These results show a significant difference between the two groups (Fisher test, CPR p=0.0004 and CLBR p=0.0002). The non-radical group had a 21.9- fold estimated odds (95% CI: 1.9-1216.4) higher chance of having a live birth compared to the radical group. The miscarriage rate was 50% and 17% in the radical and non-radical group, respectively. Three pregnancies (60%, 3/5) in the

radical group resulted in a first-trimester miscarriage and only one pregnancy (17%, 1/7) in the non-radical group. In the radical group two patients (40%, 2/5) had a second-trimester loss, whereas no second trimester loss was reported in the non-radical group. The implantation rate was significantly higher in the non-radical group, with 37 % compared to only 8% in the radical group (Fisher-test, p=0.0017).

Table 5. Outcomes of in vitro fertilization after fertility-sparing surgery in the non-radical compared to the radical group

	Group			
	All patients	**Non-radical group**	**Radical group**	**P value**
Patients, n	36	6	30	
Stimulation cycles, n	91	11	80	
Embryos, n	311	37	274	
Embryo transfers, n	95	11	84	
Pregnancies, n	17	7	10	
Miscarriage, n (%)	35% (6/17)	17% (1/7)	50% (5/10)	**0.3043**
1 st trimester miscarriage, n	4	1	3	
2 st trimester miscarriage, n	2	0	2	
Implantation rate, %	11% (19/167)	37% (7/19)	8% (12/148)	**0.0017**
CLBR per oocyte retrieval, %	12% (11/91)	55% (6/11)	6% (5/80)	**0.0002**
Clinical PR per embryo transfer, %	18% (17/95)	64% (7/11)	12% (10/84)	**0.0004**
Women with live birth, %	28% (10/36)	83% (5/6)	17% (5/30)	**0.0035**
Preterm birth <37 weeks of pregnancy, n (%)	63.6 % (7/11)	50 % (3/6)	100 % (5/5)	**0.1818**
24-32 weeks	14.3% (1/7)	0% (0/3)	40% (2/5)	
32-37 weeks	85.7% (6/7)	100% (3/3)	60% (3/5)	
Average gestational age at birth, w	33.5	35.5	31	**0.0758**
Average fetal birth weight, g	2203	2787	1473	**0.0515**
Note: CLBR= cumulative live birth rate; FSS= Fertility-sparing surgery; PR = pregnancy rate.				

The non-radical group had an average gestational age at birth of 35.5 weeks. In contrast, the group that received radical treatment had a lower average gestational age at birth of 31 weeks, indicating a higher incidence of prematurity in these patients. Within the radical treatment group, 40% of patients (2/5) delivered with significant prematurity (before 32 weeks), which is where most neonatal morbidity and mortality occurs. However, there was no significant prematurity in the non-radical group. The average fetal birth weight was 2787 grams and 1473 grams in the non-radical and radical groups, respectively.

3.   Exploring Innovative Approaches in Fertility Preservation

Patient 1

Patient 1 self-referred to our clinic with a history of primary subfertility for 2 years. She had experienced secondary amenorrhea after discontinuing the oral contraceptive pill. Before attending our clinic, she had previously undergone four cycles of ovulation induction prescribed by her gynaecologist. Because of resistance to clomiphene citrate, the patient had received HP-hMG (Menopur®; Ferring Pharmaceuticals A/S, Copenhagen, Denmark) at a daily dose of 75 IU, resulting in the recruitment of a single dominant follicle. Ovulation had been triggered using 5000 IU hCG (Pregnyl®, Organon, MSD, Haarlem, The Netherlands). After the third round of ovulation induction, the patient had presented at the emergency department with increasingly severe and persistent lower abdominal pain and nausea, 2 days after hCG administration. An explorative laparoscopy had been performed, which revealed two enlarged and rotated ovaries with a diameter of 12 cm and 10.5 cm. Because the right ovary and fallopian tube had shown persistent dark discoloration and complete absence of blood flow in the ovarian vessels after derotation, the gynaecologist had decided to perform a unilateral adnexectomy. The contralateral ovary had been derotated and recovered quickly. The histology report confirmed the diagnosis of necrosis of the right ovary. After self-referral to our fertility clinic, hormonal analysis was performed which was compatible with functional hypothalamic amenorrhea (WHO I anovulation, Table 6).

Table 6: Baseline patient characteristics and IVM cycle outcome

	Patient 1		Patient 2
Baseline patient characteristics*			
Age (years)	25		30
BMI (kg/m^2)	16.5		19.4
AMH (ng/mL)	24.5		12.3
AFC (N)	60		30
FSH (IU/L)	<0.1		7.5
LH (IU/L)	<0.1		8.8
Progesterone (nmol/L)	1.34		0.64
E2 (ng/L)	32.0		28.0
IVM cycle outcome	Cycle 1	Cycle 2	
COC retrieved (N)	70	77	30
MII oocytes (N)	35	37	25
2PN oocytes (N)	25	22	21
Cleavage-stage embryos (N)	17	7	20
Cryopreserved embryos (N/stage)	0	7 (d3)	7 (d5)
Fresh ET (N/stage)	1/BL4BB (d5)	0	1/BL4AA (d5)***
eFET (N/stage)**	N/A	4	N/A
eFET no. 1		1/8c gr2 (d4)	
eFET no. 2		1/C2 gr1 (d4)	
eFET no. 3		1/5c gr3 (d4)	
eFET no. 4		2/BL1 gr2, C2 gr2 (d4)***	
Live birth	0	1	1

COC cumulus-oocyte complex, *MII* metaphase II, *2PN* two pronuclei, *ET* embryo transfer, *SET* single embryo transfer, *DET* double embryo transfer, *Y* yes, *N* no
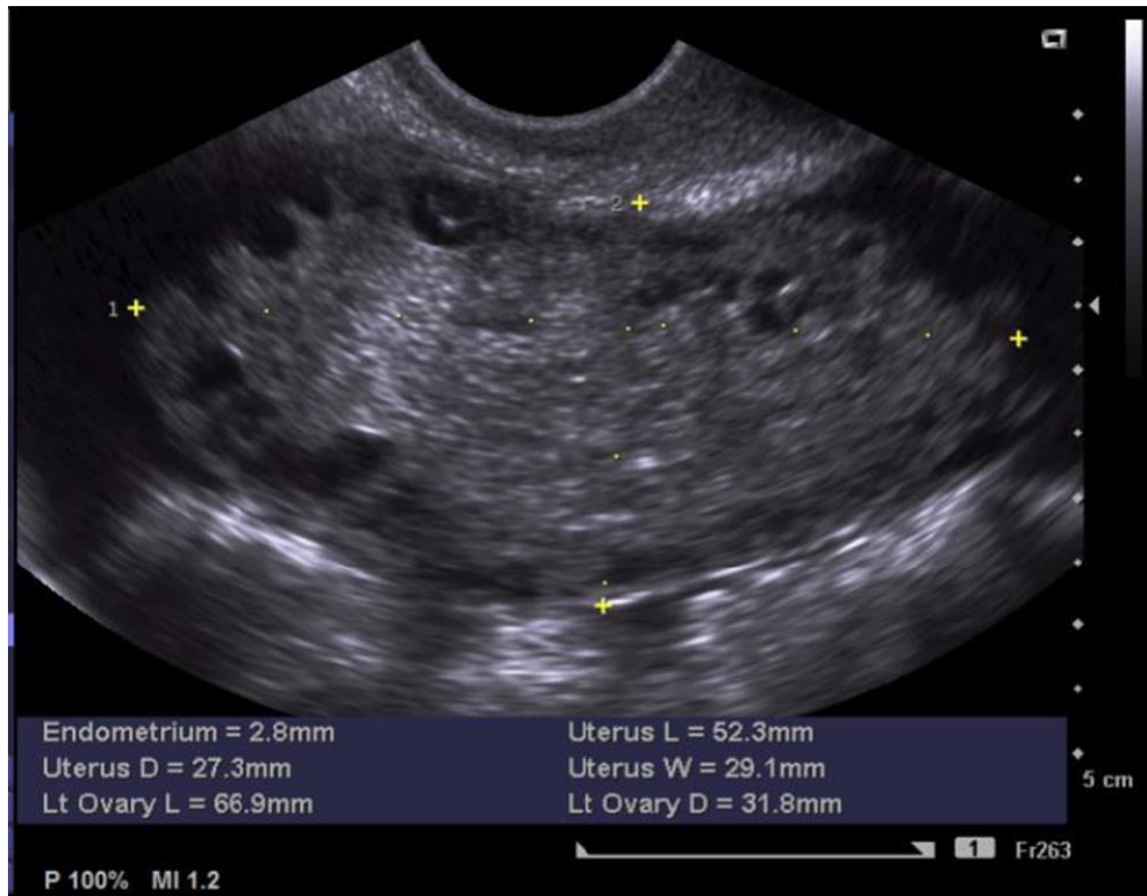
*Patient characteristics at intake (after unilateral oophorectomy)

**Cleavage-stage embryos were vitrified on day 3; embryo transfer was performed 1 day after embryo warming

***Resulting in live birth

Transvaginal ultrasound showed an antral follicle count (AFC) of 60 in the unique left ovary, a thin endometrium, and no ovarian cysts (Fig. 5).

Figure. 5: Baseline transvaginal ultrasound scan in patient 1 showing an AFC of 60 in the unique left ovary

Endometrium = 2.8mm
Uterus D = 27.3mm
Lt Ovary L = 66.9mm

Uterus L = 52.3mm
Uterus W = 29.1mm
Lt Ovary D = 31.8mm

5 cm

P 100%   MI 1.2

Fr263

The BMI was 16.5 kg/m2 and sperm analysis in the partner was normal. Because of the history of ovarian torsion after OS with gonadotropins and hCG triggering, the patient declined further attempts of OS. In view of this, in vitro maturation (IVM) of oocytes was proposed, as previously described [14]. Briefly, ovarian stimulation involved administration of 225 IU HPhMG (Menopur®) for four consecutive days. Transvaginal oocyte retrieval was performed 42 h after the last injection of HP-hMG. No hCG trigger was administered. Transvaginal ultrasound-guided oocyte retrieval was performed under general anaesthetic using a 17-gauge single-lumen needle on day 6 (K-OPS-1230-VUB; Cook Medical) at an aspiration pressure of −70 mmHg. No follicle flushing was performed. Follicular aspirates were collected in human tubal fluid (HTF) (IVF Basics® HTF HEPES, Gynotec B.V. Malden, The Netherlands) supplemented with heparin (5000 IU/mL, Heparin Leo, Leo Pharma, Belgium; final heparin concentration 20 IU/mL) and filtered through a cell strainer (Falcon®, 70-μm mesh size, BD Biosciences, CA, USA). In total, 70 cumulus-oocyte complexes (COCs) were harvested. After collection, COCs were washed and transferred to four-well dishes (Nunc, Thermo Fisher

Scientific, MA, USA) containing IVM medium (IVM System, Medicult, Origio) supplemented with 75 mIU/mL HP-hMG (Menopur®), 100 mIU/mL hCG (Pregnyl®), and 10mg/mL human serum albumin (Vitrolife, Göteborg, Sweden), followed by 32 h of group culture of 10 COCs per well in 500 µL of IVM medium with an oil overlay (Ovoil, Vitrolife) at 37 °C under 6%CO_2 and 20%O_2. In total, 35 oocytes reached MII stage after IVM. Matured oocytes were inseminated using ICSI with partner sperm, and 25 oocytes fertilized normally. Embryos were cultured in individual 25-µL droplets of sequential media (Quinn's Advantage™ Fertilisation, Fert™, Cleav™, Blast™ medium, Origio) and in G-TL™ monophasic culture medium (Vitrolife, Göteborg, Sweden) in the second cycle. Seventeen cleavage-stage embryos were observed on day 3 after ICSI, and embryo culture was continued to day 5. Luteal-phase support for an IVM cycle with fresh embryo transfer consisted of transdermal estradiol (E2) gel (Oestrogel®; Besins Healthcare, Paris, France) at a dose of 2 mg, three times daily, which was started on the day before oocyte retrieval, and 600 mg daily of vaginal micronized progesterone (Utrogestan®, Besins Healthcare, Paris, France), starting on the evening of the day of the ICSI procedure. One blastocyst of good quality (BL4BB, as graded according to the Gardner and Schoolcraft scoring system [15]) was transferred freshly. No pregnancy ensued. Unfortunately, all other blastocysts were of insufficient developmental quality to be vitrified as surplus embryos. A second IVM cycle was performed in this patient using the same protocol with 4 days of HP-hMG stimulation. Oocyte retrieval yielded 77 COCs; 37 oocytes reached MII stage after IVM, of which 22 were fertilized normally after ICSI. Seven embryos of good morphological quality were vitrified electively on day 3 after ICSI. In view of the poor embryo development beyond the cleavage stage in the previous IVM cycle, the embryos were not cultured to day 5. The patient went on to have HRT cycles for frozen embryo transfer (FET) when basal hormone levels were reached after the IVM cycle. Briefly, the endometrium was primed with transdermal Oestrogel® (two units administered three times a day). When an endometrial thickness of more than 6 mm was reached, luteal support was started using intravaginal micronized progesterone tablets (P, 200 mg three times a day; Utrogestan®, Besins Healthcare), and the embryo transfer was scheduled 5 days later. The transfer of day 3 vitrified embryos was performed 1 day after embryo warming. Administration of oestrogens and P was continued until a pregnancy test was performed and was continued until 7 weeks of gestation if the pregnancy test was positive, after which the dose was gradually reduced and discontinued 1 week later. Because no pregnancy was achieved after three consecutive HRT cycles with single vitrified-warmed embryo transfer, a diagnostic hysteroscopy with endometrium biopsy was performed which showed normal histology and no signs of endometritis. Two embryos that

had been vitrified on day 3 were transferred 1 day after warming in a further HRT cycle, which resulted in a pregnancy leading to a healthy singleton live birth at term.

Patient 2

A 30-year-old woman self-referred to our clinic with primary subfertility for 3 years based on PCOS-related anovulation. Previous first-line fertility treatment with her gynaecologist had involved five cycles of ovulation induction with clomiphene citrate and intrauterine insemination (IUI), which had not resulted in pregnancy. She had gone on to have conventional ovarian stimulation for IVF using a GnRH antagonist protocol. Because of an increased risk of OHSS, she had been prescribed 0.2 mg of GnRH agonist triptorelin (Decapeptyl, Ipsen®, Merelbeke, Belgium) for final oocyte maturation. Fifteen cumulus-oocyte complexes had been retrieved and one good-quality blastocyst had been vitrified electively. After oocyte retrieval, the patient had presented severe pelvic pain whilst in the recovery room, not responding to standard analgesia. Upon laparoscopic exploration, gross enlargement of both ovaries had been observed and the right ovary had shown livid discoloration. The torsed right ovary had been derotated laparoscopically. However, because of signs of septicaemia on the next day, the patient had been operated again by laparoscopy 48 h later and had undergone unilateral right adnexectomy because of gangrenous changes of the ovary. After self-referral to our clinic, patient 2 was diagnosed with PCOS phenotype D, based on the extended Rotterdam criteria. Her basal hormonal profile is presented in Table 1. Because of the history of ovarian torsion after OS using a GnRH antagonist protocol with GnRH agonist trigger, the patient declined further attempts of OS. In view of this, in vitro maturation (IVM) of oocytes was proposed, as described above. A short course of gonadotropins consisting of 225 IU HP-hMG (Menopur®) daily for three consecutive days was administered in patient 2. Transvaginal oocyte retrieval resulted in 30 COCs; 25 oocytes reached MII stage after IVM. All metaphase II oocytes were inseminated with ICSI, and 21 were fertilized normally. Embryos were cultured in individual 25-µL droplets of sequential media (Quinn's Advantage™Fertilisation, Fert™, Cleav™, Blast™medium, Origio). On day 5 after ICSI, seven blastocysts of good or top quality were vitrified electively. Endometrium preparation for the fresh embryo transfer consisted of administration of Oestrogel® at a dose of 2 mg, three times daily and started on the day before oocyte retrieval, and 200 mg three times daily of intravaginal micronized progesterone (Utrogestan®) starting on the first day after oocyte retrieval. One top-quality blastocyst (BL4AA, as graded according to the Gardner and Schoolcraft scoring system [15] was transferred freshly, which resulted in a healthy singleton live birth at term.

V. Discussion

1. Evaluation of oncofertility practices in Hungary

This study is the first of its kind to provide a comprehensive overview of the current landscape of oncofertility treatment in Hungary. It was conducted by means of a questionnaire survey of oncologists working intensively in this field. Despite a heterogeneous spatial distribution of respondents, with a preponderance in the capital, no statistically significant differences between different regions of the country were found in the majority of responses. However, it is important to recognize that the majority of respondents work in national institutes or university hospitals, which limits insight into the knowledge and information practices of colleagues in smaller hospitals and specialist clinics. It is plausible that those who responded to the questionnaire may have a greater interest in fertility preservation, possibly representing a more optimistic scenario than the actual situation in Hungary.

Apparently, the majority of the responding oncologists actively consider the possibility of fertility preservation for their young female and male cancer patients. In 77% of cases, respondents inquire whether patients under the age of 40 express a desire to have children in the future, while 79% systematically consider the gonadotoxic effects of treatment and discuss them with patients in 85% of cases. Compared with a similar national online survey of 102 French oncologists, the level of knowledge among Hungarian oncologists is considered favourable [8]. In particular, a significant majority of Hungarian oncologists routinely discuss the fertility implications of cancer treatment with their patients, surpassing the commitment of only 46% of their French counterparts [8].

In reality, only a limited number of patients of childbearing age are actually referred. Almost half of the respondents (45%) said that they do not or rarely refer their patients to a fertility center, and 13% do not mention fertility preservation methods to patients undergoing oncological treatment. Notably, French oncologists refer an even smaller proportion of cancer patients to fertility centers for fertility preservation. Surprisingly, in the Hungarian system, which lacks a dedicated fertility preservation network, referral to a fertility preservation center is considered more successful according to the subjective assessment of treating physicians compared to France, which has an established fertility preservation network [8].

Our study shows that oncologists are aware of the importance of fertility preservation (FP) and actively consider this aspect in the care of patients of childbearing age. However, in practice, a

significant number of patients are not referred for fertility preservation. Our findings suggest that this discrepancy may be due to the lack of a dedicated fertility preservation network, a poor patient referral system, a lack of collaboration with infertility specialists, and a lack of professional guidelines. The majority of oncologists are unsure about who is responsible for providing fertility preservation treatment, and a significant proportion do not know of any institution in Hungary that deals with this issue. These identified challenges are in line with international experience in this context [16].

There are currently no established professional guidelines for fertility preservation in Hungary. Although international guidelines exist, their use is not widespread. The data from our survey emphasize the need to inform and guide patients on the basis of established professional guidelines. Gynaecological and oncological professionals have a major responsibility in developing such guidelines, and their rapid establishment is crucial.

In addition to the lack of professional guidelines, a notable challenge is the limited awareness among oncologists of the different fertility preservation techniques. Satisfaction with knowledge ranges from 5% to 25%, depending on the method, reflecting a similar situation in France (14%) [8]. A significant majority of Hungarian oncologists surveyed (60%) believe that it would be beneficial to provide patients with adequate information in this area.

The current professional landscape is highlighted by the remarkable perception of half of the oncologists that embryo cryopreservation is not an available method, although it is one of the most commonly used assisted reproductive techniques. Embryo cryopreservation is the preferred method of fertility preservation for patients in a couple with sufficient time (2-3 weeks) before starting oncological therapy.

Fertility preservation methods are at the forefront of clinical practice, an area where there is currently a lack of training opportunities at both undergraduate and postgraduate level, indicating a need for additional training. However, it is important to emphasize that an in-depth understanding of fertility preservation techniques may not be essential for oncologists.

Their primary role is to identify patients of reproductive age with a favourable prognosis and a significantly reduced likelihood of infertility following cancer treatment, and to refer them to specialist centers [9].

The current barriers in the patient pathway are highlighted by the survey results. Two thirds of Hungarian oncologists (65%) attribute the lack of referral of young cancer patients to poor collaboration between oncologists and infertility specialists. In addition, 54% cite the lack of a

fertility preservation (FP) network and 55% cite a lack of up-to-date information. In contrast, in countries such as the UK, where the FP network has been established for several decades, the main factor influencing the oncologist's decision to refer a patient for FP is the patient's clinical condition. A 2013 online survey of 100 UK oncologists found that 93% based their decision on the patient's condition, 88% on the tumor's severity and prognosis, and 72% on the tumor's hormone receptor positivity [9].

The majority of Hungarian oncologists (56%) who responded stated that they do not refer patients for FP counselling because they prioritize cancer treatment over fertility preservation. While this perspective is understandable, in a well-functioning FP system counselling should not interfere with cancer treatment. It is also important for clinicians to raise awareness of FP options, as the majority of patients may find it difficult to think about anything other than their cancer [17].

The study highlights the importance of targeted training in fertility preservation methods. Oncologists who are better informed in this area are more likely to ask about fertility plans and refer patients to infertility centers. Collaboration between the FP network and both professions is essential to significantly improve the proportion of cancer patients undergoing fertility preservation.

2. IVF Outcomes in Early-Stage Cervical Cancer

To our knowledge, this is the largest retrospective study evaluating IVF outcomes in young, infertile cervical cancer survivors who had previously undergone FSS. This retrospective cohort study included all Hungarian patients who underwent FSS for early-stage cervical cancer, all performed by an experienced surgical team between 2004 and 2020, and followed by IVF treatment at 10 different fertility clinics between 2006 and 2022 in Hungary.

The live birth rate following IVF treatment was almost five times higher in the non-radical group than in the radical group. This statistically significant difference underlines the major impact of the radicality of fertility-sparing surgery on reproductive outcomes. Both the pregnancy rate per embryo transfer (PR) and the cumulative live birth rate per oocyte retrieval (CLBR) were significantly higher in the non-radical group.

In general, age is the primary factor affecting fertility, influencing both the quantity and quality of oocytes. Remarkably, in our study, the radical group had a lower mean age at the first oocyte retrieval but achieved a significantly lower CLBR following IVF treatment, therefore this difference have to be explained by other factors than age.

Cervical stenosis is a well-known cause of infertility after fertility-sparing cervical procedures, with an incidence of approximately 4.7% to 8.1% [18,19]. In our series, 17% of patients required isthmic dilation, either because of haematometra or difficulties with IVF. Although one would expect higher rates of stenosis following more radical surgery, there was a similar incidence of stenosis in both surgical groups. Interestingly, in our study only one patient with a history of surgery for postoperative cervical stenosis achieved a successful pregnancy and she was operated on using a non-radical technique. These results suggest that it is not the cervical stenosis itself but the radicality of the surgical procedure that may be associated with reduced fertility.

Reduced ovarian response to ovarian stimulation could affect live birth rates. Our results, as shown in Table 5, suggest that the radical group required a slightly higher total dose of FSH to obtain one mature oocyte, but the number of mature oocytes obtained was similar in both groups and there was no difference in fertilization rate. The existing literature on ovarian response after radical trachelectomy also shows conflicting results. In particular, a retrospective study by Tamauchi et al. suggests the possibility of a decreased response to ovarian stimulation (OS) after radical trachelectomy [20]. This may be related to a possible decrease in ovarian reserve due to reduced ovarian blood flow. On the other hand, a study by Muraji et al investigated the effect of inferior uterine artery branch ligation on ovarian reserve in patients undergoing open radical trachelectomy [21]. They found no statistically significant difference in anti-Müllerian hormone (AMH) levels between the study and control groups. According to our results, although higher doses of gonadotropins may be required, ovarian stimulation results and fertilization rates are similar in both radical and non-radical FSS groups.

Infertility may also be due to factors such as cervical shortening and changes in cervical mucus characteristics [22]. In addition, recent research has shown that conization can affect the vaginal microbiota, potentially leading to an increased risk of preterm birth [23]. Furthermore, a dysbiotic microbiota profile in the female reproductive tract is associated with poor reproductive outcomes in patients undergoing assisted reproduction [24]. However, these factors cannot explain the significant difference in IVF outcome between non-radical and radical procedures found in this study.

In addition to cervical changes, impaired uterine perfusion may contribute to the lower pregnancy rates observed in the radical group. It is hypothesized that patients who have undergone radical abdominal trachelectomy with extensive parametrectomy and ligation of the origin of the uterine arteries may have impaired uterine perfusion, which is essential to support

pregnancy. Klemm et al conducted a study using Doppler sonography to measure uterine blood flow, which interestingly showed that uterine perfusion remained unchanged after radical trachelectomy [25]. In contrast, Smith et al used pulse oximetry and perfusion index (PI) measurements to assess uterine perfusion and viability. Their results showed that clamping the uterine vessels significantly reduced uterine O2Sat and PI, highlighting the significant contribution of both ovarian and uterine vessels to uterine perfusion [26]. Furthermore, data show that following uterine artery embolization (UAE), uterine myometrial and endometrial perfusion is reduced, leading to suboptimal embryo implantation [27-28].

Our results showed a significantly reduced implantation rate in patients who underwent radical FSS; out of 148 transferred embryos, only 12 embryos implanted, resulting in a very low implantation rate of 8%. Therefore, the reduced implantation rate may be the key factor explaining the poorer IVF outcome in patients in whom the uterine arteries were sacrificed during FSS. Traditionally, our surgical team has used a hyper-radical technique corresponding to a C2 type parametrectomy according to the Querleu-Morrow classification. It is likely that the suboptimal CLBR (6%) is related to the increased radicality of the procedure, resulting in severe myometrial and endometrial ischaemia, leading to lower implantation rates.

Several studies have analyzed pregnancy outcomes in patients undergoing FSS and reported variable success rates based on different surgical routes and approaches. A systematic review evaluating all routes of radical trachelectomy showed a post-trachelectomy pregnancy rate of 23.9%, with the highest rate observed in the vaginal radical trachelectomy group [29]. Studies suggest that the abdominal approach may have a greater impact on reproductive function due to the complete separation of the uterine body from the vaginal wall, potentially leading to nerve and vessel disruption and pelvic adhesion [30]. Furthermore, in the context of early-stage cervical cancer, women who have undergone simple trachelectomy or conization have shown even better reproductive outcomes. A study by Plante et al showed that only 16% of patients had fertility problems after non-radical surgery [31]. Another systematic review supported these findings [18] and reported a significantly higher live birth rate (86.4±16.8%) after simple trachelectomy or conization compared to those who underwent radical vaginal trachelectomy (63.4±23.3%; p=0.04). Overall, these findings highlight the potential influence of surgical approach on fertility, which is influenced by multiple factors contributing to poor fertility outcomes.

Another important aspect of fertility-sparing procedures is their impact on obstetric outcomes. Preterm delivery is the most common complication observed in pregnancies following these

procedures. The aetiology of prematurity is multifactorial and is strongly associated with lack of mechanical support from the residual cervix and an increased risk of ascending infection and chorioamnionitis [25]. Preterm delivery after trachelectomy due to preterm premature rupture of membranes occurs in 8-77% with a mean of 27% compared to an incidence of 3-5% in the general population [25]. Our data show higher rates of prematurity and miscarriage in the radical group, although we were unable to perform statistical analysis due to limited sample size. An equally important finding was the difference in mean gestational age at delivery and fetal birth weight between the two groups. The rates of first-term miscarriage (30%) and second-term miscarriage (20%) were higher in the radical group than in the general population. Tumor size was larger in the radical FSS group; therefore, these procedures may be associated with a greater reduction in cervical length, which is an important determinant of late miscarriage and preterm birth,

There is increasing evidence that conservative surgery is safe for patients with early, low-risk cervical cancer. The recently published prospective ConCerv trial shows that conservative surgery can be a viable option for this group of patients, without compromising optimal recurrence and survival rates [32]. The randomized SHAPE trial further validated these findings, suggesting that patients can expect fewer side effects and a potentially better quality of life when treated with simple hysterectomy [33].

The recently published FERTISS study provided retrospective data on oncological outcomes from a large multicentric cohort of early stage cervical cancer undergoing FSS [34]. This study showed that non-radical cervical procedure does not confer a higher risk of recurrence in patients with tumors smaller than 2 cm compared to radical FSS. Parametrectomy has not been shown to improve prognosis in stage IB1 patients and may increase postoperative morbidity with worse perinatal outcomes [34].

In our study, we observed improved reproductive outcomes following IVF in patients who underwent non-radical fertility-sparing surgeries with the preservation of uterine arteries, compared to those in the radical surgery group. These findings demonstrate that assisted reproductive outcomes can be optimized without significantly compromising oncologic outcomes in a carefully selected group of patients.

The strengths of the study

The strengths of the study are its comprehensive coverage of patients, meticulous data collection, centralized patient management and long-term follow-up.

First, we ensured comprehensive data collection by obtaining both IVF and surgical records for each patient from all centers. In addition, centralized patient management by a dedicated team of experienced clinicians is another notable strength. This approach not only ensures consistency in treatment procedures, but also minimizes variability in patient care. Long-term patient follow-up is also particularly important, as Hungary was among the first countries to introduce fertility sparing cervical cancer surgery. In addition, by focusing specifically on IVF patients, the study provides new insights and detailed IVF outcomes that have not been reported before.

Limitations of the study

A major limitation of this study is its retrospective design and the small sample size within the non-radical group. This limitation can be attributed to the recent trend towards less radical surgical approaches for low-risk cervical cancer, which has only gained popularity in the last 10 years. To enhance the study's ability to detect differences in certain outcomes, a larger sample size would be required. However, in the light of the excellent spontaneous fertility rates following non-radical FSS, it would be time-consuming to increase the number of non-radical surgical cohort [18].

Another limitation of the study is the significant difference in tumor stage distribution between the non-radical and radical groups. This difference is expected as non-radical surgery is primarily used for smaller tumors.

The aim of this study was to compare the reproductive outcomes of IVF in patients who underwent non-radical and radical surgery. The main question is whether the stage of the tumor itself might influence the IVF success rate independently of the type of surgery. As all tumors were completely removed and no additional (adjuvant) therapies were given beyond surgery, it appears that the primary determinant of reproductive outcome was the type of surgery performed rather than the stage of the tumor itself.

These limitations highlight the need for more extensive, prospective studies that can provide more definitive and representative results regarding the impact of radical and non-radical fertility-sparing procedures on reproductive and obstetric outcomes in cervical cancer survivors.

3. Exploring Innovative Approaches in Fertility Preservation

In our study, we were able to demonstrate the safe and successful use of IVM in patients at the most severe end of the spectrum of elevated functional ovarian reserve. Not only do these patients have an increased risk of OHSS, the most common adverse event related to ovarian stimulation, but we would like to raise awareness of other potentially severe complications of fertility treatment in predicted high responders. With this report, we would like to warn against a reduced level of vigilance when treating these patients with gonadotropins in the current era, now that the incidence of severe OHSS, the worst enemy of reproductive medicine professionals, has reached an all-time low. Ovarian torsion may even occur after ovulation induction using gonadotropins in high responders, as illustrated by the first case in this report, and the combination of a GnRH agonist trigger with a freeze only strategy prevented severe OHSS in the second case, but could not prevent ovarian torsion.

Adnexal torsion in the setting of fertility treatment has an incidence ranging from 0.08 to 0.2% and can lead to the loss of an ovary [35]. Its prevalence is probably underestimated, in view of typical under-reporting of poor results. Ovarian stimulation is a known risk factor for ovarian torsion due to ovarian enlargement. There is ample literature to recommend a conservative surgical approach when ovarian torsion occurs. Indeed, although population studies have indicated that unilateral oophorectomy does not lead to premature menopause, such a procedure may result in reduced success rates after fertility treatment in an IVF population [36]. Derotation of the ovary with or without oophoropexy has been advocated several decades ago and is considered the treatment of choice. Even when complete ischaemia has developed, detorsion of the ovary will often be successful in re-establishing reperfusion and normal ovarian function [37–39]. However, untimely diagnosis may lead to significant delay of surgical intervention, compromising the viability of the ovary.

Patients with polycystic ovarian morphology (PCOM) and those with polycystic ovary syndrome (PCOS) are predicted high responders and are particularly at risk for OHSS after OS [40]. In spite of well-defined criteria for the diagnosis of PCOS and a revised threshold for PCOM of ≥20 antral follicles per ovary [41], PCOS is a heterogeneous condition and there is no single best approach that will fit all patients with PCOS. Women with PCOS who undergo OS will exhibit a continuum of ovarian response intensity, depending on intrinsic ovarian parameters, including antral follicle count (AFC) and AMH serum levels, and patient characteristics such as BMI. Although pre-stimulation AFC and AMH has been found to be reliable predictors for high ovarian response, their utility to predict OHSS is limited [42] and

there are no available literature data with regard to the prediction of the extent of ovarian enlargement and the risk of ovarian torsion in high responders. As far as the two patients described here are concerned, baseline AMH levels had not been analyzed before the initial fertility treatment. However, because serum AMH levels were strongly elevated (24.5 ng/mL in patient 1; 12.3 ng/mL in patient 2) after oophorectomy, when the patients presented at our clinic, it is likely that these levels must have been even more elevated initially. Nevertheless, although a vast amount of literature has been produced with regard to ovarian response prediction, there is a lack of knowledge regarding the correlation between ovarian parameters, such as functional ovarian reserve and ovarian volume, and the risk of ovarian torsion. In a subset of high responders, OS may result in ovarian torsion even after moderate stimulation doses, such as in the setting of ovulation induction, as observed in patient1 in this report.

We here illustrate the concept that for patients at the more severe side of the spectrum of functional ovarian reserve, IVM may be a safer alternative approach. Not only do these patients have an increased risk of side effects and adverse events related to ovarian stimulation, they also require intensified monitoring of ovarian stimulation, which may contribute to an increased level of stress during IVF treatment; on its turn, stress may lead to treatment termination before a successful pregnancy is achieved. In view of this and in spite of the existence of OHSS-free controlled ovarian stimulation protocols, a subset of high responders may be keen to embrace IVM as an alternative, lower-burden ART. To which extent these patients would accept a lower chance of pregnancy after IVM compared to standard IVF is currently unknown, although a recent survey among women with increase of OHSS has shown that about half of the patients are willing to accept a lower chance of pregnancy for a reduction of the OHSS rate [43].

Compared to conventional ovarian stimulation (OS) protocols, where oocytes are retrieved from large pre-ovulatory follicles, IVM involves the aspiration of cumulus-oocyte complexes (COCs) from antral follicles [44]. Hence, a shorter course of gonadotropins is administered, although the role of exogenous FSH has been controversial [45,46] and FSH administration before oocyte retrieval has been omitted completely in some IVM clinics [47]. Nevertheless, even if gonadotropins are administered in an IVM cycle, very little monitoring is required. The cornerstone of an efficient IVM program is proper patient selection; women with elevated functional ovarian reserve parameters will yield sufficiently high numbers of immature oocytes to make up for the inherently lower efficiency of IVM compared to standard IVF [48–50]. Nevertheless, a specific AMH cut-off at which level the efficiency of IVM may approach or perhaps surpass that of OS followed by IVF/ICSI has not been established. Although IVM has

initially been advocated as a method to eliminate OHSS, the development of OS strategies to dramatically reduce the risk of OHSS has mitigated the need for IVM as a strategy to avoid OHSS. Nevertheless, recent improvements to the IVM culture system [51] which may enhance the developmental potential of IVM embryos have refueled the interest in IVM as a more patient-friendly approach in high responders. Although in centers with sufficient expertise cumulative live birth rates per started IVM cycle in women with PCOS reach ≈40% [52–54] embryo yield and success rates are still lower as compared to standard OS protocols.

More specifically, IVM results in a relatively lower rate of embryos progressing to the blastocyst stage, but IVM embryos that do reach the blastocyst stage appear to have similar implantation potential as compared to blastocysts after OS [55]. Although the role of IVM in ART practice continues to be questioned in the modern era of agonist triggering and freeze-all strategies, we here illustrate the potential of IVM in selected patients who may have an increased risk of potentially severe complications when they undergo conventional ART. Nevertheless, future studies are required to compare the safety of IVM and conventional IVF/ICSI in a large cohort of predicted high responders. Surprisingly, one case of ovarian torsion following IVM in a patient with PCOS has been reported [56]. However, in contrast with the patients presented here, the patient described by Giulini et al. had received a bolus of hCG before oocyte retrieval, which could have contributed to the development of this complication. In our opinion, and according to the recommendation by the International PCOS Network, IVM refers to the in vitro maturation of immature cumulus-oocyte complexes collected from antral follicles without the use of an hCG trigger [44].

VI. Conclusions

1. Evaluation of oncofertility practices in Hungary:

Our study is the first step in evaluating the essential measures to establish a national oncofertility network. The cornerstone of a successful oncofertility program is effective communication and close collaboration between treating oncologists and reproductive specialists involved in fertility preservation. As a first step, our aim was to assess the level of knowledge about fertility preservation among cancer specialists in Hungary, with a particular focus on factors that hinder young cancer patients' access to a fertility preservation program.

Promisingly, the majority of responding oncologists are interested in fertility preservation. They take patients' preferences into account, discuss the adverse effects of cancer treatment on fertility, consider the gonadotoxicity of treatment, and refer patients to a fertility center for fertility preservation counselling when necessary.

However, the survey results indicate that oncologists need to be educated and trained in this area. The development of common professional guidelines and the establishment of a national fertility preservation network are considered essential. This initiative aims to provide more accurate information to patients in order to increase the proportion of patients who have access to fertility preservation treatment before starting cancer treatment.

2. IVF Outcomes in Early-Stage Cervical Cancer

For women of reproductive age diagnosed with early-stage cervical cancer, fertility-sparing strategies have emerged as a vital component of treatment, offering hope for future motherhood. Fertility-sparing surgery (FSS) aims to attain oncologic outcomes similar to radical treatment while optimizing reproductive results. Given the significant patient morbidity associated with radical fertility-sparing procedures including adverse reproductive and obstetric outcomes, there has been recently a shift toward less radical surgical approaches for low-risk cervical cancer. Further studies are needed to strengthen the existing evidence showing both oncological safety and reduced morbidity of these approaches.

Our study demonstrates that low-risk cervical cancer patients who undergo non-radical fertility-sparing surgery experience improved in vitro fertilization outcomes compared to radical surgery. Radical procedures involving uterine artery ligation were associated with decreased

implantation rate and cumulative live birth rate. These findings emphasize the importance of considering oncological safety and reproductive outcomes together when choosing FSS for early-stage cervical cancer patients, highlighting the reproductive benefit of performing less radical surgery with preservation of uterine arteries. They also highlight the need for comprehensive data to guide patient counseling and clinical recommendations.

3. Exploring Innovative Approaches in Fertility Preservation.

In a fertility preservation program, in vitro maturation (IVM) may be offered as an alternative approach when conventional ovarian stimulation is contraindicated or when there is insufficient time to delay the initiation of gonadotoxic treatment for ovarian stimulation. Due to its innovative nature, IVM as a fertility preservation technique requires specific expertise. [57].

Although centers with appropriate expertise have achieved cumulative live birth rates of around 40% per IVM cycle in women with PCOS, embryo yield and success rates remain lower compared with standard OS protocols. However, women with increased functional ovarian reserve parameters can produce sufficient numbers of immature oocytes to compensate for the inherently lower efficiency of IVM compared to standard in vitro fertilization (IVF) protocols [58].

In vitro maturation (IVM) following ex vivo oocyte retrieval from ovarian specimens can be used to maximize the potential for fertility preservation in patients undergoing surgical removal of ovarian tissue. It is possible to retrieve immature oocytes from ovariectomy specimens during tissue processing for cryopreservation. This strategy is useful when ovariectomy is part of curative treatment, such as for ovarian cancer, or when ovarian tissue is processed for cryopreservation. However, it is important to note that IVM after ex vivo retrieval is considered an experimental procedure and requires approval from a medical research ethics committee [57].

VII. Acknowledgements

VIII. References

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A termékenység megőrzése daganatos betegségekben

Egy hazai felmérés tapasztalatai

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Bevezetés: A daganatellenes kezelések egy része gonadotoxikus hatású, ezért létrejött egy viszonylag új, interdiszciplináris terület, mely a fiatal onkológiai betegek termékenységének megőrzésével foglalkozik: ez a fertilitásprezerváció, más néven onkofertilitás. A nemzetközi irányelvek ellenére Magyarországon jelenleg nincs országos fertilitásprezervációs hálózat, a betegek irányítása és tájékoztatása nem szervezetten történik.

Célkitűzés: Tanulmányunk célja, hogy felmérjük a hazánkban dolgozó onkológusok fertilitásprezervációval kapcsolatos ismereteit, és megismerjük azokat a tényezőket, amelyek a fiatal daganatos betegek termékenységmegőrzési programhoz való hozzáférését segíthetnék.

Módszer: A Magyar Onkológus Társaság (MOT) tagjainak online kérdőívet küldtünk ki a fertilitásprezerváció témakörében 2020 novemberében. A felmérést 94 onkológus szakorvos töltötte ki teljes egészében, majd a beérkezett adatokat statisztikai módszerekkel elemeztük.

Eredmények: A válaszoló magyar onkológusok többsége (77%) a daganatellenes kezelés fertilitásra gyakorolt hatását megbeszéli a páciensével, ténylegesen azonban csak kis számban kerülnek beutalásra a termékeny korban lévő páciensek. A válaszolók fele nyilatkozott úgy, hogy betegeit nem vagy csak ritkán irányítja tovább meddőségi centrumba; ennek hátterében a fertilitásprezervációs hálózat, a megfelelő képzés és a hazai irányelvek hiányát jelölik meg. A válaszadók többsége (86%) véli úgy, hogy az onkológus és meddőségi szakemberek szorosabb együttműködésének megszervezése szükségszerű Magyarországon.

Következtetés: Tanulmányunk egy nemzeti onkofertilitás-hálózat létrehozásához szükséges teendők felmérésének első lépése. Eredményeink szerint szükséges a betegeket kezelő onkológusok és a fertilitásprezervációval foglalkozó reproduktív szakemberek közötti megfelelő együttműködés kialakítása, valamint az onkológus kollégák ismereteinek bővítése ezen a szakterületen.

Orv Hetil. 2022; 163(6): 246–252.

Kulcsszavak: fertilitásprezerváció, onkofertilitás, onkológusok

Fertility preservation in cancer patients

Hungarian experiences and attitudes

Introduction: Fertility preservation or oncofertility is a relatively new interdisciplinary field dealing with the preservation of female and male reproductive functions before the administration of gonadotoxic therapy. Despite recommendations from different international scientific bodies, Hungary still does not have a national fertility preservation network, patient referral is unorganised.

Objective: As the first step towards establishing a national fertility preservation program, a study was designed to evaluate the Hungarian oncologists' knowledge, attitudes and practice in the field of oncofertility.

Method: A national online survey was sent to the physician members of the Hungarian Society of Clinical Oncology between November 2020 and February 2021. The survey was completed by 94 physicians and the results were analysed statistically.

Results: The majority of the oncologists (77%) discusses reproductive health issues before starting gonadotoxic therapy. However, almost half of these physicians do not refer patients for fertility preservation consultation or treatment.

Physicians report lack of organised fertility preservation network, lack of knowledge and clinical practice guidelines as major barriers in referring their patients for fertility preservation. The majority (86%) proposes that a better collaboration between cancer and fertility centers needs to be organized in Hungary.

Conclusion: This study is the first nationwide survey to assess oncologists' attitude, knowledge and practice in the field of oncofertility in Hungary. It highlights the need for more education and increased collaboration between oncologists and reproductive specialists. This is an important step towards the establishment of a national fertility preservation network which is our ultimate goal.

Keywords: fertility preservation, oncofertility, oncologists, Hungary

Rövidítések

ECOG = (Eastern Cooperative Oncology Group) Keleti Kooperatív Onkológiai Csoport; OTC = (ovarian tissue cryopreservation) petefészekszövet fagyasztása; OTT = (ovarian tissue transplantation) petefészekszövet transzplantációja

A daganatos megbetegedések incidenciája az életkorral nő. Mivel a családalapítás ideje egyre jobban kitolódik, folyamatosan nő azon daganatos betegek száma, akiknél az onkológiai kezelések termékenységre gyakorolt hatása komoly jelentőséggel bírhat. Az elmúlt évtizedben az onkoterápiás kezelések utáni élet minősége is felértékelődött a kezelések hatékonyságában bekövetkezett jelentős javulásnak köszönhetően. A fertilitás elvesztésének lehetősége egy fiatal nő számára majdnem akkora lelki megterheléssel jár, mint megküzdeni magával a daganatos betegséggel [1].

Magyarországon 2016-ban a Nemzeti Rákregiszter adatai alapján a 40 év alatti, fertilis korú nőknél 1574 rosszindulatú daganatos megbetegedést diagnosztizáltak. Azon megbetegedések aránya, amelyek kezelése toxikus a petefészkekre és/vagy a herékre (a továbbiakban: gonádok), vagy sugárterápiát igényel, és nagy valószínűséggel csökkenti a később sikeres fogantás és kihordott terhesség esélyeit, az összes daganatos megbetegedés mintegy kétharmada. Az emlő rosszindulatú daganatát 531, nőgyógyászati eredetű rosszindulatú daganatot 384, vérképző szervi daganatot 127 esetben állapítottak meg.

A fertilis korú, emlőrákkal diagnosztizált nőknél gyakrabban fordul elő olyan agresszívebb molekuláris-genetikai szubtípusú daganat, amely gonadotoxikus kemoterápiát igényel; ez a nők 38%-ának okoz termékenységi problémát a kezelést követően [2]. A gyermekszülés esélye tovább csökken, ha szükséges az onkoterápiás kezelés kiegészítése endokrin terápiával, mely további 5–10 évvel kitolhatja a gyermekvállalás idejét. A fiatal leukémiás pácienseknél ugyancsak rendkívül fontos a termékenység megőrzése, hiszen a myeloablatív kondicionálás következtében, az őssejt-transzplantációt követően a korai petefészek-kimerülés kockázata rendkívül magas (80–100%). A nőgyógyászati eredetű daganatok esetén a női reproduktív szervek műtéti és sugárterápiás kezelése jelenti a legjelentősebb kockázatot a későbbi termékenységre. A bőrráknak, a pajzsmirigy rosszindulatú daganatának, illetve a vastagbél és a végbél rosszindulatú daganatának kezelésében alkalmazott onkoterápia a termékenységet kisebb mértékben csökkenti. A korai petefészek-kimerülés kialakulásának veszélye függ a páciens életkorától, a kezelés jellegétől, irradiáció esetén a kumulatív dózistól és a besugárzás helyétől. A méh radioterápiája nem csupán az embrió sikeres implantációjának esélyét csökkenti, hanem a várandósság alatt előforduló szövődményeket is növeli, például a koraszülések gyakoriságát is [3].

A korszerű és eredményes multidiszciplináris onkológiai kezelések következményeként tehát a páciensek esélye a gyermekszülésre nagymértékben csökkenhet, ezért fontos a termékenység megőrzése [4]. Európai és amerikai, evidenciákon alapuló szakmai irányelvek alapján, amennyiben az onkoterápiás kezelés következtében kialakuló meddőség kockázata közepes vagy magas fokú, minden fertilis korú nő számára termékenységmegőrzési eljárást szükséges felajánlani [5, 6].

Az érvényes nemzetközi szakmai irányelvek alapján az onkológiai konzultációkon a beteggel ismertetni kell a daganatellenes kezelés termékenységet érintő káros következményeit, függetlenül a daganat prognózisától, a páciens életkorától, a páciens családi állapotától. Amennyiben a gyermekvállalási szándék még nem zárult le, a kezelés előtt a pácienst minden esetben onkofertilitásban jártas asszisztált reprodukciós szakemberhez szükséges irányítani. A betegek tájékoztatása, meddőségi centrumba irányítása és a termékenység megőrzését célzó eljárások felajánlása nagymértékben javítja a páciensek életminőségét, és csökkenti a gyermekvállalással kapcsolatos szorongásukat. Az Amerikai Klinikai Onkológiai Társaság (American Society of Clinical Oncology, ASCO) állásfoglalása alapján az onkológiai diagnózis időpontjában a nőbetegek felét érdekli a kezelés fertilitásra gyakorolt hatása, azonban csak nagyon kevesen kapnak érdemi tá-

jékoztatást a termékenység megőrzését célzó lehetőségekről [7].

A nemzetközi gyakorlathoz igazodó, jól működő magyarországi onkofertilitási hálózat kialakításához elengedhetetlen azoknak a tényezőknek a feltárása, amelyek miatt a páciensek jelenleg nem kerülnek szakmai beutalásra a fertilitásmegőrzésben jártas szakemberekhez, és így nem kapnak időben megfelelő tájékoztatást sem. A jelen tanulmány célja a magyar onkológusok szakismereteinek, a fertilitásmegőrzési technológiákról való tájékoztatási szokásainak felmérése a páciensek hatékonyabb informálása érdekében.

Módszerek

Irodalmi adatok alapján [8–10] elkészítettünk egy kérdőívet a termékenységmegőrzés témakörében, amely a Magyar Onkológus Társaság elnökségének segítségével a társaság tagjainak 2 alkalommal került kiküldésre online kérdőív (SurveyMonkey) formában. A felmérést 154, onkológiával foglalkozó szakember kezdte el, közülük 94 orvos teljesen kitöltötte a kérdőívet. Az eredményeket a teljesen kitöltött 94 kérdőív alapján értékeltük. Egy ember csak egy kérdőívet tölthetett ki. A kitöltés önkéntes volt.

Az adatokat az R statisztikai program (4.1.0. verzió) segítségével elemeztük. Szignifikánsnak a p<0,05 értéket tekintettük. A leíró statisztikánál az egyes jellemzők relatív előfordulási gyakoriságát a teljes populációhoz viszonyítva százalékban adtuk meg.

Eredmények

A kitöltő orvosok több mint fele (55%) férfi volt, 96%-uk rendelkezett szakvizsgával. A válaszadók mintegy kétharmada országos intézményben vagy egyetemi központban dolgozó orvos, túlnyomó többségük a fővárosban (72%) dolgozott, és már 15–25 év gyakorlattal (30%) rendelkezett. A kutatásban részt vevő onkológusok demográfiai és szakmai jellemzőit az *1. ábra* mutatja be.
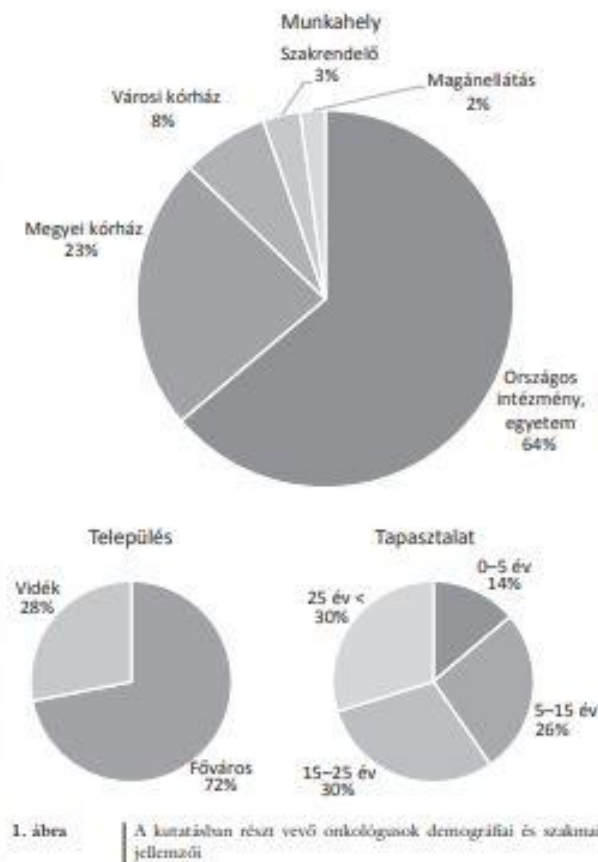
A résztvevők szakvizsgák szerinti megoszlása a *2. ábrán* látható. A három leggyakoribb szakterület a klinikai onkológia, a sugárterápia és a belgyógyászat volt. A résztvevők többsége (75%) úgy nyilatkozott, hogy a sugár- és kemoterápiás kezelések gonadotoxikus hatásáról közepes mértékben vagy nagymértékben rendelkeznek információval, viszont csak 9 válaszoló (9,5%) érzi úgy, hogy a legfrissebb onkofertilitási eljárásokról közepes mértékben vagy akár nagymértékben informált. A szakmai tapasztalat függvényében úgy tűnik, hogy minél több éve foglalkozik egy orvos onkológiával, annál inkább tisztában van a kezelések gonadotoxikus hatásával (Spearman-féle ró [ρ] = 0,4214, p<0,05). A szakemberek közel felének (48%) van tudomása olyan magyarországi intézetről, ahol onkofertilitással foglalkoznak, 40 válaszoló bizonytalan (42%), míg 9 válaszoló (9,5%) egyáltalán nem ismer olyan ellátóhelyet, ahol az általa
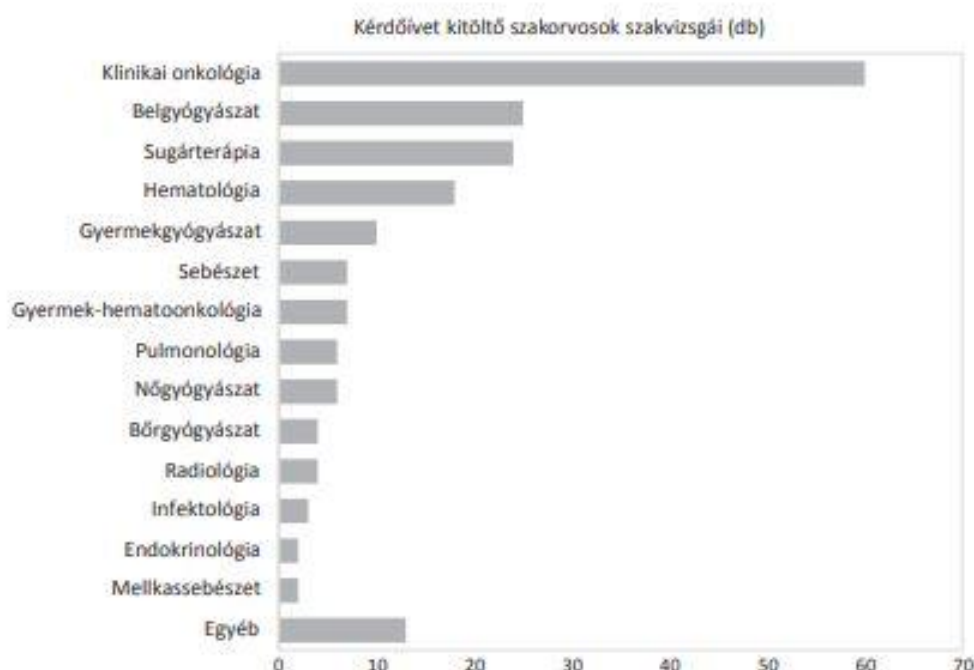
kezelt páciensek termékenységmegőrzésével foglalkoznának. A válaszadók többségére jellemző, hogy megkérdezik 40 év alatti pácienseiktől, szeretnének-e még gyermeket (77%), gyakran mérlegelik a kezelés gonadotoxicitását fertilis korú pácienseknél (79%), és általában meg is beszélik ezt a páciensekkel (85%).

Ennek ellenére a válaszadók majdnem fele (45%) nyilatkozott úgy, hogy betegeit nem vagy csak ritkán irányítja tovább meddőségi központba, 13%-uk pedig semmilyen termékenységmegőrző módszert nem említ meg az onkológiai kezelésben részt vevő páciensnek.

A felvázolt fertilitásprezervációs módszerek közül a legismertebb és leggyakrabban javasolt eljárás a spermium- és petesejtfagyasztás, míg a legkevésbé ismert és legkevésbé javasolt az embriófagyasztás. A különböző módszereket és az onkológusok ezekről alkotott véleményét, szokásait részletesen ismerteti az *1. táblázat*.

A páciensek onkofertilitási kezelésre irányításában a legtöbb válaszoló (86%) megjelölte, hogy segítséget jelentene egy onkofertilitásról szóló irányelv, emellett pedig a felsorolt válaszlehetőségek közül a többség szerint a célirányos oktatás, onkofertilitási hálózat és kapcsolattartó elérhetőség voltak azok a tényezők, amelyek elősegítenék a betegek termékenységmegőrző kezelésre való beutalását. Az egyes válaszlehetőségek megjelölésének gyakoriságát a *3. ábra* mutatja be.

1. ábra | A kutatásban részt vevő onkológusok demográfiai és szakmai jellemzői

Kérdőivet kitöltő szakorvosok szakvizsgái (db)

2. ábra | A kérdőívet kitöltő orvosok szakvizsgái

Milyen tényezők jelentenének segítséget a páciensek termékenységmegőrző
eljárásra való irányításában?
(a válaszok száma, db)

3. ábra | Az onkofertilitási kezelésre való betegirányításban szerepet játszó tényezők

A legfontosabb szempontok, amelyek miatt nem küldik a betegeket termékenységmegőrző eljárásra, a következők voltak: a nem megfelelő együttműködés a szakemberek között, a daganat sürgős kezelése, az onkológiai terápia – mind a beteg, mind az orvos részéről való – elsődlegessége, a hiányos információk, valamint a fertilitásprezervációs hálózat hiánya. Az egyes válaszlehetőségek megjelölésének arányát a 2. *táblázat* mutatja be.

1. táblázat | Termékenységmegőrzési módszerek és a kérdőívet kitöltők ezekről alkotott véleménye

	Legalább kismértékben rendelkezik információval a módszerről	Úgy gondolja, a módszer kísérleti jellegű	Elérhetőnek tartja a módszert	Megemlíti a módszert a betegnek
Spermiumfagyasztás (n)	88% (82)	3% (3)	90% (85)	77% (72)
Petesejtfagyasztás (n)	80% (74)	11% (10)	77% (72)	61% (57)
GnRH-analógok használata (n)	65% (60)	5% (5)	51% (48)	19% (18)
Herészövet-fagyasztás (n)	58% (54)	43% (40)	25% (23)	18% (17)
Petefészekszövet-fagyasztás (n)	55% (51)	37% (35)	33% (31)	34% (32)
Petefészek-transzpozíció (n)	46% (43)	39% (37)	28% (26)	15% (14)
Embriófagyasztás (n)	44% (41)	46% (43)	26% (24)	13% (12)

GnRH = gonadotropin-felszabadító hormon

Az utóbbi kérdésnél a megkérdezetteknek lehetőségük volt szabadszavas választ is adni; ilyen válaszként a felsoroltakon kívül a következő megjegyzések érkeztek:
– 18 év alatti betegeket nem fogadnak a meddőségi centrumok, és a spermafagyasztáson kívül semmilyen módszer nem áll rendelkezésre ezen páciensek fertilitásmegőrzésére;
– időnként maga a beteg utasítja el a termékenység megőrzését célzó kezelést;
– az orvos bizonyos esetekben nem tartja helyesnek a termékenység megőrzését.

2. táblázat | Tényezők, amelyek miatt az onkológusok nem irányítják a beteget termékenységmegőrző eljárásra

Válasz	Megjelölés (db)
Nem megfelelő az onkológus és a meddőségi szakemberek együttműködése.	64
A daganat sürgős kezelést igényel, emiatt nincs idő a termékenység megőrzésére.	58
A beteg számára a daganatkezelés sokkal fontosabb, mint termékenységének megőrzése.	55
A termékenység megőrzésével kapcsolatban nem naprakészek az információim.	54
A termékenységmegőrzési hálózat hiánya.	53
A betegek nem tudnak arról, hogy a daganat kezelése és a termékenység megőrzése párhuzamosan is folyhat.	51
A daganat felfedezésekor a beteg számára komoly pszichés terhet jelent a termékenység elvesztésével foglalkozni.	35
Hormonreceptor-pozitív nőgyógyászati és emlőrák esetén a petefészek-stimulációt veszélyesnek tartom.	32
A konzultációs idő rövidsége.	29
Nem teljesen világos számomra, hogy kinek a feladata a beteg tájékoztatása a fertilitás megőrzésével kapcsolatban.	24
Emlőrák esetén tartok a későbbi terhességek onkológiai kockázatától.	16
A beteg számára ijesztő a lombikkezelés lehetősége.	8
Az asszisztált reprodukciós eljárások sikerességét alacsonynak tartom.	2
Egyéb	7

A fővárosban az asszisztált reprodukciós intézetek száma a vidékhez képest felülreprezentált, így valószínűleg a társszakmák közötti szakmai kapcsolatok is gazdagabbak, mint vidéken. A fővárosi orvosok több mint felének (55%) van tudomása olyan intézményről, ahol fertilitásprezervációs kezelést végeznek, míg ez az arány a vidéki orvosok között csak 39%.

Megbeszélés

A jelen felmérés tudomásunk szerint az első, amely a magyarországi onkofertilitás helyzetének feltárásával foglalkozik, a kérdésben leginkább érintett onkológiával foglalkozó orvosok kérdőíves megkérdezése alapján. Bár a válaszadók területi eloszlása egyenetlen (fővárosi túlsúly), a válaszok többségében nem találtunk statisztikai különbségeket az ország különböző régiói között. Mivel a kitöltők többsége országos intézetben vagy egyetemi klinikán dolgozik, nincs elég információ a kisebb kórházakban, szakrendelőkben dolgozó kollégák ismereteiről, tájékoztatási szokásairól. Valószínűnek tartjuk, hogy a kérdőívet kitöltő kollégák érdeklődőbbek a termékenység megőrzésének kérdéskörében, ezért a valódi magyar helyzet a kérdőíves válaszokból kirajzolódó képnél kedvezőtlenebb lehet.

Világosan látszik, hogy a választ adó onkológusok többsége gondol a fiatal női és férfi daganatos páciensei termékenységmegőrzésének lehetőségére. A válaszadók 77%-a az esetek többségében megkérdezi a 40 év alatti páciensektől, hogy szeretnének-e még gyermeket, 79%-uk mérlegeli a kezelés gonadotoxicitását, és 85%-uk meg is beszéli ezt a páciensekkel. Egy hasonló, nemzeti, 102 onkológus bevonásával készült online francia vizsgálat eredményeivel összevetve a magyar onkológusok tájékozottsága jónak tekinthető. A magyar onkológusok többsége a daganatellenes kezelés fertilitásra vonatkozó következményeit megbeszéli a páciensével, miközben ez az arány a francia onkológusoknál mindössze 46% volt [8].

Ténylegesen azonban csak kis számban kerülnek beutalásra a termékeny korban lévő páciensek, ugyanis a válaszolók közel fele nyilatkozott úgy, hogy betegeit nem vagy csak ritkán irányítja tovább meddőségi cent-

Reducing radicality in fertility-sparing surgery is associated with improved in vitro fertilization outcome in early-stage cervical cancer: A national retrospective study

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HIGHLIGHTS

- IVF outcomes were analyzed in cervical cancer survivors treated by fertility-sparing surgery.
- Radical fertility sparing procedures were associated with lower cumulative live birth rates.
- Reduced implantation rate may be the key factor explaining worse IVF outcome in patients with uterine artery ligation.
- Decreased radicality and uterine artery sparing is advocated to optimize reproductive outcomes.

ARTICLE INFO

ABSTRACT

Objective. Fertility-sparing surgery (FSS) aims to achieve oncological outcomes that are non-inferior to radical treatment while preserving fertility and optimizing reproductive results. This study assesses in vitro fertilization (IVF) outcomes in early-stage cervical cancer survivors following FSS, comparing radical and non-radical approaches.

Methods. This retrospective analysis used data from Hungary's National Health Insurance Fund (2004–2022) on patients who underwent IVF treatment following FSS for early-stage cervical cancer at ten Hungarian fertility clinics. Patients were classified into radical and non-radical surgical groups, with the uterine arteries being spared in the non-radical procedures. RStudio (R software version: 4.2.2) was used for statistical analysis. Student's *t*-test was used to compare group means, and Fisher's exact test was applied to assess independence and distributions between categorical variables, and to estimate odds.

Results. The study analyzed data from 122 IVF treatment cycles involving 36 patients. The non-radical group had a significantly higher live birth rate (83%, 5/6 compared to the radical group (17%, 5/30). Additionally, the non-radical group had a significantly higher implantation rate and cumulative live birth rate per oocyte retrieval (37%, 7/19 and 55%, 6/11 respectively) compared to the radical group (8%, 12/148 and 6%, 5/80 respectively).

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E-mail address: novak.zoltan@oncol.hu (Z. Novák).
[1] We would like to acknowledge the recent passing of János Konc in the year 2023.

Conclusion. This is the largest study to evaluate IVF outcomes in young cervical cancer survivors who have undergone FSS. The findings suggest that less radical procedures are associated with significantly better IVF outcomes. These results emphasize the importance of considering oncological safety and reproductive outcomes together when choosing FSS for early-stage cervical cancer patients. It also highlights the reproductive benefits of performing less radical surgery.

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide. Despite successful screening programs in high-resource countries, the impact of cervical cancer remains significant, particularly in women aged 35 to 49, with 40% of cases diagnosed during reproductive years [1].

Conventional treatment for early-stage cervical cancer involves radical hysterectomy with pelvic lymphadenectomy, which results in immediate fertility loss [2]. Fertility-sparing surgery (FSS) aims to achieve oncological outcomes that are non-inferior to radical hysterectomy while optimizing reproductive outcomes, including fertility preservation and minimizing the risk of preterm birth [2].

In a radical trachelectomy, the cervix, vaginal vault, and supporting ligaments are removed, leaving the uterine corpus intact [3]. Radical trachelectomy is associated with excellent oncological outcomes and a low recurrence rate. However, it is also associated with significant patient morbidity, including adverse reproductive outcomes such as reduced fertility [4] and increased rates of first- and second-trimester miscarriage and preterm birth [5].

There is a growing body of evidence supporting the safety of non-radical surgery in patients with early-stage, low-risk cervical cancer. The recently published prospective ConCerv trial demonstrated that conservative surgery, like cervical conization can be a viable option for this patient population, maintaining optimal recurrence and survival rates without compromise [6].The randomized SHAPE trial further validated these findings. It suggests that selected low-risk cervical cancer patients can expect fewer side effects and a potentially better quality of life when treated with simple hysterectomy instead of radical hysterectomy with non-inferior oncological outcomes [7].

Studies evaluating fertility outcomes in patients following FSS have reported variable success rates. Recent data from a systematic review showed a moderate clinical pregnancy rate (53.2%) among patients attempting to conceive after fertility-sparing surgery (FSS) [8]. The mode of conception was predominantly spontaneous (79%), with a smaller proportion using assisted reproductive technology (ART). The same study reported a higher live birth rate in patients who underwent simple trachelectomy or conization compared to those who underwent radical trachelectomy [8]. Another review suggests that infertility treatment is required for the majority of pregnancies following radical abdominal trachelectomy [9].

Although infertility treatment is not infrequent in this population, there is limited knowledge about the effectiveness of ART treatment in women undergoing FSS. Obtaining comprehensive information on in vitro fertilization (IVF) outcomes is essential to provide patients with accurate data for informed decision-making regarding their post-cancer pregnancy options. The aim of our study was to assess IVF outcomes in patients with early-stage cervical cancer who underwent fertility-sparing procedure and to compare the results between radical and non-radical procedures.

2. Materials and methods

2.1. Study design and setting

This retrospective cohort study included all Hungarian patients who underwent fertility-sparing surgery (FSS) for early-stage cervical cancer performed by an experienced surgical team between 2004 and 2020, followed by IVF treatment between 2006 and 2022. Data were obtained from the database of the National Health Insurance Fund of Hungary (NEAK) [10].

The inclusion criteria were cervical cancer patients who desired to preserve their fertility; had histological confirmation of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma or other epithelial tumors; had stage IA1 to IB3 disease according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 revised staging of cervical cancer [11].

The exclusion criteria were previous neoadjuvant chemotherapy, pelvic radiotherapy or total hysterectomy. We attempted to reduce the impact of maternal age by excluding patients over 40 years of age at the time of their first oocyte retrieval, as one of the major factors contributing to IVF treatment failure is advanced maternal age.

A team of six experienced gynecologic oncologists performed the FSS procedures at the designated centers. The team has extensive experience spanning two decades of performing FSS in patients diagnosed with early-stage cervical cancer. Patients were categorized into radical and non-radical surgical groups based on the type of their FSS procedure. Non-radical surgical procedures consistently preserved the uterine arteries. Patients in the non-radical group underwent simple trachelectomy or modified radical trachelectomy with preservation of the uterine arteries [12]. In contrast, the radical group included patients who underwent classic abdominal radical trachelectomy with bilateral ligation of the uterine arteries. The latter procedure was previously detailed in the publication by Ungar et al. [13]. Non-radical surgery was introduced after 2015, earlier almost all patients were operated by a radical procedure.

Patients who underwent FSS and required fertility treatment were referred to assisted reproductive technology (ART) centres. Patients who underwent IVF treatment(s) between 2006 and 2022 following previous FSS performed between 2004 and 2020 for early-stage cervical cancer were included in the study. All Hungarian fertility clinics actively participated in this study, providing comprehensive data concerning patient characteristics and IVF outcomes. Patients were contacted and surgical/pathological reports were obtained to provide detailed clinical data. The National Central Ethical Committee approved the study: BMEÜ/2366–1 / 2022/EKU.

2.2. Outcome measures

The primary outcome of this study was live birth among women who underwent fertility treatment. This indicator was chosen to

ensure the statistical independence of the sample elements and to estimate the odds, despite differing from the most commonly used outcome indicators in IVF treatments [14]. Both patient groups were analyzed for secondary outcomes including clinical pregnancy rate per transfer, cumulative live birth rate (CLBR) per oocyte retrieval, ovarian stimulation (OS) response, number of retrieved oocytes per cycle, fertilization rate, clinical pregnancy rate (PR) per embryo transfer cycle, miscarriage rate, cumulative live birth rate per aspiration, implantation rate, gestational age at birth and fetal birth weight.

2.3. Statistical analysis

For most variables, we calculated simple means, medians, or frequency values to describe the characteristics of the groups. The statistical analysis was performed using the RStudio program (R software version: 4.2.2). Student's t-test was used to compare group means, and Fisher's exact test was applied to assess independence and distributions between categorical variables, and to estimate odds.

3. Results

In the initial data retrieval process, we identified 148,155 in vitro fertilization treatment cycles performed between 2006 and 2022 in the database of the National Health Insurance Fund of Hungary (NEAK). (Fig. 1). Of these cycles, 132 were performed in 40 patients who had previously undergone FSS for early-stage cervical cancer. After exclusion of four patients (with 10 cycles) - two due to advanced age (>40), one who had undergone a fertility preservation cycle prior to FSS, and one due to coding error- the study included 36 patients representing 122 cycles. These cycles comprised 91 ovarian stimulation cycles and 31 frozen embryo transfer (FET) cycles. Out of the 91 ovarian stimulation cycles, 11 and 80 occurred in the non-radical group and radical group, respectively.

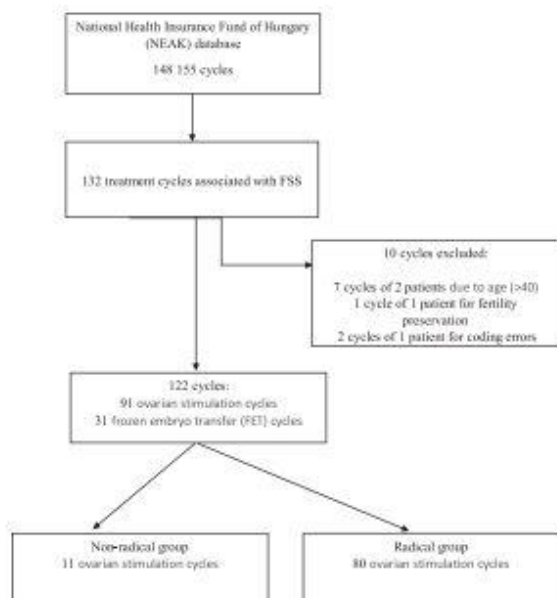An overview of the study course is presented in Fig. 1.

Fig. 1. Overview of the study course.

A total of 36 patients were included in the study, with 6 in the non-radical group and 30 in the radical group. Table 1 summarizes patient and tumor characteristics.

Patient characteristics were generally similar and are shown in Table 1. The mean age at the time of fertility-sparing surgery (FSS) was 31.7 years (range: 23–37 years) for all patients, with comparable ages of 31 and 30.2 years in the non-radical and radical groups, respectively. Most patients were nulliparous (86%), while 14% had one previous child prior to the trachelectomy procedure. Most patients had FIGO stage IB1 tumors (66.7%). The remainder had stage IA1 (11.1%), IA2 (8.3%), IB2 (8.3%), or IB3 (5.6%). All patients with tumors>2 cm underwent abdominal radical trachelectomy with bilateral ligation of uterine arteries. Patients were categorized into radical and non-radical surgical groups according to the type of their FSS procedure. The majority of the patients with stage IB1 tumors (95.8%) underwent radical surgery; only one patient underwent modified abdominal radical trachelectomy with preservation of the uterine arteries. 71.4% of the patients with stage IA had received non-radical surgery. No patients in our database received adjuvant treatment (XRT and/or chemotherapy) after fertility-sparing surgery (FSS). However, the radical and non-radical groups seemed unbalanced in terms of tumor stage. The Fisher exact test showed a statistically significant difference ($p < 0.01$) in the tumor stage (IA vs. IB stadium) distribution between the non-radical and radical groups. Six patients (16.7%) have developed documented cervical stenosis after FSS: 1 out of 6 patients in the non-radical group, and 5/30 patients in the radical group. All had subsequent successful cervical dilatation under general anesthesia. Oncological outcomes were evaluated and showed 100% recurrence-free survival and overall survival in non-radical patients in our study with a median follow-up of 13.6 years. It's important to note that due to the limited number of patients in our study, we cannot comment in detail on oncological safety.

3.1. Reproductive outcomes

Regarding ovulation stimulation outcomes, the mean time interval from FSS to the first oocyte retrieval for all patients, was 1681 days. The mean age at the first oocyte retrieval was 34.9 years for all patients, and there was no statistically significant difference between the two groups ($p = 0.4703$). Furthermore, there was no significant difference between the two groups in terms of Body Mass Index (BMI) (22.9 kg/m2) and Anti-Mullerian Hormone (AMH) levels (2.5 ng/ml) ($p = 0.2264$ and $p = 0.2878$ respectively). The study also found that the radical group had four cases of male infertility, while the non-radical group had none. In addition, the radical group had ten cases of other causes of female infertility, compared to two cases in the non-radical group. On average, patients underwent 2.4 cycles of ovarian stimulation cycles. The radical group had more cycles (2.7) than the non-radical group (1.7). There was no significant difference in the mean number of retrieved oocytes between the non-radical and radical groups during the first cycle ($p = 0.46$). The mean FSH dosage at the first cycle (IU) showed no significant difference between the two groups ($p = 0.9597$). The fertilization rates were also similar, with 55% and 53% in the non-radical and radical groups, respectively.

Table 3 summarizes the IVF outcomes. Live births occurred in 10 patients (28%), with one woman having two deliveries, resulting in 11 babies. No multiple births were recorded. The live birth rate after fertility treatment was significantly higher in the non-radical group, with 83% of patients achieving a live birth compared to only 17% in the radical group (Fisher test, $p = 0.0035$). In the non-radical group, the clinical pregnancy rate per embryo transfer (CPR) and the CLBR per oocyte retrieval were 64% and 55%, respectively. In contrast, the radical group had a CPR per embryo transfer of 12% and a CLBR per oocyte retrieval of 6%. These results show a significant difference between the two groups (Fisher test, CPR $p = 0.0004$ and CLBR $p = 0.0002$). The non-radical group had a 21.9- fold estimated odds (95% CI: 1.9–1216.4) higher chance of having a live birth compared to the radical group.

Table 1

Patient and tumor characteristics.

	Group			P value
	All patients	Non-radical group	Radical group	
Number of patients, n	36	6	30	
Mean age at FSS, y (range)	31.7 (23–37)	31 (26–35)	30.2 (23–37)	
Nulliparous, n (%)	31 (86.1%)	5 (83.3%)	26 (86.7%)	
Stage distribution (FIGO 2018)				<0.01
IA1, n (%)	4 (11.1%)	4 (66.7%)	0 (0%)	
IA2, n (%)	3 (8.3%)	1 (16.7%)	2 (6.7%)	
IB1, n (%)	24 (66.7%)	1 (16.7%)	23 (76.7%)	
IB2, n (%)	3 (8.3%)	0 (0%)	3 (10%)	
IB3, n (%)	2 (5.6%)	0 (0%)	2 (6.7%)	
Hystology				
Squamous cell carcinoma	20 (55.6%)	3 (50%)	17 (56.7%)	
Adenocarcinoma	12 (33.3%)	1 (16.7%)	11 (36.7%)	
Adenosquamous carcinoma	2 (5.6%)	2 (33.3%)	0 (0%)	
Other epithelial tumors	2 (5.6%)	0 (0%)	2 (6.7%)	
Type of FSS				
ART with bilateral ligation of uterine arteries, n (%)	30 (83.3%)	0 (0%)	30 (100%)	N/A
ART with preservation of uterine arteries non radical, n (%)	1 (2.8%)	1 (16.7%)	0 (0%)	
Simple trachelectomy non radical, n (%)	5 (13.9%)	5 (16.7%)	0 (0%)	
Cervical stenosis, n (%)	6 (16.7%)	1 (16.7%)	5 (16.7%)	**1**
Median follow-up, y	13.6	16.4	13.2	

Note: FSS = Fertility-sparing surgery; ART = Abdominal radical trachelectomy.

The miscarriage rate was 50% and 17% in the radical and non-radical group, respectively. Three pregnancies (60%, 3/5) in the radical group resulted in a first-trimester miscarriage and only 1 pregnancy (17%, 1/7) in the non-radical group. In the radical group two patients (40%, 2/5) had a second-trimester loss, whereas no second trimester loss was reported in the non-radical group. The implantation rate was significantly higher in the non-radical group, with 37% compared to only 8% in the radical group (Fisher-test, $p = 0.0017$).

The non-radical group had an average gestational age at birth of 35.5 weeks. In contrast, the group that received radical treatment had a lower average gestational age at birth of 31 weeks, indicating a higher incidence of prematurity in these patients. Within the radical treatment group, 40% of patients (2/5) delivered with significant prematurity (before 32 weeks), which is where most neonatal morbidity and mortality occurs. However, there was no significant prematurity in the non-radical group. The average fetal birth weight was 2787 g and 1473 g in the non-radical and radical groups, respectively.

4. Discussion

To our knowledge, this is the largest retrospective study evaluating IVF outcomes in young, infertile cervical cancer survivors who had previously undergone FSS. This retrospective cohort study included all Hungarian patients who underwent FSS for early-stage cervical cancer, all performed by an experienced surgical team between 2004 and 2020, and followed by IVF treatment at 10 different fertility clinics between 2006 and 2022 in Hungary.

The live birth rate per patient following IVF treatments was at least 1.9 folds higher in the non-radical group compared to the radical group. This statistically significant difference underscores the major impact of the radicality of fertility-sparing surgery on reproductive outcomes. In the non-radical group, both the pregnancy rate per embryo transfer (PR) and the cumulative live birth rate per oocyte retrieval (CLBR) were considerably higher.

In general, age is the primary factor affecting fertility, influencing both the quantity and quality of oocytes. Remarkably, in our study, the radical group had a lower mean age at the first oocyte retrieval but achieved a significantly lower CLBR following IVF treatment, therefore this difference have to be explained by other factors than age.

Impaired uterine perfusion may contribute to the lower pregnancy rates observed in the radical group. It is hypothesized that patients who have undergone abdominal radical trachelectomy involving extensive parametrectomy and the ligation of the origin of uterine arteries may experience compromised uterine blood flow, which is essential for supporting pregnancy. Klemm et al. conducted a study using Doppler sonography to measure uterine blood supply, which interestingly showed that uterine perfusion remained unchanged after radical trachelectomy [15]. In addition, the results of the study by Escobar et al., based on real-time intraoperative angiographic observations, suggest that preservation of the uterine artery during radical trachelectomy is not necessary to maintain uterine viability. [16]. In contrast, data show that following uterine artery embolization (UAE) the uterine myometrial and endometrial perfusion is reduced, leading to suboptimal embryo implantation [17,18]. Our results showed significantly decreased implantation rate in patients undergoing radical FSS; out of 148 transferred embryos only 12 embryos implanted, resulting a very low, 8% implantation rate. Therefore, reduced implantation rate may be the key factor explaining worse IVF outcome in patients where uterine arteries were sacrificed during the FSS. Traditionally our surgical team used a hyperradical technique, which corresponds to a C2 type parametrectomy according to the Querleu-Morrow classification. Probably the suboptimal CLBR (6%) may be associated with the increased radicality of the procedure resulting severe myometrial and endometrial ischemia leading to decreased implantation rates.

Various studies analyzed pregnancy outcomes in patients who underwent FSS and have reported diverse success rates based on different surgical routes and approaches. A systematic review assessing all routes of radical trachelectomy revealed a post-trachelectomy pregnancy rate of 23.9%, with the highest rate observed in the vaginal radical trachelectomy group [19]. The studies suggest that the abdominal approach may have a greater impact on reproductive function due to the complete separation of the uterine body from the vaginal wall, potentially leading to disruptions of nerves and vessels, as well as pelvic adhesion [20]. Moreover, in the context of early-stage cervical cancer, women undergoing simple trachelectomy or conization have shown even better reproductive outcomes. A study by Plante et al. demonstrated that only 16% of patients experienced fertility problems after non-radical surgery [4]. Another systematic review supported these findings, [8] reporting a significantly higher live birth rate (86.4 ± 16.8%) following simple trachelectomy or conization when compared to those who underwent vaginal radical trachelectomy (63.4 ± 23.3%; $p = 0.04$). In the same systematic review, the radical abdominal trachelectomy group had a low pregnancy rate of 18%, with 45% achieving pregnancy through ART (IVF and IUI). Conversely, the cold-knife conisation and simple

Table 2

Ovarian stimulation outcomes, and patient characteristics.

	Group			P value
	All patients	Non-radical	Radical	
Mean time interval from FSS to first oocyte retrieval, days	1681	1864	1644	**0.6938**
Mean age at the first oocyte retrieval, y	35.1	36.2	34.9	**0.4703**
BMI, mean (kg/m^2)	22.9	24.3	22.7	**0.2264**
Amh, mean (ng/ml)	2.5	4.1	2.3	**0.2878**
Male infertility	4 (11.1%)	0 (0%)	4 (13.3%)	
Other causes of infertility in women	12 (33.3%)	2 (33.3%)	10 (33.3%)	
Stimulation cycles	91	11	80	
Mean number of ovarian stimulation cycles (per patient)	2.4	1.7	2.7	
Mean number of retrieved oocytes in the first cycle	7.1	8.3	6.8	**0.4647**
Fertilization rate	53% (311/585)	55% (37/67)	53% (274/518)	
Mean FSH dosage at the 1. cycle (IU)	1811	1800	1815	**0.9597**
OS response (mean FSH dosage per matured oocyte at the 1. cycle) (IU)	282	243	303	

Note: OS = Ovarian stimulation; FSS=Fertility-sparing surgery.

trachelectomy group had a higher pregnancy rate of 46%, with only 6% achieving pregnancy with the help of ART [8].

A reduced ovarian response to ovarian stimulation may affect live birth rates. However, according to the study findings presented in Table 2, the type of fertility-sparing surgery (FSS) did not affect ovarian response. Specifically, there were no significant differences in anti-Müllerian hormone (AMH) levels, ovarian stimulation outcomes, or fertilization rates between radical and non-radical FSS groups. The literature on ovarian response after radical trachelectomy has conflicting results. Tamauchi et al. conducted a retrospective study that suggests a possible decrease in ovarian reserve due to reduced ovarian blood flow, which may result in a diminished response to ovarian stimulation (OS) after radical trachelectomy [21]. However, Muraji et al. conducted a study on the effect of inferior uterine artery branch ligation on ovarian reserve in patients who underwent open radical trachelectomy [22]. The study found no statistically significant difference in AMH levels between the study and control groups. Overall, these findings underscore the potential influence of the surgical approach on fertility, shaped by various factors contributing to poor fertility outcomes.

Cervical stenosis is a well-known cause of infertility following fertility sparing cervical procedures, with an incidence ranging from approximately 4.7% to 8.1% [8,23]. In our series, 17% of the patients required isthmic dilatation due to either haematometra or difficulties performing IVF. Although one would expect higher rates of stenosis following more radical surgery, there was a similar incidence of stenosis in both surgical groups. In our study, only one patient with a history of surgery for postoperative cervical stenosis achieved a successful pregnancy and, importantly, this individual underwent a non-radical procedure. These

findings suggest that reduced fertility may not be solely due to the cervical stenosis itself, but may be related to the radical nature of the surgical procedure. It is important to acknowledge that it is not possible to draw definitive conclusions about the relationship between cervical stenosis and reduced fertility due to the limited number of successful pregnancies, making it difficult to infer whether it was the radicality or the stenosis that played a predominant role.

Infertility may also be attributed to factors such as cervical shortening and alterations in cervical mucus characteristics [24]. Moreover, recent research has shown that conization can affect the vaginal microbiota, potentially leading to a higher risk of preterm birth [25]. Furthermore, a dysbiotic microbiota profile in the female reproductive tract is associated with poor reproductive outcomes in patients undergoing assisted reproduction [26]. However, it is important to note that we did not test the vaginal microbiome of the participants in our study. Testing the impact of microbiota on reproductive outcomes in both study arms would be a valuable initiative for future studies.

Another significant aspect of fertility-sparing procedures is their impact on obstetric outcomes. Preterm delivery is the most common complication observed in pregnancies following these procedures. The etiology of prematurity is multifactorial and strongly associated with the lack of mechanical support by the residual cervix and an elevated risk of ascending infection and chorioamnionitis. [15]. Premature delivery following trachelectomy due to preterm premature rupture of membranes occurs in 8–77% with a mean of 27% compared to an incidence rate of 3–5% in the average population [15]. Our data shows higher rates of prematurity and miscarriages in the radical group, although we could not perform statistical analysis due to limited sample

Table 3

Outcomes of in vitro fertilization after fertility-sparing surgery in the non-radical compared to the radical group.

	Group			P value
	All patients	Non-radical group	Radical group	
Patients, n	36	6	30	
Stimulation cycles, n	91	11	80	
Embryos, n	311	37	274	
Embryo transfers, n	95	11	84	
Pregnancies, n	17	7	10	
Miscarriage, n (%)	35% (6/17)	17% (1/7)	50% (5/10)	**0.3043**
1 st trimester miscarriage, n	4	1	3	
2 st trimester miscarriage, n	2	0	2	
Implantation rate, %	11% (19/167)	37% (7/19)	8% (12/148)	**0.0017**
CLBR per oocyte retrieval, %	12% (11/91)	55% (6/11)	6% (5/80)	**0.0002**
Clinical PR per embryo transfer, %	18% (17/95)	64% (7/11)	12% (10/84)	**0.0004**
Women with live birth, %	28% (10/36)	83% (5/6)	17% (5/30)	**0.0035**
Preterm birth <37 weeks of pregnancy, n (%)	63.6% (7/11)	50% (3/6)	100% (5/5)	**0.1818**
24–32 weeks	14.3% (1/7)	0% (0/3)	40% (2/5)	
32–37 weeks	85.7% (6/7)	100% (3/3)	60% (3/5)	
Average gestational age at birth, w	33.5	35.5	31	**0.0758**
Average fetal birth weight, g	2203	2787	1473	**0.0515**

Note: CLBR = cumulative live birth rate; FSS = Fertility-sparing surgery; PR = pregnancy rate.

size. An equally important finding was the difference between the two groups' average gestational week of delivery and fetal birth weight. First-term miscarriages (30%) and second-term miscarriages (20%) in the radical group were higher than those observed in the general population. Tumor size was bigger in the radical FSS group; therefore, these procedures may be associated with a more important reduction of the cervical length, which is a major determinant of late miscarriage and premature delivery.

An increasing body of evidence has emerged about the safety of conservative surgery for early-stage, low-risk cervical cancer patients. The recently published FERTISS study provided retrospective data on oncological outcomes from a large multicentric cohort of early stage cervical cancer undergoing FSS [27]. This study showed that non-radical cervical procedure does not confer a higher risk of recurrence in patients with tumors smaller than 2 cm compared to radical FSS. Parametrectomy has not been shown to improve prognosis in stage IB1 patients and may increase postoperative morbidity with worse perinatal outcomes [27].

In our study, we observed improved reproductive outcomes following IVF in patients who underwent non-radical fertility-sparing surgeries with the preservation of uterine arteries, compared to those in the radical surgery group. These findings demonstrate that assisted reproductive outcomes can be optimized without significantly compromising oncologic outcomes in a carefully selected group of patients.

4.1. The strenghts of the study

The strengths of the study are its comprehensive coverage of patients, meticulous data collection, centralised patient management and long-term follow-up.

First, we ensured comprehensive data collection by obtaining both IVF and surgical records for each patient from all centres. In addition, centralised patient management by a dedicated team of experienced clinicians is another notable strength. This approach not only ensures consistency in treatment procedures, but also minimises variability in patient care. Long-term patient follow-up is also particularly important, as Hungary was among the first countries to introduce fertility sparing cervical cancer surgery. In addition, by focusing specifically on IVF patients, the study provides new insights and detailed IVF outcomes that have not been reported before.

4.2. Limitations of the study

A major limitation of this study is its retrospective design and the small sample size within the non-radical group. This limitation can be attributed to the recent trend toward less radical surgical approaches for low-risk cervical cancer, which has only gained popularity in the last 10 years. To enhance the study's ability to detect differences in certain outcomes, a larger sample size would be required. However, in the light of the excellent spontaneous fertility rates following non radical FSS, it would be time-consuming to increase the number of non radical surgical cohort [8].

Another limitation of the study is the significant difference in tumor stage distribution between the non-radical and radical groups. This difference is expected as non-radical surgery is primarily used for smaller tumors.

The aim of this study was to compare the reproductive outcomes of IVF in patients who underwent non-radical and radical surgery. The main question is whether the stage of the tumor itself might influence the IVF success rate independently of the type of surgery. As all tumors were completely removed and no additional (adjuvant) therapies were given beyond surgery, it appears that the primary determinant of reproductive outcome was the type of surgery performed rather than the stage of the tumor itself.

These limitations highlight the need for more extensive, prospective studies that can provide more definitive and representative results

regarding the impact of radical and non-radical fertility-sparing procedures on reproductive and obstetric outcomes in cervical cancer survivors.

5. Conclusions

For women of reproductive age diagnosed with early-stage cervical cancer, fertility-sparing strategies have emerged as a vital component of treatment, offering hope for future motherhood. Fertility-sparing surgery (FSS) aims to attain oncologic outcomes similar to radical treatment while optimizing reproductive results. Given the significant patient morbidity associated with radical fertility-sparing procedures including adverse reproductive and obstetric outcomes, there has been recently a shift toward less radical surgical approaches for low-risk cervical cancer. Further studies are needed to strengthen the existing evidence showing both oncological safety and reduced morbidity of these approaches.

Our study demonstrates that low-risk cervical cancer patients who undergo non-radical fertility-sparing surgery experience improved in vitro fertilization outcomes compared to radical surgery. Radical procedures involving uterine artery ligation were associated with decreased implantation rate and cumulative live birth rate. These findings emphasize the importance of considering oncological safety and reproductive outcomes together when choosing FSS for early-stage cervical cancer patients, highlighting the reproductive benefit of performing less radical surgery with preservation of uterine arteries. They also highlight the need for comprehensive data to guide patient counseling and clinical recommendations.

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Dóra Vesztergom: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Gyöngyvér Téglás:** Methodology, Software. **Kiarash Bahrehmand:** Data curation. **Attila Török:** Data curation. **Levente Balla:** Data curation. **Vince Forgács:** Data curation. **János Konc:** Data curation. **Zoltán Tándor:** Data curation. **Ákos Várnagy:** Data curation. **Péter Boga:** Data curation. **János Zádori:** Data curation. **Miklós Sipos:** Data curation. **Zoltán Mánfai:** Data curation. **Zoltán Novák:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors report no conflict of interest.

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ASSISTED REPRODUCTION TECHNOLOGIES

Live births after in vitro maturation of oocytes in women who had suffered adnexal torsion and unilateral oophorectomy following conventional ovarian stimulation

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Abstract

Purpose To report the first successful application of in vitro maturation (IVM) of oocytes resulting in live births in two anovulatory women who had suffered oophorectomy following ovarian torsion after stimulation with gonadotropins.

Methods Data abstraction was performed from medical records of two subfertile women with excessive functional ovarian reserve. Both women had previously received gonadotropins for ovulation induction or ovarian stimulation, resulting in ovarian torsion. They were offered IVM of oocytes retrieved from antral follicles after mild ovarian stimulation, insemination of mature oocytes using ICSI, and embryo transfer. Outcome measures were the incidence of complications and live birth after fertility treatment.

Results Transvaginal retrieval of cumulus-oocyte complexes from a unique ovary was conducted. One patient had a singleton live birth after vitrified-warmed embryo transfer in the second IVM cycle. The other patient had a singleton live birth after transfer of a fresh blastocyst in her first IVM cycle.

Conclusions Although approaches have been developed to prevent ovarian hyperstimulation syndrome (OHSS) and to increase the safety profile of fertility treatment in predicted high responders, women with an excessive functional ovarian reserve may have a non-negligible risk of ovarian torsion. For these patients, IVM should be considered as a safer alternative approach.

Keywords IVF · IVM · Ovarian stimulation · Ovarian torsion · High responder

Introduction

Ovarian stimulation (OS) with gonadotropins is the cornerstone of assisted reproductive technologies. Whilst women who have an elevated functional ovarian reserve are at increased risk of ovarian hyperstimulation syndrome (OHSS) after OS, the emergence of OS protocols using GnRH agonists triggering final oocyte maturation and elective embryo vitrification has changed the landscape of modern reproductive medicine. Indeed, avoidance of severe OHSS is now a reality in high responders, and "freeze-only" strategies after GnRH agonist triggering can combine avoidance of severe OHSS with optimal cumulative live birth rates [1, 2]. Although OS in high responders generally results in increased cumulative live birth rates (CLBRs) compared to normal responders [3], ovarian enlargement in a proportion of these women may result in significant abdominal discomfort, or can even lead to ovarian torsion [4]. Ovarian stimulation with gonadotropins is also commonly used for ovulation induction in women with WHO I and II anovulation, including PCOS.

We here present two anovulatory patients with elevated functional ovarian reserve who had previously suffered ovarian torsion after OS with gonadotropins. Despite the general recommendation of conservative surgical management of ovarian torsion, both patients had undergone unilateral

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oophorectomy. After self-referral to our centre, they were offered in vitro maturation (IVM) of oocytes as a mild-approach alternative, which resulted in a live birth in both patients.

Methods

Data were obtained from chart review and reported without any patient identifiers. Patients signed informed consent regarding publishing their data. Publication of this case series was approved by the local ethical committee (no. B1432020000125).

Results

Patient 1

Patient 1 self-referred to our clinic with a history of primary subfertility for 2 years. She had experienced secondary amenorrhea after discontinuing the oral contraceptive pill. Before attending our clinic, she had previously undergone four cycles of ovulation induction prescribed by her gynaecologist. Because of resistance to clomiphene citrate, the patient had received HP-hMG (Menopur®; Ferring Pharmaceuticals A/S, Copenhagen, Denmark) at a daily dose of 75 IU, resulting in the recruitment of a single dominant follicle. Ovulation had been triggered using 5000 IU hCG (Pregnyl®, Organon, MSD, Haarlem, The Netherlands). After the third round of ovulation induction, the patient had presented at the emergency department with increasingly severe and persistent lower abdominal pain and nausea, 2 days after hCG administration. An explorative laparoscopy had been performed, which revealed two enlarged and rotated ovaries with a diameter of 12 cm and 10.5 cm. Because the right ovary and fallopian tube had shown persistent dark discolouration and complete absence of blood flow in the ovarian vessels after derotation, the gynaecologist had decided to perform a unilateral adnexectomy. The contralateral ovary had been derotated and recovered quickly. The histology report confirmed the diagnosis of necrosis of the right ovary. After self-referral to our fertility clinic, hormonal analysis was performed which was compatible with functional hypothalamic amenorrhea (WHO I anovulation, Table 1). Transvaginal ultrasound showed an antral follicle count (AFC) of 60 in the unique left ovary, a thin endometrium, and no ovarian cysts (Fig. 1). The BMI was 16.5 kg/m^2 and sperm analysis in the partner was normal.

Because of the history of ovarian torsion after OS with gonadotropins and hCG triggering, the patient declined further attempts of OS. In view of this, in vitro maturation (IVM) of oocytes was proposed, as previously described [5]. Briefly, ovarian stimulation involved administration of 225 IU HP-hMG (Menopur®) for four consecutive days. Transvaginal

oocyte retrieval was performed 42 h after the last injection of HP-hMG. No hCG trigger was administered. Transvaginal ultrasound-guided oocyte retrieval was performed under general anaesthetic using a 17-gauge single-lumen needle on day 6 (K-OPS-1230-VUB; Cook Medical) at an aspiration pressure of −70 mmHg. No follicle flushing was performed. Follicular aspirates were collected in human tubal fluid (HTF) (IVF Basics® HTF HEPES, Gynotec B.V. Malden, The Netherlands) supplemented with heparin (5000 IU/mL, Heparin Leo, Leo Pharma, Belgium; final heparin concentration 20 IU/mL) and filtered through a cell strainer (Falcon®, 70-μm mesh size, BD Biosciences, CA, USA). In total, 70 cumulus-oocyte complexes (COCs) were harvested. After collection, COCs were washed and transferred to four-well dishes (Nunc, Thermo Fisher Scientific, MA, USA) containing IVM medium (IVM System, Medicult, Origio) supplemented with 75 mIU/mL HP-hMG (Menopur®), 100 mIU/mL hCG (Pregnyl®), and 10mg/mL human serum albumin (Vitrolife, Göteborg, Sweden), followed by 32 h of group culture of 10 COCs per well in 500 μL of IVM medium with an oil overlay (Ovoil, Vitrolife) at 37 °C under 6% CO_2 and 20% O_2. In total, 35 oocytes reached MII stage after IVM. Matured oocytes were inseminated using ICSI with partner sperm, and 25 oocytes fertilized normally. Embryos were cultured in individual 25-μL droplets of sequential media (Quinn's Advantage™ Fertilisation, Fert™, Cleav™, Blast™ medium, Origio) and in G-TL™ monophasic culture medium (Vitrolife, Göteborg, Sweden) in the second cycle. Seventeen cleavage-stage embryos were observed on day 3 after ICSI, and embryo culture was continued to day 5.

Luteal-phase support for an IVM cycle with fresh embryo transfer consisted of transdermal estradiol (E2) gel (Oestrogel®; Besins Healthcare, Paris, France) at a dose of 2 mg, three times daily, which was started on the day before oocyte retrieval, and 600 mg daily of vaginal micronized progesterone (Utrogestan®, Besins Healthcare, Paris, France), starting on the evening of the day of the ICSI procedure. One blastocyst of good quality (BL4BB, as graded according to the Gardner and Schoolcraft scoring system [6]) was transferred freshly. No pregnancy ensued. Unfortunately, all other blastocysts were of insufficient developmental quality to be vitrified as surplus embryos.

A second IVM cycle was performed in this patient using the same protocol with 4 days of HP-hMG stimulation. Oocyte retrieval yielded 77 COCs; 37 oocytes reached MII stage after IVM, of which 22 were fertilized normally after ICSI. Seven embryos of good morphological quality were vitrified electively on day 3 after ICSI. In view of the poor embryo development beyond the cleavage stage in the previous IVM cycle, the embryos were not cultured to day 5. The patient went on to have HRT cycles for frozen embryo transfer (FET) when basal hormone levels were reached after the IVM cycle. Briefly, the endometrium was primed with transdermal

Table 1 Baseline patient characteristics and IVM cycle outcome

	Patient 1		Patient 2
Baseline patient characteristics*			
Age (years)	25		30
BMI (kg/m^2)	16.5		19.4
AMH (ng/mL)	24.5		12.3
AFC (N)	60		30
FSH (IU/L)	<0.1		7.5
LH (IU/L)	<0.1		8.8
Progesterone (nmol/L)	1.34		0.64
E2 (ng/L)	32.0		28.0
IVM cycle outcome	Cycle 1	Cycle 2	
COC retrieved (N)	70	77	30
MII oocytes (N)	35	37	25
2PN oocytes (N)	25	22	21
Cleavage-stage embryos (N)	17	7	20
Cryopreserved embryos (N/stage)	0	7 (d3)	7 (d5)
Fresh ET (N/stage)	1/BL4BB (d5)	0	1/BL4AA (d5)***
eFET (N/stage)**	N/A	4	N/A
eFET no. 1		1/8c gr2 (d4)	
eFET no. 2		1/C2 gr1 (d4)	
eFET no. 3		1/5c gr3 (d4)	
eFET no. 4		2/BL1 gr2, C2 gr2 (d4)***	
Live birth	0	1	1

COC cumulus-oocyte complex, MII metaphase II, 2PN two pronuclei, ET embryo transfer, SET single embryo transfer, DET double embryo transfer, Y yes, N no

*Patient characteristics at intake (after unilateral oophorectomy)

**Cleavage-stage embryos were vitrified on day 3; embryo transfer was performed 1 day after embryo warming

***Resulting in live birth

Oestrogel® (two units administered three times a day). When an endometrial thickness of more than 6 mm was reached, luteal support was started using intravaginal micronized

Fig. 1 Baseline transvaginal ultrasound scan in patient 1 showing an AFC of 60 in the unique left ovary

progesterone tablets (P, 200 mg three times a day; Utrogestan®, Besins Healthcare), and the embryo transfer was scheduled 5 days later. The transfer of day 3 vitrified embryos was performed 1 day after embryo warming. Administration of oestrogens and P was continued until a pregnancy test was performed and was continued until 7 weeks of gestation if the pregnancy test was positive, after which the dose was gradually reduced and discontinued 1 week later. Because no pregnancy was achieved after three consecutive HRT cycles with single vitrified-warmed embryo transfer, a diagnostic hysteroscopy with endometrium biopsy was performed which showed normal histology and no signs of endometritis. Two embryos that had been vitrified on day 3 were transferred 1 day after warming in a further HRT cycle, which resulted in a pregnancy leading to a healthy singleton live birth at term.

Patient 2

A 30-year-old woman self-referred to our clinic with primary subfertility for 3 years based on PCOS-related anovulation. Previous first-line fertility treatment with her gynaecologist

had involved five cycles of ovulation induction with clomiphene citrate and intrauterine insemination (IUI), which had not resulted in pregnancy. She had gone on to have conventional ovarian stimulation for IVF using a GnRH antagonist protocol. Because of an increased risk of OHSS, she had been prescribed 0.2 mg of GnRH agonist triptorelin (Decapeptyl, Ipsen®, Merelbeke, Belgium) for final oocyte maturation. Fifteen cumulus-oocyte complexes had been retrieved and one good-quality blastocyst had been vitrified electively. After oocyte retrieval, the patient had presented severe pelvic pain whilst in the recovery room, not responding to standard analgesia. Upon laparoscopic exploration, gross enlargement of both ovaries had been observed and the right ovary had shown livid discolouration. The torsed right ovary had been derotated laparoscopically. However, because of signs of septicaemia on the next day, the patient had been operated again by laparoscopy 48 h later and had undergone unilateral right adnexectomy because of gangrenous changes of the ovary. After self-referral to our clinic, patient 2 was diagnosed with PCOS phenotype D, based on the extended Rotterdam criteria. Her basal hormonal profile is presented in Table 1.

Because of the history of ovarian torsion after OS using a GnRH antagonist protocol with GnRH agonist trigger, the patient declined further attempts of OS. In view of this, in vitro maturation (IVM) of oocytes was proposed, as described above. A short course of gonadotropins consisting of 225 IU HP-hMG (Menopur®) daily for three consecutive days was administered in patient 2. Transvaginal oocyte retrieval resulted in 30 COCs; 25 oocytes reached MII stage after IVM. All metaphase II oocytes were inseminated with ICSI, and 21 were fertilised normally. Embryos were cultured in individual 25-μL droplets of sequential media (Quinn's Advantage™ Fertilisation, Fert™, Cleav™, Blast™ medium, Origio). On day 5 after ICSI, seven blastocysts of good or top quality were vitrified electively. Endometrium preparation for the fresh embryo transfer consisted of administration of Oestrogel® at a dose of 2 mg, three times daily and started on the day before oocyte retrieval, and 200 mg three times daily of intravaginal micronized progesterone (Utrogestan®) starting on the first day after oocyte retrieval. One top-quality blastocyst (BL4AA, as graded according to the Gardner and Schoolcraft scoring system [6]) was transferred freshly, which resulted in a healthy singleton live birth at term.

Discussion

We here illustrate the safe and successful use of IVM in patients at the severest side of the spectrum of elevated functional ovarian reserve. Not only do these patients have an increased risk of OHSS, the most common adverse event related to ovarian stimulation, but we would like to raise awareness of other potentially severe complications of fertility treatment in predicted high responders. With this report, we would like to warn against a reduced level of vigilance when treating these patients with gonadotropins in the current era, now that the incidence of severe OHSS, the worst enemy of reproductive medicine professionals, has reached an all-time low. Ovarian torsion may even occur after ovulation induction using gonadotropins in high responders, as illustrated by the first case in this report, and the combination of a GnRH agonist trigger with a freeze-only strategy prevented severe OHSS in the second case, but could not prevent ovarian torsion.

Adnexal torsion in the setting of fertility treatment has an incidence ranging from 0.08 to 0.2% and can lead to the loss of an ovary [7]. Its prevalence is probably underestimated, in view of typical under-reporting of poor results. Ovarian stimulation is a known risk factor for ovarian torsion due to ovarian enlargement. There is ample literature to recommend a conservative surgical approach when ovarian torsion occurs. Indeed, although population studies have indicated that unilateral oophorectomy does not lead to premature menopause, such a procedure may result in reduced success rates after fertility treatment in an IVF population [8]. Derotation of the ovary with or without oophoropexy has been advocated several decades ago and is considered the treatment of choice. Even when complete ischaemia has developed, detorsion of the ovary will often be successful in re-establishing reperfusion and normal ovarian function [9–11]. However, untimely diagnosis may lead to significant delay of surgical intervention, compromising the viability of the ovary.

Patients with polycystic ovarian morphology (PCOM) and those with polycystic ovary syndrome (PCOS) are predicted high responders and are particularly at risk for OHSS after OS [12]. In spite of well-defined criteria for the diagnosis of PCOS and a revised threshold for PCOM of ≥20 antral follicles per ovary [13], PCOS is a heterogeneous condition and there is no single best approach that will fit all patients with PCOS. Women with PCOS who undergo OS will exhibit a continuum of ovarian response intensity, depending on intrinsic ovarian parameters, including antral follicle count (AFC) and AMH serum levels, and patient characteristics such as BMI. Although pre-stimulation AFC and AMH has been found to be reliable predictors for high ovarian response, their utility to predict OHSS is limited [14] and there are no available literature data with regard to the prediction of the extent of ovarian enlargement and the risk of ovarian torsion in high responders. As far as the two patients described here are concerned, baseline AMH levels had not been analysed before the initial fertility treatment. However, because serum AMH levels were strongly elevated (24.5 ng/mL in patient 1; 12.3 ng/mL in patient 2) after oophorectomy, when the patients presented at our clinic, it is likely that these levels must have been even more elevated initially. Nevertheless, although a vast amount of literature has been produced with regard to ovarian response prediction, there is a lack of knowledge

regarding the correlation between ovarian parameters, such as functional ovarian reserve and ovarian volume, and the risk of ovarian torsion. In a subset of high responders, OS may result in ovarian torsion even after moderate stimulation doses, such as in the setting of ovulation induction, as observed in patient 1 in this report.

We here illustrate the concept that for patients at the more severe side of the spectrum of functional ovarian reserve, IVM may be a safer alternative approach. Not only do these patients have an increased risk of side effects and adverse events related to ovarian stimulation, they also require intensified monitoring of ovarian stimulation, which may contribute to an increased level of stress during IVF treatment; on its turn, stress may lead to treatment termination before a successful pregnancy is achieved. In view of this and in spite of the existence of OHSS-free controlled ovarian stimulation protocols, a subset of high responders may be keen to embrace IVM as an alternative, lower-burden ART. To which extent these patients would accept a lower chance of pregnancy after IVM compared to standard IVF is currently unknown, although a recent survey among women with increase of OHSS has shown that about half of the patients are willing to accept a lower chance of pregnancy for a reduction of the OHSS rate [15].

Compared to conventional ovarian stimulation (OS) protocols, where oocytes are retrieved from large pre-ovulatory follicles, IVM involves the aspiration of cumulus-oocyte complexes (COCs) from antral follicles [16]. Hence, a shorter course of gonadotropins is administered, although the role of exogenous FSH has been controversial [17, 18] and FSH administration before oocyte retrieval has been omitted completely in some IVM clinics [19]. Nevertheless, even if gonadotropins are administered in an IVM cycle, very little monitoring is required. The cornerstone of an efficient IVM program is proper patient selection; women with elevated functional ovarian reserve parameters will yield sufficiently high numbers of immature oocytes to make up for the inherently lower efficiency of IVM compared to standard IVF [20–22]. Nevertheless, a specific AMH cut-off at which level the efficiency of IVM may approach or perhaps surpass that of OS followed by IVF/ICSI has not been established. Although IVM has initially been advocated as a method to eliminate OHSS, the development of OS strategies to dramatically reduce the risk of OHSS has mitigated the need for IVM as a strategy to avoid OHSS. Nevertheless, recent improvements to the IVM culture system [23] which may enhance the developmental potential of IVM embryos have refuelled the interest in IVM as a more patient-friendly approach in high responders. Although in centres with sufficient expertise cumulative live birth rates per started IVM cycle in women with PCOS reach ≈40% [24–26], embryo yield and success rates are still lower as compared to standard OS protocols. More specifically, IVM results in a relatively lower rate of embryos progressing to the blastocyst stage, but IVM embryos that do reach the blastocyst stage appear to have similar implantation potential as compared to blastocysts after OS [27]. Although the role of IVM in ART practice continues to be questioned in the modern era of agonist triggering and freeze-all strategies, we here illustrate the potential of IVM in selected patients who may have an increased risk of potentially severe complications when they undergo conventional ART. Nevertheless, future studies are required to compare the safety of IVM and conventional IVF/ICSI in a large cohort of predicted high responders.

Surprisingly, one case of ovarian torsion following IVM in a patient with PCOS has been reported [28]. However, in contrast with the patients presented here, the patient described by Giulini et al. had received a bolus of hCG before oocyte retrieval, which could have contributed to the development of this complication. In our opinion, and according to the recommendation by the International PCOS Network, IVM refers to the in vitro maturation of immature cumulus-oocyte complexes collected from antral follicles without the use of a hCG trigger [16].

Conclusion

Even though ovarian torsion is an infrequent complication of fertility treatment, with this report we would like to raise awareness of the risk of ovarian torsion after reproductive treatment in a subset of high responders to ovarian stimulation. We advocate that IVM should be considered as a safe and promising alternative ART in patients with strongly elevated markers of a high functional ovarian reserve, who are prone to develop adverse effects of gonadotropin stimulation. Moreover, ovarian stimulation in women with very high levels of AMH may also be cumbersome because of the non-linear dose-response curve. Further research should result in the identification of a specific category of high responders who have an elevated risk of ovarian torsion. As ovarian enlargement is more pronounced in women with high antral follicle counts, research efforts could be directed towards the establishment of a cut-off for AFC and AMH above which conventional ovarian stimulation may be too hazardous. In this category of patients, IVM may be considered as a safer option.

Data availability All data were obtained from chart review and are available from the corresponding author (M.D.V.) on request.

Code availability Not applicable.

Declarations

Ethics approval Publication of this case series was approved by the local ethical committee (no. B1432020000125).

Consent to participate Patients signed informed consent regarding publishing their data.

Consent for publication Patients signed informed consent regarding publishing their data.

Conflict of interest D.V., I.S., L.M., and C.B. declare no competing interests. M.D.V. has received speaker honoraria from MSD, Ferring and Gedeon Richter, and a grant from MSD, outside the submitted work.

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