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ASSISTED REPRODUCTION

Previous tubal ectopic pregnancy raises the incidence of repeated ectopic pregnancies in In Vitro fertilization-embryo transfer patients

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Abstract

Purpose To investigate the incidence of Tubal Ectopic Pregnancies (TEP) in IVF-ET patients with respect to the status of the fallopian tubes after a previous TEP.

Material and methods This retrospective study compares patients undergoing 481 IVF-ET cycles after conservatively or surgically treated TEP(s) with a Control Group (idiopathic or male factor for IVF-ET indication). Medical reports of surgery and/or hysterosalpingograms prior to the IVF cycles classified the status of the fallopian tubes.

Results 12 TEPs (8.95%/Pregnancies (PR)) occurred in the Study Group. In the Control Group one TEP (0.75%/PR; $p<0.001$) was found. Smoking increased the probability of TEPs ($p=0.0028$) and of pathological pregnancies (abortion, biochemical and ectopic PR; ($p=0.0411$)). For statistic evolution logistic regression (PROC GENMOD) and a repeated measure model were applied.

Conclusion Women with a previous TEP should be informed about the significantly increased risk for a further TEP in IVF-ET treatment, especially if they are smoking.

Keywords Ectopic pregnancy · IVF-ET · Assisted reproduction · Tubal surgery · Pregnancy rate

Capsule Tubes after a Tubal ectopic pregnancy (TEP) and smoking lead to a significant higher number of repeated TEPs in following IVF-ET programs.

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Introduction

A number of different tubal damages have been associated with varying results of In Vitro Fertilization-Embryo Transfer (IVF-ET) treatment. Hydrosalpinx [1, 2, 3], pelvic inflammatory disease, and bacterial infection [4], as well as smoking habits [5, 6], are known to be negative influencing factors. Furthermore, a previous (tubal) ectopic pregnancy (TEP) [7, 8] and surgery [5] affect the fertility of women.

Numerous investigations deal with "tubal factors" as a common reason for sterility and as an affecting factor on the rate of Ectopic Pregnancies [9]. No data are available on IVF-ET patients, who had a treated TEP prior to an IVF-ET treatment.

The primary objective of this study was to investigate the incidence of recurrence of TEPs with respect to the status of the fallopian tubes and to recommend a specific kind of (surgical) treatment for an acute ectopic pregnancy.

Material and methods

This retrospective study contains in the Study Group the data of women ($n=181$) suffering from secondary infertility

Table 1 Study Group divided into 6 subgroups concerning the condition of the fallopian tubes

	Tube I	Tube II
Group I–VI	**Study Group**	**Study Group**
Group I	Salpingectomy	Salpingectomy
Group II	Patent	Patent
Group III	Not patent	Not patent
Group IV	Salpingectomy	Patent
Group V	Salpingectomy	Not patent
Group VI	Patent	Not patent

after tubal ectopic pregnancies in a spontaneous menstrual cycle and therefore undergoing IVF-ET treatment (n=481 cycles) in an Outpatient Infertility Clinic in Vienna/Austria.

The Control Group evaluated 429 IVF-ET cycles of 377 women without a history of TEP, but male or idiopathic indication for IVF-ET. The status of the fallopian tubes was not available for the patients in this group.

The groups were matched for cycles with performed Embryo-Transfer (ET), and the age of patients. Because they do not influence the rate of pregnancy or TEP, for cancelled cycles of the Study Group no matching procedure was performed.

The status of the fallopian tube was evaluated by reviewing medical reports of the surgical procedure and/or radiologic reports of hystero-salpingograms a short time before the IVF-ET treatment. With respect to these results the Study Group was divided into six Groups (Group I–Group VI, Table 1): Both tubes surgically excised with salpingectomy (Group I), or were patent (Group II), or not patent (Group III). In other cases one tube had been excised and the other one was patent (Group IV) or not patent (Group V). The last Group included women with one patent and one non-patent tube (Group VI).

For controlled ovarian hyperstimulation either a combined stimulation with clomiphen citrate and human menopausal gonadotropin [10] or an "ultra short-flare up protocol" [11] with a gonadotropin releasing hormone agonist, and pure follicle-stimulating hormone was used. Some patients were stimulated with a long down regulation protocol [12].

Outcome was defined as a positive fetal heartbeat at 8 weeks of gestation on an ultrasound scan. Biochemical pregnancies, early pregnancy loss (abortion), and ectopic and heterotopic pregnancies were described as pathological. All TEPs were proven with laparoscopic surgery and/or ultrasound. Additionally we investigated the number of oocytes retrieved during follicle aspiration as well as the number of oocytes fertilized, used for ET or for freezing.

Statistics

Statistics were performed by the Institute for Medical Statistics, Vienna; by Mag. Pernicka Elisabeth, Mag. Gruber Diego, and Dr. Bauer Peter.

Logistic regression (PROC GENMOD) was used to determine which factors influence the outcome variable. As most women had repeated attempts, a repeated measure model was applied.

The outcome variables were dichotomous: Pregnancy (pathological pregnancies were also included), pathological pregnancy and tubal pregnancy.

The population was defined by the number of cases (n=176), which consisted of 414 IVF-ET attempts.

For each outcome a logistic regression was performed. The following variables were considered for inclusion into the logistic regression model when the data were restricted to the Study Group: Age; number of attempts; controlled hyperstimulation programme; number of oocytes retrieved, fertilized, transferred, and frozen; endometrium; smoking status; the embryo-score and the status of the tubes (subgroups). Step by step non-significant variables were eliminated and the significant variables were included into the new model.

Table 2 IVF-ET parameters for the Study- and the Control Group: number of cycles, number of cycles with embryo transfer (ET) and its percentage; mean age, outcome—pregnancy rate (PR) /ET; tubal ectopic pregnancy (TEP), TEP/ET, TEP/ pregnancy (PR)/ET—results are average values ± standard deviation

	Cycles	Cycles with ET	%	Age	PR/ET in %	path. PR/ET%	TEP n	TEP/ET in %	TEP/PR/ ET%
Group I–VI (SG)	**481**	**414**	**86.1**	**33.8±4.8**	**32.1**	**9.2**	**10+1bilateral (12)**	**2.9**	**8.95**
Group I	72	62	86.1	35.4±3.9	33.9	6.5	2	3.2	9.5
Group II	56	49	87.5	34.1±4.6	38.8	12.3	0	0	0
Group III	53	47	88.7	33.5±4.7	27.7	4.3	1	2.1	7.7
Group IV	177	151	85.3	33.9±4.5	30.5	10.6	3+1heterotopic P(4)	2.7	8.7
Group V	75	65	86.7	32.5±5.1	38.5	15.4	3+1bilateral TEP (5)	7.7	24
Group VI	48	40	83.3	33.2±5.5	22.5	2.5	0	0	0
Control Group	**429**	**414**	**100**	**33.8±4.9**	**32.5**	**9.5**	**1**	**0.24**	**0.75**

Table 3 Number and percentage of pregnancies/ET in the Study- and Control Group

	Cycles withET	Biochem. PR		Abortion		Singleton		Twins		Triplets		TEP/ET		TEP/ Pregnancies
	n	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	%
Study group	414	8	1.9	19	4.6	80	19.3	13	3.1	2	0.5	**12**	**2.9**	**8.95**
Control group	414	15	3.6	23	5.6	74	18.0	17	4.1	4	1.0	**1**	**0.24**	**0.75**

The same procedure was applied for the case control study (n=844 attempts), which consisted of the previously described population and the matched controls. As the number of attempts was not available for the CG, this variable as well as the subgroups could not be included into the model for the data of the case control study. The variable group (Study Group vs. Control Group) was added into the model and the same procedure was applied.

For all statistical analyses the SAS 9.1 system was used.

A p-value of <0.05 was considered to be statistically significant.

Results

The Study- and Control Group showed statistically equally distributed results in terms of age, controlled ovarian hyperstimulation, oocyte parameters and the thickness of endometrium on the day of ET.

The different IVF-ET parameters and the outcome for the SG, divided into 6 subgroups concerning the status of the fallopian tubes, are presented in Table 2.

In the SG the mean PR/ET was 32.1%, the pathological PR/ET 9.2%. The Control Group achieved a mean PR/ET of 32.5% and a pathological PR/ET of 9.5%.

The Study-and the Control Group contained similar numbers of abortions and biochemical pregnancies (Table 3). A statistically significant (p=0.001), increased number of TEPs (n=12 versus n=1) was found in the Study Group. The cancellation rate was equally distributed between the different subgroups of the Study Group.

The PR/ET was 22.5% (Group VI) to 38.8% (Group II; Subgroups of SG: see Table 1). Concerning the PR/ET, a direct comparison of the study groups showed no statistically significant difference (p=0.08–0.57). A trend to a better PR/ET was found in Group II (p=0.08), Group I (p=0.13) and Group V (p=0.15). Group V (p=0.09) had a higher probability of pathological pregnancy, but group membership showed no significant influence to pathological pregnancy (Table 2).

The percentage of TEPs/ET was 0% (Group II and VI), 2.1% (Group III), 2.7% (Group IV), 3.2% (Group I), and 7.7% (Group V), respectively. In Group V three TEPs and one heterotopic pregnancy occurred, while in Group IV three TEP and even one bilateral TEP was found (Table 2). Three out of 12 TEPs (25%) took place in the cornual stump after (bilateral) salpingectomy. Although a number of patients were repeat ones, none of the TEPs recurred in the same woman.

As the number of TEP events was too low, further assessment of effects of different subgroups on the risk for a TEP could not be performed.

Seventy-five percent of women who had a repeated TEP in the IVF-ET program were smokers. Non-smoking reduced the probability of getting a TEP in the SG (p=0.0028). The estimates indicated that the likelihood of a TEP was three times lower among non-smokers. Furthermore, smoking (p=0.041) increased the probability of pathological pregnancy.

The Control Group had a significantly (p=0.001) lower probability of a TEP. The chance of TEP was 45 times higher in the Study- Group than in the Control-Group.

Table 4 Statistical analysis with the targeted variable TEP comparing Study (SG)-and Control Group (CG) concerning 95% Confidence Interval and p-value

Target variable: Tubal pregnancy n=844	Estimate	95% Confidence Interval	p-value
Study group	45	23.0388–67.5054	<.0001
Control group	Reference group to group		
Smoker	−35951	−6.3142–(−0.8760)	0.0096
Nonsmoker	Reference to smoker		
Age SG	−0.1280	−0.2903–0.0343	0.1221
Age CG	0.8202	0.3311–1.3093	0.0010
No of oocytes for ET/SG	0.0662	−0.6815–0.8138	0.8623
No of oocytes for ET/CG	27540	1.0210–4.4870	0.0018
Intercept	437149	−66.1266–(−21.3033)	0.0001

Furthermore, the number of embryos transferred (p=0.0018) and increasing age (p=0.001) raised the probability of an ectopic pregnancy in the Control Group, while this variable had apparently no such clear effect on the Study Group (p=0.122). (Statistical analysis: Table 4)

Discussion

A number of case controlled studies provided evidence that several factors are involved in the aetiology of TEP. The resulting damage to the fallopian tubes may cause secondary infertility and is therefore one of the major reasons (25%, [13]) to undergo IVF-ET.

The primary objective of this study was to investigate the influence of the condition of the fallopian tubes in women, who experienced a TEP in a previous pregnancy, on the incidence of a repeated TEP in an IVF-ET program. The cause for the TEP in the natural cycles was unknown, but a previous TEP excludes—more or less—other important factors—male, immunological, idiopathic—for infertility.

We examined the parameters with respect to the condition of both fallopian tubes, reviewed from the medical surgical reports and/or verified by a hysterosalpingography prior to the IVF-ET treatment. However, this intention and an insufficient number of solely medically treated TEPs disallowed us to discuss an influence of antipodal (medically and surgically, respectively) therapy-methods applied.

In our collective, 13 TEPs occurred out of 267 pregnancies, whereas in the Study Group twelve TEPs (p=0.012) were found. This is a percentage of about 8.95% TEPs/pregnancies in comparison to IVF-ET cycles caused by other factors of infertility (0.75%/PR in our control group; 1.3% [14] up to 18.7%/PR [15] depending on the different assisting reproduction methods applied [16, 17]).

Although a systemic review [18] found no significant differences in long term follow-up concerning repeated ectopic and intrauterine pregnancies in natural cycles with respect to the treatment assessed (medical, surgical or combined, respectively), we hypothesize, that a TEP as well as the conservative and the surgical treatment causes alterations in tubal motility, ciliarfunction, and uterus contractions [19–21].

These negative effects seem to be amplified by smoking [22]. Seventy-five percent of the women in our study who became pregnant with a repeated TEP were smokers. Non-smoking significantly reduced the risk of generating a TEP (p=0.0028) and pathological pregnancy (p=0.0411).

In our evaluation a direct comparison of the subdivided Study Groups showed no statistically significant difference concerning the PR/ET, although a trend (p=0.08) to a better PR/ET was found in the group of patients with bilateral patent tubes or bilateral excised ones (p=0.13). The small number of TEPs regrettably precluded assessment of effects of different subgroups on the risk for a TEP.

In three out of 12 cases, an ectopic pregnancy occurred even in the stump of the tubes. Women seem to be at a particular risk for a pregnancy in the corn or in the stump [23] if they had undergone (bilateral) salpingectomy. The placement of the embryo in the uterus appears to be an additional determinant for TEPs. So a deep fundal transfer as well as the quantity of serum fluid used for ET increased the risk of EP [24]. A greater transfer distance from the fundus led to a significantly increased PR as well as lower ectopic rates [25].

In our study the number of embryos transferred also increased (p=0.0018) the probability of an ectopic pregnancy. Therefore in our institute a maximum of three embryos is transferred and placed midfundally, guided by ultrasound.

All women with a prior TEP have to be informed about the significantly increased risk for a further ectopic pregnancy even in IVF-ET treatment, especially if they are smoking. After (bilateral) salpingectomy physicians are called to reduce the number of embryos for transfer and to perform subfundal ET to reduce the risk for a repeated (cornual) TEP.

Further studies have to be performed to recommend a special mode of treatment for an acute tubal pregnancy following an IVF-ET.

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