Couple-related factors of ART outcome

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Summary

Purpose of investigation: Although assisted reproductive technologies (ART) are the current mainstay of infertility treatment, several mechanisms leading to ART failure are still unclear. The aim of the present study was to determine possible health-related risk factors in both counterparts of the couple affecting the ART outcome. *Material and Methods:* The authors recruited 100 consecutive couples who were undergoing ART procedure. All subjects filled out a health questionnaire, and the presence of bacterial vaginosis in females and/or prostatitis in males was evaluated. *Results:* Success of the ART procedure was 30.2%, failure being most significantly related to woman's age (OR = 0.24, 95% CI 0.09–0.66, $p = 0.003$) and excess body weight (OR = 0.08, 95% CI 0.01–0.63, $p = 0.002$). Male factors, previous conceptions, and presence of children increased the likelihood of ART success. Bacterial vaginosis and prostatitis did not significantly compromise the effectiveness of the ART procedure in this study. *Conclusion:* In 100 consecutive infertile couples scheduled for ART procedure, pregnancy was achieved in 30.2%, with female age and overweight and previous children from male side being the most significant factors affecting the ART outcome.

Key words: Infertility; Assisted reproductive technology; In vitro fertilization; Intracytoplasmic sperm injection; Bacterial vaginosis; Prostatitis.

Introduction

Assisted reproductive technologies (ART) have been successfully used to treat infertility for several decades, where mainly in vitro fertilization (IVF) and its submethod intracytoplasmic sperm injection (ICSI) [1] have yielded clinical pregnancies in up to 30% of treated patients [2].

The outcome of both IVF and ICSI depends on several factors such as age, BMI, lifestyle factors, and concomitant diseases in one or both partners [3, 4], but also low response to hormonal pre-IVF stimulation, poor embryo quality, as well as early post-IVF miscarriage [5]. Inflammatory diseases of the urogenital tract have also been shown to increase the risk of infertility, miscarriages or preterm labor [6, 7], with bacterial vaginosis being one of the most prevalent diagnoses in women [8, 9] and (chronic) prostatitis in men [10, 11]. However, the effect of either condition on IVF/ICSI outcome is uncertain and available results non-conclusive [12-15]. Also, there are very few studies where both counterparts of the couple have been simultaneously studied, although such data may turn out to be more informative and potentially leading to higher public awareness and better options in determining avoidable or treatable causes of infertility.

Therefore, the aim of this study was to determine possible health-related risk factors in both counterparts of the couple affecting the IVF/ICSI outcome, including the possible effect of bacterial vaginosis and/or prostatitis.

Material and Methods

Study group

The study group consisted of couples undergoing IVF or ICSI procedure in one fertility clinic in 2011, recruiting 100 consecutive couples who were willing to participate and thereafter gave an informed consent for study-related procedures. Study subjects' age ranged from 25 to 58 years (average 35.7), with female partners being significantly younger than their male counterparts (34.1 *vs.* 37.4 years, respectively; $p < 0.05$).

Health data and questionnaires

Data about general health and lifestyle, sexual and reproductive health, previous or current (biochemical or clinical) pregnancies, ART procedures, and clinical diagnoses of the study subjects were obtained from the physicians and through gender-specific questionnaires administered to all study participants. All study subjects had been tested for STI (chlamydiosis, gonorrhoea, trichomonosis, and mycoplasmosis) before commencing ART, therefore all recruited subjects were STI-free. None of the study subjects had received antimicrobial therapy within two months.

Nugent scoring of bacterial vaginosis

The diagnosis of bacterial vaginosis was based on the Nugent scoring system [16], using Gram stained slides of vaginal samples. Nugent score was evaluated on the basis of quantitative ratios of Lactobacillus, Gardnerella vaginalis, and Mobiluncus morphotypes seen in high-power magnification.

Semen sample assessment

Semen samples were obtained by masturbation and ejaculated into a sterile collection tube in a private room near the laboratories. The analysis of semen was performed according to WHO guidelines [17].

Level of leukocytes in seminal fluid (leukocytospermia) was determined in semen smears that were air-dried, Bryan-Leishman stained, and examined with the use of oil immersion microscopy. Significant level of leukocytospermia was estimated at ≥ one million leukocytes/ml of semen (WBC/ml) [17], whereas a lower threshold value (≥ 0.2 million WBC/ml) suggested by several recent studies [18, 19] was also used for comparison.

ART

Controlled ovarian stimulation was performed with recombinant FSH ~~(Gonal-F; Merck Serono, or Puregon; MSD)~~. Prevention of premature ovulation was performed with gonadotropin releasing hormone antagonist ~~(Cetrotide; Merck Serono, or Orgalutran; MSD)~~. Human chorionic gonadotropin ~~(Ovitrelle; Merck Serono)~~ was administered when two or more follicles reached the size of ≥ 17 mm in diameter and ovum pick-up (OPU) was performed 36 hours later. ART used in study couples was ICSI in 62% and IVF in the latter 38% of cases.

Statistical methods

The effect of various factors on the ART procedure was assessed using the logistic regression model, the odds ratio (OR), and 95% confidence interval (CI) were calculated using statistical software package STATA 12 ~~(StataCorp LP)~~. For significance probability (~~p;~~ *p*-value) calculation, Fisher's exact test and Mann-Whitney U-test were used. Statistical significance was assumed at $p < 0.05$.

Ethical Consideration

Participation in the study was voluntary. Informed consent was obtained from all study subjects. The study was approved by the Ethics Review Committee on Human Research of the University of Tartu.

Results

Main study results are summarized in Table 1. Among the study cohort (100 couples), conception was achieved in and embryos were transferred to 96 female subjects. Thereafter, biochemical pregnancy was seen in 34 and clinical pregnancy in 29 females, thus achieving the IVF/ISCI success rate of 30.2%.

The present results showed that ART failure was moderately related to health problems and lifestyle factors, but significantly associated with female age (average 34.1 years, range 25-46) and excess body weight (22.4% of female subjects with BMI ≥ 25), although male subjects were significantly older than their female counterparts (average 34.1 *vs.* 37.4 years, $p < 0.05$) and 64.0% of men were overweight (BMI ≥ 25). In couples where male and female counterparts belonged to different age groups, with males being 36 years or older, the likelihood of conception was lower, but did not reach statistical significance.

Male factors, previous conceptions, and the presence of children increased the likelihood of IVF success (Table 1). The sperm quality did not affect ART result in the present subjects, however, decrease in sperm quality was observed in 61% of men with no children compared to 49% in men who had fathered 1 or more children.

Table 1. — *Selected characteristics of the study subjects and their effect on IVF outcome.*

	Embryo transferred (total N=96)	IVF procedure success (N, %)	OR (95% CI)	*p*[1]
Female study subjects				
Age 25-35	55	23 (41.8%)	1	
36+	41	6 (14.6%)	0.24 (0.09-0.66)	0.003
BMI ≤ 24.9	73	28 (38.4%)	1	
≥ 25.0	21	1 (4.8%)	0.08 (0.01-0.63)	0.002
Earlier miscarriages	28	9 (32.1%)	1.14 (0.44-2.94)	0.389
Earlier ectopic pregnancy	16	4 (25%)	0.73 (0.22-2.40)	0.432
Earlier abortions	23	10 (43.5%)	2.19 (0.82-5.80)	0.094
Previous deliveries	30	11 (36.7%)	1.54 (0.62-3.87)	0.413
Endometriosis	29	11 (37.9%)	1.66 (0.66-4.19)	0.199
Tubal occlusion	27	10 (37.0%)	1.55 (0.60-3.97)	0.251
Absent fallopian tubes	19	5 (26.3%)	0.79 (0.25-2.44)	0.456
Salpingo-oophoritis	21	8 (39.1%)	1.58 (0.57-4.37)	0.263
Nugent score 0-6	81	25 (30.9%)	1	
Nugent score 7+	15	4 (26.7%)	0.81 (0.24-2.81)	0.504
Earlier pregnancies				
None	32	7 (21.9%)	1	
Yes, 1 to 3	58	19 (32.8%)	1.74 (0.64-4.74)	0.330
Yes, 4 or more	6	3 (50.0%)	3.57 (0.59-21.75)	0.255
Earlier IVF experience				
None	32	10 (31.3%)	1	
Yes, 1-3 times	46	16 (34.7%)	1.17 (0.44-3.07)	0.238
Yes, 4+ times	18	3 (16.6%)	0.44 (0.10-1.87)	0.134
Male study subjects				
Age 25-35	44	16 (36.4%)	1	
36+	52	13 (25.0%)	0.58 (0.24-1.40)	0.162
BMI ≤ 24.9	36	11 (30.6%)	1	
≥ 25.0	60	18 (30.0%)	0.97 (0.40-2.29)	0.565
Decreased sperm quality	53	16 (30.2%)	1.00 (0.42-2.40)	0.585
Leukocytospermia (M WBC/ml)				
≤ 0.99	87	23 (26.4%)	1	
≥ 1.00	7	4 (57.1%)	0.81 (0.24-2.81)	0.504
Partner's previous pregnancies				
None	39	7 (17.9%)	1	
Yes, with former partner	25	11 (37.9%)	2.31 (0.89-6.00)	0.070
Yes, with current partner	40	16 (55.2%)	2.21 (0.91-5.35)	0.062
Children				
None	54	11 (20.4%)	1	
Yes, with former partner	20	8 (27.6%)	1.75 (0.63-4.87)	0.210
Yes, with current partner	25	13 (44.8%)	3.72 (1.42-9.75)	0.007
Couples studied				
Age both 25-35y	34	14 (41.2%)	1	
one aged 36+	31	11 (35.5%)	0.79 (0.29-2.14)	0.415
both aged 36+	31	4 (12.9%)	0.21 (0.06-0.74)	0.011
BMI both ≤ 24.9	27	11 (40.7%)	1	
one ≥ 25.0	53	17 (32.1%)	0.69 (0.26-1-79)	0.300
both ≥ 25.0	14	1 (7.1%)	0.11 (0.01-0.98)	0.025
Smoking, neither	25	10 (40.0%)	1	
one partner yes	44	14 (31.8%)	0.70 (0.25-1.94)	0.334
both partners yes	25	5 (20.0%)	0.38 (0.11-1.33)	0.108

[1] Fisher's exact test.

Prevalence of bacterial vaginosis was 15.0% and that of prostatitis 7.1%, according to WHO standard ($\geq$ one million leukocytes in one ml of seminal fluid) while 36.7% when lower threshold value (≥ 0.2 M WBC/ml) from the authors' previous studies [19] was applied. No statistically significant relationship was found in the present study between these conditions and IVF/ICSI outcome.

Discussion

In the present study of 100 consecutive infertile couples scheduled for ART procedure, pregnancy was achieved in 30.2% of the female subjects, with female age, overweight, and previous children from male side being the most significant factors affecting the ART outcome.

Importance of female age in achieving pregnancy has been repeatedly shown in other studies [3, 20], where higher age also indicated significantly lower ART success as well as increased probability for performing additional IVF/ICSI cycle(s). It has been estimated that every additional year of infertility decreases the likelihood of ART success by 2% [20].

Overweight is also a major risk factor of infertility [3, 4, 20, 21]. Overweight female subjects were found to have approximately half the chance of IVF/ICSI success when compared to females with normal weight [21]. Although the study group was relatively small, the chances of overweight females to conceive were still significantly lower (OR = 0.08; 95% CI 0.01–0.63; $p = 0.002$) in the present study.

Health problems described in subjects of this study were etiologically related to infertility as well as indications for ART procedure. Most prevalent findings in females were tubal factor infertility (52.0%), which was most often presented as partial or complete tubal occlusion (27.0%). Male subjects presented mostly with decline in sperm parameters (55.0%), where several problems (changes in sperm concentration, motility, and/or morphology) tended to present simultaneously.

Most subjects (67.0%) had a previous experience with ART procedure(s) and pregnancy was mostly (55.2%) achieved within three first cycles, which corresponds to previously published data [5]. It has also been pointed out that after the fourth IVF cycle, women with earlier IVF-pregnancies had a significantly higher chance of conceiving than those who had not achieved any pregnancies during earlier IVF attempts [5]. This tendency could not be evaluated in the present study due to small study sample, however, the authors noted that history of earlier pregnancies and children still increased the likelihood of next pregnancy.

Smoking did not correlate with ART success in the present study, however, meta-analysis of 18 published studies where correlations between ART outcome and smoking were estimated, showed that smoking was a significant factor of IVF/ICSI failure in women, but not in men [22]. The

present authors were unable to confirm alcohol consumption as a risk factor of IVF failure in this study, with similar results in a larger sample (221 couples) being published earlier [23].

One of the goals of this study was to estimate the prevalence of bacterial vaginosis and inflammatory prostatitis in ART subjects as well as to evaluate their correlation to ART outcome. Bacterial vaginosis (as measured by Nugent score) was present in 15% of women, but no correlation with ART outcome could be seen. Similar results have been reported in significantly larger study sample (307 patients) [12], although bacterial vaginosis prevalence was somewhat lower in that group (9.5%). However, in some studies bacterial vaginosis has been shown to be associated with early spontaneous abortion [24].

Inflammatory prostatitis also did not affect ART outcome in the present study, with similar results published in several earlier studies [14, 15], although some studies have shown possible negative effects of leukocytospermia on ICSI outcome [25, 26]. Number of couples where both counterparts were simultaneously affected by above-mentioned conditions was small, therefore possible negative effect on ART outcome could not be estimated.

The main drawback of this study was its small sample size, which also signified that the number of subjects with conditions or risk factors that could possibly interfere with ART outcome on a larger scale was very small in this study. Therefore, significantly larger study groups are required in further studies about correlations between health conditions and risk factors on one side and ART results on the other.

In conclusion, the most significant female factors affecting ART outcome are age and overweight, while previously fathered children is the most important factor in the male counterpart.

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