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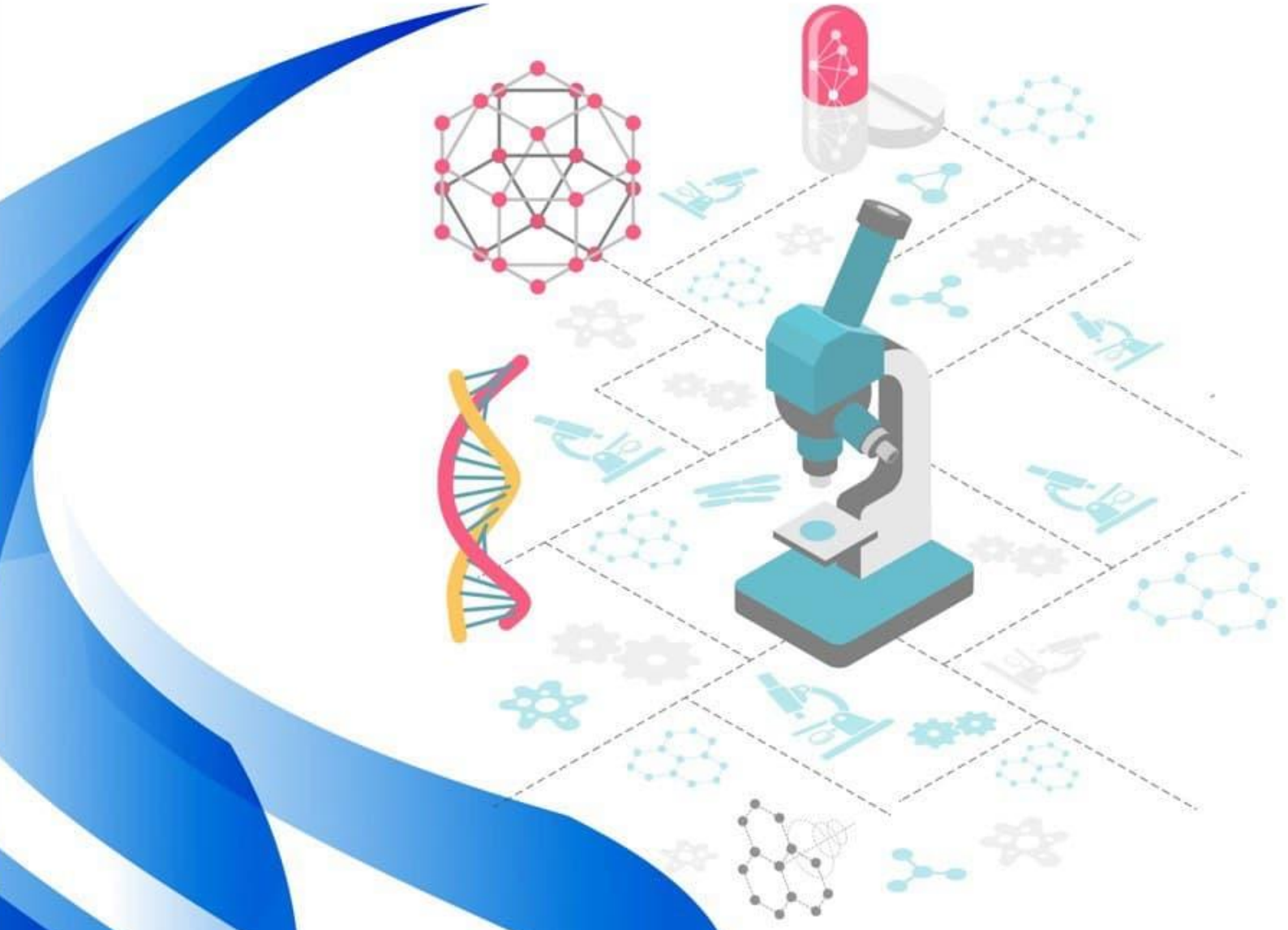

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EARLY PREGNANCY LOSS AFTER TREATMENT WITH ASSISTED REPRODUCTIVE TECHNOLOGIES

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Summary. In women receiving assisted reproductive technology (ART), early miscarriage reduces initial success. However, risk factors for non-developing pregnancy have not been comprehensively studied. This study evaluates some potential risk factors for ART pregnancy. In this article, we have presented our findings on improving outcomes regarding early pregnancy loss after ART.

Relevance. The problem of protecting the health of mother and child is the most important component of public health and is of paramount importance for the formation of a healthy generation of people from the earliest period of their lives. One of the most important problems of practical obstetrics is miscarriage [2,5,9]. The frequency of miscarriage is 10-25% of all pregnancies, 5-10% are preterm births. Preterm infants account for over 50% of stillbirths, 70–80% of early neonatal mortality, and 60–70% of infant mortality [1,3,10]. Premature babies die 30-35 times more often than full-term babies, and perinatal mortality in miscarriage is 30-40 times higher than in term births.Despite a comprehensive study of the problem of infertility, insufficiently studied prognostic, therapeutic and preventive aspects of maintaining pregnancy and their complexity, as well as socio-economic factors, make this topic very relevant, requiring more in-depth study of clinical diagnostic, hormonal, and genetic aspects of this problem [4,6,7,8]. In assisted reproductive technology (ART), miscarriage prior to clinical detection by ultrasound scanning is also commonly referred to as biochemical pregnancy. Although studies conducted in the general population can provide some estimates of the risk of a miscarriage, the sample size in these studies has generally limited the statistical power to examine in detail potential risk factors for a miscarriage. Women receiving ART are regularly monitored for early detection of pregnancy by measuring serum hCG concentration on a specific day, usually 14–17 days after oocyte retrieval, equivalent to ovulation in the general population, and again by ultrasound scan approximately 6–7 weeks later . pregnancy. Thus, they represent an ideal population to study potential risk factors for miscarriage, and the results may be applicable to the general population.

Key words: ART, early pregnancy loss, risk factors.

Purpose of the study: to determine the factors leading to early pregnancy loss and improve the outcome of pregnancies after the use of ART.

Research materials and methods: We examined 117 women in Bukhara and Karshi with a threatened abortion in the first trimester for the period 2020-2022, of which 1 group of 51 pregnant women with a risk of threatened abortion after IVF, 2 - a group of 46 pregnant women after termination before the 14th week of pregnancy with unsuccessful IVF and a 3rd control group of 20 pregnant women with a physiological course of pregnancy. Risk factors studied included maternal age, body mass index (BMI), smoking status and polycystic ovary syndrome (PCOS), infertility

etiology, response to stimulation, quality and quantity of embryos to be replaced, and type of treatment.

While hCG measurement was usually performed on the morning of day 16 after oocyte retrieval (85% of the study population), a small proportion of patients had hCG measured on day 15 or 17. HCG was measured using an automated fluorometric enzyme immunoassay using two monoclonal antibodies (Stratus II; Baxter, Miami, FL, USA). The sensitivity of the assay was 2 IU/L with coefficients of variation consistently <5% over a wide dynamic range (2–500 IU/L). Sensitivity was 2 IU/L and coefficients of variation were 5–8% over the dynamic range of the assay (2–1000 IU/L).Pregnancy was defined as a serum hCG concentration ≥10 IU/l on the 16th day after ovulation (equivalent to the 30th day after the last menstrual period in the general population). After initial confirmation of pregnancy following an increase in hCG levels, a non-progressive pregnancy was established either by a reported miscarriage before 6 weeks of gestation, or by the absence of an embryo sac or empty embryo sacs detected by ultrasound around 6–7 weeks of gestation. Loss of pregnancy thereafter was not included in this study.

Results of the study: The total percentage of non-developing pregnancy was 16%. The risk of miscarriage was not linearly related to either age or BMI. Although women over 40 had an increased risk, this was not significant after adjusting for other factors. The risk for both lean (BMI <18.5 kg/m2) and very obese (BMI>35 kg/m2) women was also not significantly higher on multivariate analysis. There was no effect of PCOS. Smoking or "poor quality" embryo transfers were associated with a significantly increased risk of non-progressive pregnancy after adjusting for other factors.

The risk factors for non-progressive pregnancy studied in this study were: maternal age, body mass index (BMI, kg/m2), smoking status and polycystic ovary syndrome (PCOS), infertility etiology, response to stimulation (both maximum concentration of estradiol and number of oocytes retrieved), quasi-measurement of embryo quality (see Table I for details), and type of treatment. Patient age and BMI were classified for clarity in data analysis and presentation of results. Four age subgroups were formed: age ≤30 years, 30.1–35 years, 35.1–40 years, and >40 years. BMI subgroups were: <18.5 kg/m2 (lean), 18.5–25 kg/m2 (normal), 25.1–30 kg/m2 (overweight), 30.1–35 kg/m2 m 2 (obesity 1-degree) and ≥35.1 kg. / m 2 (obesity 2-degree). In 73 cases (6%), BMI was not recorded and was considered absent in the analysis. PCOS was defined by both ultrasound scans and hormonal measurements as previously defined. Analysis of variance (ANOVA) and χ 2 test or Fisher's exact test using SPSS (version 10.0 for Windows, Chicago, USA) were used. The results were presented as an odds ratio (OR) and its 95% confidence interval (CI) calculated using a logistic regression model.

The mean age of the study group at the time of treatment was 32.7 years (SD = 4.7, range 19.2–47.1). Mean BMI was 24.7 kg/m 2 (SD = 5.0, range 14.8–50.9). Sixty-eight percent of the women were ≤35 years of age. Fifty-nine percent had a

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normal BMI (18.5–25 kg/m 2), while obese women (BMI > 30 kg/m 2) and grade 2 obesity (BMI > 35 kg/m 2) accounted for 13 % of the study population.

A total of 19 (16%) pregnancies ended as miscarriages in the study population. There was no clear linear trend in the risk of non-developing pregnancy depending on age or BMI (table 1). In women under 40 years of age, the risk of non-progressive pregnancy was very similar at about 15–17%, while in women over 40 years of age the risk was significantly increased (23%) compared with the rest (P<0.05). There were some differences in the risk of EPL between BMI groups, with the lowest risk of non-progressive pregnancy (12%) observed in overweight women (25–30 kg/m2), while thin women (<18.5 kg/m 2) had a much greater risk, 35% (P < 0.01) and very obese women (>35 kg/m 2) had a slightly increased risk (20%, P= 0.16). Normal weight women (18.5–25 kg/m 2) also had a significantly higher risk of non-progressive pregnancy than the overweight group (18% vs 12%, P < 0.05). There was a significant increase in risk (P < 0.05) in women treated with IVF compared with those treated with ICSI or GIFT (in combination).Smoking was associated with a significant increase in risk (P < 0.001) in a missed pregnancy. There appeared to be little effect on the level of response to ovarian stimulation, as determined either by peak estradiol concentration or by the number of oocytes retrieved. Women who transferred the worst “quality” embryo(s), characterized by unjustified single embryo transfer, were at highest risk (P < 0.01) in contrast to multiple embryo transfers, especially planned two or three embryo transfers, when women were likely to receive embryos of the highest quality. Patients' PCOS status was not significantly (P=0.05) associated with an increased risk, while the etiology of infertility was not associated with any significant increased risk of non-progressive pregnancy.

Discussion

In this population, there were 16% of non-developing pregnancies. Although both smoking and the lowest quality embryo transfer were significant risk factors for a miscarriage, there was no evidence that the other factors considered in the study had a significant impact on the risk of a miscarriage.

Both in the general population and in the population receiving ART, there is a high loss of pregnancy in the form of non-developing pregnancy. The risk of miscarriage, 16%, indicated in this study is lower than estimates given for the general population. However, a direct comparison of the two populations can be problematic because, generally speaking, general population studies have used more sensitive assays, earlier hCG measurement, and a lower hCG criterion for detecting pregnancy. Another possible factor that may complicate early detection of pregnancy in ART is the widespread use of high doses of hCG to induce ovulation or support lutein. Early work, however, suggested that residual hCG, either as a result of ovulation induction or lutein support, could be reduced to undetectable levels during early pregnancy diagnosis. The practice of multiple embryo transfer in ART also means that some non-progressive pregnancies may be "hidden" by the continued growth of the companion embryo(s).It is likely that the actual risk of a miscarriage will be higher in

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the ART population than in the general population, although direct evidence to support this claim remains to be obtained. In fact, there are many methodological differences between reported miscarriages in the ART population, which may explain the different risks of reported miscarriages. The risk of a miscarriage of 16% reported in this study is broadly in the range of several other reports of the ART population using similar criteria. The hCG level used here to determine pregnancy was within the sensitivity of the hCG assay, although it was below the accepted clinical criterion for a positive pregnancy (>30–50 IU/L) that is commonly used to inform patients and is considered conservative. On the other hand, since the criterion used in this study, hCG > 10 IU/L at day 16, was much higher than the criterion used in the general population studies, it can be expected that some very early miscarriages were not accounted for.

Couples who are planning a pregnancy want to be aware of the potential dangers, while those undergoing fertility treatment try to avoid any potential risk factors for pregnancy loss. Because a missed pregnancy causes a large reduction in the initial success of ART, it reduces its effectiveness and increases the psychological stress load on infertile couples. Thus, the establishment of risk factors for non-developing pregnancy is of great clinical importance for improving the effectiveness of ART treatment, as well as for improving understanding of the possible mechanisms of miscarriage in the early stages. The link between embryo quality and the risk of miscarriage is another interesting finding that needs to be confirmed. Although the quality of the embryo as defined here is not a direct measurement, it is known that selection from a large number of available embryos results in a higher clinical pregnancy rate. Thus, the high risk of miscarriage experienced by embryos transferred with little or no selection does suggest that current selection criteria seem to be capable of distinguishing the ability of embryos to grow after the initial stage of implantation. The lack of data due to the retrospective nature of the study did not allow us to adjust for their possible effect, and this may have reduced the sensitivity of the study.Another limitation of this study is the relatively high proportion of patients (38%) who did not return for an early pregnancy test, even if they had a luteal period of perhaps more than 16 days. The reasons why patients did not return for early pregnancy detection were usually personal. The comparison showed that this group was older by 0.8 years and had a lower BMI, 0.5 kg/m 2 less, both statistically significant.

However, given the fact that age and BMI were not risk factors for a miscarriage, small differences may not matter. On the other hand, there was no difference in the likelihood that they smoked or transferred poor quality embryos. Finally, smoking status was based on self-reports, which can be a source of error, in particular underreporting. However, in the present study, physicians obtained data at the time of consultation, and the population can be characterized as seeking specialized care for a long period of time. Even if underreporting were a likely

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scenario in this study, then the observed effect of smoking would be a conservative estimate rather than a reversal of the effect.

Thus, this study examined many factors for their potential association with the risk of miscarriage and found that smoking doubles the risk of miscarriage, and poor embryo quality is also associated with an increased risk of miscarriage. The influence of age, obesity and some other factors on the risk of non-developing pregnancy was not obvious.

Table I. Baseline and Adjusted Risk (OR) of Early Pregnancy Loss by Analysis
Not developing pregnancy (%) or 95% CI
* Seventy-three cases with missing BMI values.
**Embryo quality is defined as: 1 for selective transfer of one or two embryos; 2 for selective transfer of three embryos; 3 for non-selective transfer of two or three embryos; 4 for non-elective single embryo transfer.

Age (years) ≤30	Happening	Happening	Happening	Happening
	338	54 (16)	1,00	1,65
30.1–35	479	71 (15)	0,92	0,60–1,38
35.1–40	310	54 (17)	1,06	0,66–1,69
>40	69	16 (23)	1,52	0,72–3,19
BMD* <18,5	26	9 (35)	2,27	0,89–5,81
18,5–25	701	124 (18)	1,00	1,34
25.1–30	243	29 (12)	0,63	0,40–1,00
30.1–35	107	17 (16)	0,83	0,45–1,50
>35	46	9 (20)	1,34	0,59–3,01
IVF	501	96 (19)	1,00	1,52
IKSI	598	88 (15)	0,74	0,47–1,14
Smoking				
No	1060	155 (15)	1,00	2,33
Yes	136	40 (29)	2.00	1,27–3,15
Estradiol:				
<4 nmol/l	246	40 (16)	1,00	3,4
≥4 nmol/l	950	155 (16)	1,21	0,74–2,00

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Oocytes <4	88	20 (23)	1,00	1,21
4–6	213	39 (18)	1,02	0,48–2,15
7–9	250	41 (16)	1.13	0,50–2,56
10–12	225	40 (18)	1,23	0,52–2,90
13+	420	55 (13)	0,95	0,39–2,27
Embrions quality **				
1 (best)	606	79 (13)	1,00	1,56
2	207	33 (16)	0,96	0,57–1,62
3	330	64 (19)	1,34	0,88–2,11
4 (the poorest)	53	19 (36)	3,26	1,46–7,26
POS				
Нет	1076	16 (15)	1,00	2,44
да	120	31 (26)	1.30	0,57–2,04
Patients etiology				
Tubal obstruction	270	50 (19)	1,00	1,05
Endometriosis	107	20 (19)	1,05	0,56–1,97
Men`s etiology	416	65 (16)	1,06	0,62–1,79
Inexplicable	144	20 (14)	0,76	0,41–1,38
Other	259	40 (15)	1.13	0,64–1,98

OUTPUT:

1. Smoking and poor quality embryo transfer increased the % of miscarriages, while the effect of age, obesity, and other risk factors was not significant in multivariate analysis.
2. With the help of pre-gravid preparation, it is possible to increase the % of embryo survival and achieve normal gestational age.
3. By eliminating risk factors, it is possible to significantly reduce the percentage of embryo losses in the early stages of development after IVF.

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JAN-APR 2022
https://doi.org/10.5281/zenodo.6414056

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