



Full length article

Endometriosis doubles odds for miscarriage in patients undergoing IVF or ICSI



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ABSTRACT

Objective: To identify and estimate the importance of risk factors on pregnancy loss until the end of the second trimester after clinical pregnancy was achieved by either *in vitro* fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

Study design: Retrospective cohort study including 588 cycles with fresh embryo transfers and 150 cycles with frozen-thawed embryo transfers using logistic regression.

Results: The rate of miscarriages subsequent to a fresh embryo transfer was significantly increased by a diagnosis of endometriosis ($p = 0.02$), as well as significantly influenced by the age of the female patient at the time of oocyte retrieval ($p < 0.01$) and the serum level of testosterone ($p = 0.02$). The time between freezing and thawing of the pronuclear stages for a frozen-thawed embryo transfer revealed a trend to a higher rate of miscarriages ($p = 0.06$).

Conclusion: Endometriosis significantly decreases the chance of having a baby even with IVF or ICSI.

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Introduction

One of the most important issues confronting patients and their consulting physicians is calculating the risk of a miscarriage once the patient becomes pregnant. The psychological anxiety associated with this topic is quite severe, thereby necessitating the generation of reliable data for the practical advisement of patients. Consequently, it was the aim of this study to identify risk factors and their importance in *in vitro* fertilisation (IVF) treatments to support physicians in personalising their consultations. Furthermore, understanding the negative impact of these risk factors on embryonic development could lead to an improved take-home baby rate.

Risk factors, for which irrefutable evidence exist regarding their respective influences on pregnancy development, were included in this study in order to range their influence. These factors included thyroid pathologies as measured by thyroid-stimulating hormone (TSH) analyses, body mass index (BMI), nicotine abuse, and the patient's age at the point of oocyte retrieval. In addition, factors with an as yet unclear relation to the process of embryonic development were added to the study, including endometrial

thickness and endometriosis, testosterone serum level of the female patient, estradiol value prior to oocyte retrieval, intracytoplasmic sperm injection (ICSI), parity status, and the age of the male patient.

Endometriosis-associated factors

Studies examining the prevalence of endometriosis in women undergoing tubal ligation show a range from 1% to 7%, while studies examining women with infertility demonstrate a higher prevalence from 9% up to 50%. Thus the different prevalence of endometriosis suggests that this disease might be associated with infertility. Nevertheless, a lack of exact data exists concerning the prevalence of endometriosis in the general population as the diagnosis requires a surgical procedure. Consequently further research is hindered by the difficulty of creating a control group required in the design of a research study [1].

In addition, several attempts have been made to discover if any relationship exists between the different stages of endometriosis, as classified by the American Society for Reproductive Medicine (ASRM), and fertility [2]. A 2013 meta-analysis by Harb et al. discovered significant correlations only to ASRM stages III and IV, and only in terms of a lowered rate of clinical pregnancies and a decreased implantation rate. Concerning this group of progressed endometriosis, reduction of live births was reported only as a trend [3]. Moreover, a 2002 meta-analysis showed that endometriosis is

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negatively correlated with important sub-items of fertility, such as the absolute pregnancy rates (positive human chorionic gonadotropin) and the number of oocytes retrieved after hormonal stimulation compared to infertility patients without endometriosis. This meta-analysis indicates a stronger negative impact of the severe stages of this disease on the fertility of patients [4].

Age-associated factors

The significant effect of female age on pregnancy outcome is a well-established fact, but more clarification might be required for the areas of IVF and ICSI. Baker et al. stated that female age only affects pregnancy loss during the first 19 weeks, not later [5]. In this study, to account for the difference between the age of the eggs and the female's age with frozen embryo transfer (FET) cycles, the female age in the FET cycle analysis was specified at both the oocyte retrieval and the transfer date.

Hormone-associated factors

Being one of the so called Rotterdam criteria to diagnose polycystic ovary syndrome (PCOS), clinical and/or biochemical hyperandrogenism is strongly affiliated with this common syndrome [6]. The latest Rotterdam consensus agreed that miscarriage rates in PCOS patients show a range from normal rates following natural conceptions to increased rates after fertility treatment [7]. Testosterone serum level itself had no predictive value on the progress of an early pregnancy if measured at four to six weeks of gestation [8].

There is strong evidence that overt hypothyroidism and raised TSH-levels have a negative impact on pregnancy development, including an increased risk for spontaneous miscarriages, gestational hypertension or preeclampsia, as well as an association with an impaired neuropsychological development of the unborn child [9–11].

Less data has been published concerning estradiol values prior to oocyte retrieval. A 2004 published review summarizing the impact of the estradiol value at the date of human chorionic gonadotropin (hCG) administration, found conflicting findings in the various studies. Two of the reviewed studies found a higher pregnancy rate associated with higher E2 levels, two studies a lower rate, and five studies no association [12].

Lifestyle-associated factors

In addition to the numerous negative effects on general health, nicotine abuse was significantly associated with a higher spontaneous miscarriage rate, as well as with a lower birth rate per cycle and an overall lower pregnancy rate [13].

An increased maternal BMI has also been associated with a higher risk for foetal death and stillbirth [14]. It was found that in conceptions following IVF or ICSI treatment, overweight or obese patients have a decreased clinical pregnancy and live birth rate, as well as an increased miscarriage risk [15].

Treatment-associated factors

Baker et al. showed a reduced risk for a miscarriage in the first 12 weeks of pregnancy subsequent to ICSI when compared to treatment using only IVF [5].

Regarding cryopreservation of supernumerous oocytes no significant influence regarding the storage period of the embryos on the pregnancy rate, live birth rate or miscarriage rate has, to date, been discovered [16–18].

Materials and methods

Patients

All patients treated at the University Clinic of Düsseldorf, Germany, who achieved clinical pregnancy subsequent to IVF or ICSI between January 2007 and December 2011, were included in this retrospective cohort study. Every patient was included only with her first pregnancy even if she got pregnant more times during the recorded time period. Hormonal parameters like FSH, LH and testosterone were determined prior to the treatment start. During the controlled ovarian hyperstimulation estradiol was monitored, and the latest value before oocytal retrieval was used for the analysis. A clinical pregnancy was defined as the proof of a gestational sac by ultrasonic testing in the seventh week of pregnancy. The ultrasonic control was performed in all patients showing adequate and consecutively increasing hCG values. The hCG value was checked two weeks after oocyte retrieval and again one week later to verify the formation and development of a pregnancy. Ectopic pregnancies and cases with incomplete data were excluded from logistic regression.

Treatment protocol

Controlled ovarian stimulation was achieved by an antagonist protocol or an agonist protocol using recombinant and/or urinary gonadotrophins. Subsequent to retrieval, the oocytes were fertilised utilizing either IVF or ICSI. Any additional zygotes at the pronuclear stage (PN) were cryopreserved one day after IVF or ICSI. Two to five days after the retrieval, one to three embryos were transferred back. The luteal phase was supported by the administration of progesterone via the vagina for a period of two weeks.

Between 2007 and 2011 no methodological changes occurred to the slow freezing protocol, nor any changes to the medium (Sydney IVF Cryopreservation Kit, Cook Medical) or devices (CTE920, controlled rate freezer, Cryo Technik Erlangen). When required, PNs were thawed and transferred into the uterus after preceding hormonal preparation of the female patient.

Statistical analysis

The study population was divided into a fresh embryo transfer (ET) and a frozen-thawed embryo transfer (FET) group. Descriptive statistical analyses including all metric and non-metric data were performed separately for both groups (Tables 1–4). One-step binary logistic regression was then used to estimate the impact of the variables on a possible miscarriage (Tables 5–6). Predefined outcomes were either a miscarriage prior to the 24th week of pregnancy or a live birth, which included singletons, twins and triplets.

Variables tested in the fresh ET cycles included the female's BMI, the female's TSH value prior to oocyte retrieval, nicotine abuse (even occasionally), a living child born in the past, the male's age, the female's age at the date of oocyte retrieval, histological confirmation of endometriosis, thickness of the endometrium, testosterone serum level and the estradiol value measured before oocyte retrieval, as well as IVF vs. ICSI.

The same variables were also applied to the FET cycles, excluding only testosterone due to a lack of current serum levels in these patients. Female's age at the time of transfer and time between freezing and thawing of the PNs were added. Endometrial thickness and the estradiol value included in the logistic regression were measured before transfer.

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