DOI: 10.4274/anatoljmed.2023.87597
Anatol J Gen Med Res 2023;33(3):305-9

CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

ANATOLIAN JOURNAL of GENERAL MEDICAL RESEARCH

Pregnancy Rates Following High-quality Blastocyst Transfer in Patients with Variable Indications for ART Treatment

ART Tedavisi için Değişken Endikasyonları Olan Hastalarda Yüksek Kaliteli Blastokist Transferi Sonrası Gebelik Oranları

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Cite as: Köse C. Pregnancy Rates Following High-quality Blastocyst Transfer in Patients with Variable Indications for ART Treatment. Anatol J Gen Med Res 2023;33(3):305-9

Abstract

Objective: In recent years, blastocyst transfer has emerged as a significant advancement in assisted reproductive technology (ART), offering improved implantation potential and higher pregnancy rates than earlier-stage embryo transfers. This study aimed to investigate pregnancy outcomes following blastocyst transfer among diverse etiologies of infertility.

Methods: Analyses were conducted on 378 patients who underwent ART treatment between 2013 and 2022 at the Clinic of Obstetrics and Gynecology of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital. Subgroups were formed based on the causes of infertility: Poor ovarian reserve, hormonal ovulatory deficiency, male factor, tubal factor, and unexplained infertility. Demographic characteristics of patients, causes of infertility, blastocyst transfer outcomes, and resulting pregnancy rates were collected and analyzed.

Results: Three hundred seventy-eight patients underwent blastocyst transfer, and among them, 202 were pregnancy positive, resulting in a pregnancy rate of 53%. The subgroup success rates were as follows: Unexplained infertility, 16.4%; poor ovarian reserve, 6.1%; hormonal ovulatory deficiency, 17.8%; male factor, 18.3%; and tubal factor, 3.2%.

Conclusion: Our results showed that clinical pregnancy rates do not vary significantly across different etiologies.

Keywords: Assisted reproductive technology, poor ovarian reserve, hormonal ovulatory deficiency, blastocyst transfer

Öz

Amaç: Son yıllarda blastosit transferi, yardımla creme teknolojisinin (ART) önemli bir ilerlemesi olarak ortaya çıkmıştır; önceki dönem embriyo transferleri ile karşılaştırıldığında daha iyi implantasyon potansiyeli ve daha yüksek gebelik oranlar sunmaktadır. Bu çalışma, infertiliteye farklı etiyolojileri plan hastalarda blastosit transferi sonrası gebelik sonuçlarını araştırmayı amaçlamaktadır.

Yöntem: Sağlık Bilimleri Üniversitesi, İzmir Tepecik Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'nde 2013 ve 2022 yıllar arasında yardımla üreme teknolojisi (ART) tedavisi alan 378 hasta üzerinde analizler gerçekleştirilmiştir. İnfertilite nedenlerine göre aşağıdaki alt gruplar oluşturuldu: Düşük over rezervi, hormonal ovulasyon yetmezliği, erkek faktörü, tubal faktör, açıklanamayan infertilite. Hastaların demografik özellikleri, infertilite nedenleri, blastosit transferi sonuçları ve elde edilen gebelik oranları toplandı ve analiz edildi.

Bulgular: Üç yüz yetmiş sekiz hastada blastosit transfer yapıldı ve bunlardan 202'si menelik testi pozitif sonuçlandı, bu da %53'lük bir gebelik oranına işaret etti. Alt grup başarı oranları şöyleydi: Açıklanamayan infertilite %16,4, düşük over rezervi %6,1, hormonal ovülasyon yetmezliği %17,8, erkek faktörü %18,3, tübal faktörü %3,2.

Sonuç: Sonuçlarımız, klinik gebelik oranlarının farklı etiyolojiler arasında anlamlı öçlüde değişmediğini göstermektedir.

Anahtar Kelimeler: Yardımcı üreme teknolojisi, zayıf yumurtalık rezervi, hormonal yumurtlama eksikliği, blastosist transferi

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Received/Geliş tarihi: 27.09.2023
Accepted/Kabul tarihi: 18.10.2023
Online publication date/
Online yayın tarihi: 19.10.2023

Introduction

The World Health Organization, defines infertility as the incapacity to achieve pregnancy without medical intervention following twelve months of consistent, unprotected sexual activity. Frequently, infertility represents a form of reduced fertility in which expert assistance is required for successful conception. Reduced fertility can be primary or secondary. Primary reduced fertility denotes a postponement in achieving pregnancy for couples without any prior gestations, whereas secondary reduced fertility refers to a delay in conceiving for couples who have experienced previous pregnancies. In recent years, assisted reproductive assisted reproductive technology (ART) have revolutionized the field of infertility treatment, offering hope to couples struggling to conceive naturally. The causative factors are evenly shared between males and females. The majority of couples facing infertility encounter one of three principal factors, which encompass male-related issues, dysfunctional ovulation or tubal-peritoneal disease[1]. Infertility affects approximately 10% of the world's population. Worldwide, more than 7 million children have now been born by ART[2]. ART includes standard in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). The main objective of ART treatment is to achieve the birth of a single, healthy infant for individuals undergoing such procedures.

Male infertility is mostly related to deficiencies in sperm transport or spermatogenesis. The diagnosis can be confirmed by evaluating semen analyzes gonadotropin and other assays[3].

Routinely, ART embryos are typically transferred into the uterus on either the second or third day after fertilization, when they have reached the stage of development of four to eight cells, i.e., cleavage stage embryos. This approach did not result in high pregnancy rates (PRs) compared with embryos transferred at the blastocyst stage[4]. Improvement of culture media allowed extended embryo culture, facilitating daily monitoring of embryos up to the 5th day after fertilization. In terms of the natural selection and transfer of the embryo with the highest chances of implantation and clinical pregnancy, blastocyst culture and transfer are advantageous compared with day 3 cleavage stage transfers[5]. Blastocyst transfer, which involves the transfer of embryos at the blastocyst stage (typically on day 5 or 6 of development), has gained popularity because of its potential to yield higher implantation and pregnancy rates. Despite its advantages, there remains a need to understand how blastocyst transfer outcomes vary across different patient indications for ART treatment. However, there have been few studies on the effect of infertility etiology. Thus, we assessed the role of etiology in ART pregnancy outcomes in a retrospective cohort study. The aim of this study was to understand the variation in pregnancy outcomes among different etiologies of infertility. This is essential for tailoring treatment approaches and optimizing ART success.

Materials and Methods

This was a retrospective review of medical records of patients who underwent ART treatment at a single tertiary infertility clinic in the Clinic of Obstetrics and Gynecology in University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital between 2013 and 2022 years. The study was approved by the Institutional Clinical Research Ethics Committee (date: August 23; number: 2023/07-17). The inclusion criteria encompassed patients who underwent high-quality blastocyst transfer, as determined by embryologists based on well-defined morphological criteria. Patients with varied indications for ART treatment, including male factor infertility, female factor infertility, and unexplained infertility, were included in the study. The exclusion criteria involved patients with severe endometriosis, uterine abnormalities, and other medical conditions that could impact the ART outcome.

Ovarian stimulation in females was performed using the gonadotropin-releasing hormone antagonist protocol, accompanied by recombinant follicle stimulating hormone (Gonal F, Merck Serono). Upon the attainment of a size exceeding 17-18 mm in diameter for more than two follicles, an injection of 10,000 IU human chorionic gonadotropin (hCG) (Ovitrelle, Merck Serono) was administered, leading to oocyte retrieval occurring 36 h after the hCG trigger. The collected oocyte cumulus complexes were purified in GMOPS Plus medium. After removing the cumulus cells attached to the oocyte by denudation in 80 IU hyaluronidases, the collected oocytes were cultured in G1 Plus medium (Vitrolife) for 15-30 min. ICSI was used according to our practice in all cases. After the preparation of the ICSI dish, an inverted Olympus microscope (IX 71) equipped with a Narishige micromanipulator (Narishige, Tokyo, Japan) and heated stage was used for the ICSI procedure. Sperm selection was performed under ×200-×400 magnification and sperms with near normal morphology were injected into the oocyte. Fertilization was assessed 16-18 h after insemination by the appearance of two distinct pronuclei and two polar bodies. The zygotes were cultured in G1 Plus medium (Vitrolife) at 37 °C in a Miri Esco incubator (6% CO_2, 5% O2, and 89% N2).

On day 3, embryo cell number and morphology were scored, and all embryos were subsequently transferred to medium G2 for a further 48 h of culture until day 5 of development. The embryos were transferred on day 5. Verification of pregnancy was achieved by assessing the β-hCG concentration (>80 mIU/mL) within the bloodstream precisely 10-12 days following embryo transfer (ET), with a subsequent twofold increase in β-hCG levels within 48 h. Clinical confirmation of pregnancy relied on the identification of a gestational sac through ultrasonography, which was conducted during the 7th on 8th week of gestation.

Blastocyst grading was performed according to the Gardner et al. [6] grading system:

1. An early blastocyst is defined asa blastocele with less than half the volume of the embryo.

2. A blastocyst is defined asa blastocele greater than or equal to half of the volume of the embryo.

3. A full blastocyst is defined as the blastocele completely filling the embryo.

4. Expanded blastocyst is defined asa blastocele volume larger than that of the early embryo and thinning of the zona pellucida.

5. Hatching blastocyst is defined as the trophectoderm that has started to herniate through the zona pellucida.

6. Hatched blastocyst is defined asa blastocyst that has completely escaped from the zona pellucida.

For blastocysts 3, 4, 5, and 6, the development of the inner cell mass (ICM) grading is as follows: A. tightly packed, many cells; B. loosely grouped, several cells; C. very few cells. The trophectoderm (TE) grading is as follows: (A) many cells forming a tightly knit epithelium; (B) few cells; and (C) very few cells forming a loose epithelium.

According to this grading system, embryos were selected for transfer on day 5. Patients were assigned to top-scoring blastocysts for transfer as (≥3AA). Optimal blastocysts were those with trophectoderm cells and inner cell mass in the A and/or B groups, as shown in Figures 1-3.

Statistical Analysis

In the statistical evaluation, SPSS v.28 (IBM) program was used. The chi-square test was employed for comparing categorical data. If the p-value was less than 0.05 in the comparisons, it was considered statistically significant.

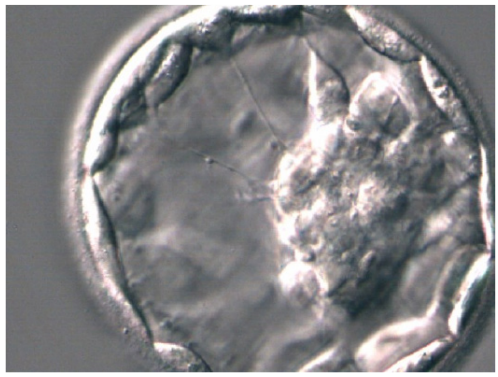

Figure 1. Good quality expanded blastocyst with a large compact shaped ICM. ZP is thinned. There appears to be cytoplasmic strings extending from the ICM to the TE

ICM: Inner cell mass, TE: Trophectoderm

Figure 2. Hatching blastocyst showing a large, compact ICM. There are very many TE cells of equivalent size making up a cohesive epithelium. Several TE cells have herniated out through a breach in the ZP

ICM: Inner cell mass, TE: Trophectoderm

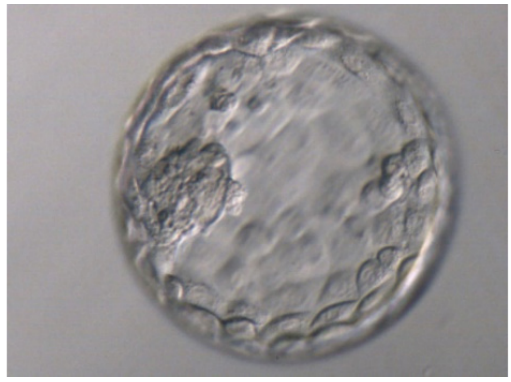

Figure 3. Blastocyst showing a large ICM. The ICM is made up of many cells that are tightly compacted. TE cells of equivalent size making up a cohesive epithelium

ICM: Inner cell mass, TE: Trophectoderm

Results

This study had a relatively small sample size with inadequate power to analyze differences between the subgroups. preliminary data analysis demonstrated 378 patients who met the inclusion criteria. The cohort consisted of patients with unexplained infertility, poor ovarian reserve (POR), hormonal ovulatory deficit (HOD), male factor, and tubal factor.

In our clinical practice, the indications for performing IVF are listed in Table 1, based on the reporting and payment criteria of social security institutions. These indications have been categorized under a single heading by evaluating the couples at one dominant parameter.

The overall pregnancy rate following high-quality blastocyst transfer was 53% across all indications.

Number of cases depending on IVF indications were.

Unexplained infertility was 117, POR was 39, HOD was 70, male factor was 120, and tubal factor was 32.

Out of 117 unexplained infertility cases, 62 cases were pregnancy positive, which yielded 30.7% of all pregnancy-positive results and 53% of success within the group. Twenty-three cases out of 39 were positive for POR, yielding 11,4% of all pregnancy-positive results and 59% of success within the group. Thirty-six cases out of 70 were positive for HOD, yielding 17.8% of all pregnancy-positive results and 51.4% of success within the group. 69 cases out of 120 were positive for the male factor, yielding 34.2% of all pregnancy-positive results and 57.5% of success within the group. 12 cases out of 32 were positive for the tubal factor, yielding 5.9% of all pregnancy-positive results and 37.5% of success within the group.

The cumulative pregnancy rates with the available data were calculated as follows:

A total of 378 patients underwent blastocyst transfer, and among them, 202 were pregnancy positive, resulting in a pregnancy rate of 53%. The subgroup success rates were as follows: unexplained infertility, 16.4%; poor ovarian reserve, 6.1%; hormonal ovulatory deficiency, 17.8%; male factor, 18.3%; and tubal factor, 3.2%. Our results show that clinical pregnancy rates do not vary significantly across different etiologies.

Discussion

Female infertility may occur in the form of poor ovarian reserve, hormonal ovulatory deficiency, tubal factors, and unexplained cases. Male infertility factor is low semen quality, which is determined as reduced production of motile and normal sperm. Genetic abnormalities, hormonal imbalances, congenital abnormalities, and infections are common reasons for infertility in women and men. Lifestyle factors such as obesity, diet, metabolic disorders, smoking, and alcohol consumption, along with exposure to environmental chemicals and advanced age, have been identified as infertility modifiers[7].

In our clinical practice, the indications for performing IVF may be shaped by the reporting and payment criteria of social security institutions. These indications were categorized under a single heading by evaluating couples based on the dominant parameter. Although this simple classification may initially appear to be user-friendly for clinicians, it has become both mandatory and restrictive at a certain stage. IVF treatments, which do not have a long history, may have been initially useful for ease of classification, but in today's context, stating that the infertility is solely due to male factor or solely due to female factor or both are normal, may not accurately reflect the reality after a detailed evaluation of both partners. Some dominant parameters are essential and useful for diagnosis, but experts in reproductive medicine are aware that such classification may overlook certain subgroups. For instance, a couple diagnosed with a male factor due to azoospermia may also have some problems identified in the female partner. In a couple diagnosed with a tubal factor, the male partner may have cryptozoospermia.

Table 1. Results of IVF embryo transfer according to etiology

Etiology	Pregnancy rates (within the etiological subgroup)	Etiological distribution of pregnancy rates	Cumulative pregnancy rate	p-value
Unexplained infertility	62/117 (53%)	62/202 (30.7%)	62/378 (16.4%)	0.323
POR	23/39 (59%)	23/202 (11.4%)	23/378 (6.1%)	
HOD	36/70 (51.4%)	36/202 (17.8%)	36/378 (17.8%)	
Male factor	69/120 (57.5%)	69/202 (34.2%)	69/378 (18.3%)	
Tubal factor	12/32 (37.5%)	12/202 (5.9%)	12/378 (3.2%)	

IVF: In vitro fertilization, POR: Poor ovarian reserve, HOD: Hormonal ovulatory deficit

Not including dual diagnoses alongside the dominant diagnosis when evaluating couples may result in the inability to create subgroups and perhaps lead to disregarding the principle that there is no disease but rather an infertile patient in infertility practice. The absence of differences between indications in our study or in other words, our results show that clinical pregnancy rates do not vary significantly across different etiologies, which may be due to this limitation in diagnosis.

Choosing the best quality embryo for transfer is one of the most complex clinical dilemmas within ART treatment. The objective of embryo grading at any developmental stage is to identify embryos with superior implantation potential. By possessing the capability to forecast which embryos are most optimal for transfer, we can enhance implantation and pregnancy success rates while concurrently reducing the likelihood of multiple pregnancies[6].

Blastocyst transfers offer several advantageous[8], including improved timing for implantation, prolonged selection of superior embryos with robust developmental potential, theoretical augmentation of blastocyst implantation rates, which may permit the transfer of one or two embryos with favorable pregnancy outcomes, and the possibility of cryopreservation of blastocyst-stage embryos.

The findings of this study emphasize the importance of considering patient-specific indications when assessing the success of high-quality blastocyst transfers in ART treatment. The variation in pregnancy rates among different indications underscores the complexity of infertility cases and highlights the need for tailored treatment approaches. Blastocyst transfer, involving the transfer of embryos at the blastocyst stage, has gained prominence because of its potential to achieve higher implantation rates and ultimately increase the chances of successful pregnancies. However, it remains to be shown whether blastocyst transfer is the most suitable modality for all patients undergoing IVF[9]. Furthermore, it is not clear whether patients with poorer prognoses would fare better with day 3 ET combined with assisted hatching. Additional research is required to help elucidate this issue. Factors such as embryo quality, uterine receptivity, and underlying medical conditions play pivotal roles in determining the success of blastocyst transfer[10]. Few clinical studies have analyzed the results of blastocyst transfer in terms of pregnancy outcomes in different etiologies. The existing literature does not yet provide conclusive evidence regarding whether there is a proportional difference in pregnancy outcomes after the transfer of good-quality blastocysts in different etiologies. Our results show that clinical pregnancy rates do not vary significantly across different etiologies. This should be supported by future clinical trials.

Study Limitations

The main limitation of this study that can be addressed and overcome in future research is the relatively limited sample size.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital's Non-Interventional Research Ethics Committee (decision no: 2023/07-17, date: 02.08.2023).

Informed Consent: Retrospective study.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Forti G, Krausz C. Clinical review 100: Evaluation and treatment of the infertile couple. J Clin Endocrinol Metab 1998;83:4177-88.
2. Zegers-Hochschild F, Adamson GD, Dyer S, et al. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril 2017;108:393-406.
3. Jungwirth A, Giwercman A, Tournaye H, et al. European Association of Urology guidelines on Male Infertility: the 2012 update. Eur Urol 2012;62:324-32.
4. Bavister BD. Culture of preimplantation embryos: facts and artifacts. Hum Reprod Update 1995;1:91-148.
5. Ahlström A, Westin C, Reismer E, Wikland M, Hardarson T. Trophectoderm morphology: an important parameter for predicting live birth after single blastocyst transfer. Hum Reprod 2011;26:3289-96.
6. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril 2000;73:1155-8.
7. Bala R, Singh V, Rajender S, Singh K. Environment, Lifestyle, and Female Infertility. Reprod Sci 2021;28:617-38.
8. Bolton VN, Wren ME, Parsons JH. Pregnancies after in vitro fertilization and transfer of human blastocysts. Fertil Steril 1991;55:830-2.
9. Gardner DK, Schoolcraft WB. No longer neglected: the human blastocyst. Hum Reprod 1998;13:3289-92.
10. Bashiri A, Halper KI, Orvieto R. Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions. Reprod Biol Endocrinol 2018;16:121.