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Overlooked Details on Cleavage Versus Blastocyst Transfers When only One Embryo is Available

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Introduction

I read with interest the article entitled "When only one embryo is available, is it better to transfer on day 3 or to grow on?" published in Reproductive Biomedicine Online. This retrospective cohort study included a total of 1384 fresh and frozen cycles within 8 years of retrospective data [1].

When comparing cleavage (D3) and blastocyst stage (D5) outcomes in couples with exactly 1 embryo available on day 3 baseline patient characteristics, embryo grades and blastomere numbers on day3 were found to be mostly comparable. On the contrary, D3 transfers appear to increase both the chance of chemical and clinical pregnancy and also live birth compared to D5.

Despite the benefits of blastocyst transfers, it has been speculated that an in vitro environment is inferior to an in vivo environment. Higher blastocyst transfer cancelation rates are mainly attributed to the suboptimal conditions of the extended in vitro culture [2]. Performing a cleavage transfer reduces the risk of cancelation of the transfer for those patients.

However, when examining the publication, it is seen that there appear to be some critical flaws.

The study, which spans approximately 8 years, has exposed evolving practices, notably the increased utilization of blastocyst transfers and adoption of freeze-all cycles, potentially introducing biases. In particular, patients subjected to embryo biopsy were not excluded. As seen, biopsy procedures were performed at the blastocyst stage. It is known that the main indications for embryo biopsy include advanced maternal age, repeated implantation failure, and recurrent loss of pregnancy, which could accumulate patients with lower expectation of conception in the D5 group. The lower probability of pregnancy and live birth in the D5 group adds another layer of potential bias to the study.

On the other hand, statistically significant variations in gravidity and parity favor the D3 group, suggesting a probable higher prevalence of primary infertility in the D5 group, which also contributes to potential bias.

On examination of the supplementary materials, particularly Tables 2 and 3, the reader can access the results presented per embryo transfer, both for total and fresh cycles. Clinical pregnancy and live birth rates per embryo transfer were significantly reduced after blastocyst transfers. In this context, we understand that we are dealing with a critical flaw.

The current body of literature demonstrates that D5 embryo transfers are not inferior to D3, when analyzed both per transfer and also per patient [3-9]. D5 transfers have been shown to provide a more cost-effective and time-efficient policy (lower mean cycles and mean days per live birth), and higher ongoing pregnancy and live birth rates [10,11]. Recent evidence even reports higher cumulative live birth rates [12]. When examined, the study of Clua et.al., has represented lower results in the day-3 group. This randomized controlled trial has been prematurely stopped after poor initial results in the day 3 arm after interim analysis.

Embryo selection aims to shorten the time-to-pregnancy, while minimizing reproductive risks. Transfer of euploid blastocysts in an apparently receptive uterine environment offers the highest chance of embryo implantation [13]. Extended culture to blastocyst stage has been extensively demonstrated as an efficient strategy for reducing the rate of aneuploid embryos due to the selection of euploid embryos. Aneuploid embryos undergo delayed development and developmental arrest more frequently due to incomplete DNA replication, complex and/or chaotic aneuploidies, segmental duplications, and combination of meiotic and mitotic errors [14-21].

In this study, it is seen that there are potential differences between the characteristics of both groups. The results are also contradictory to current evidence and routine clinical practice. I believe that the above-mentioned details will be useful for future research.

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