Healthy live birth after blastocyst transfer following instant direct cleavage of the zygote into a three-blastomere embryo

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INTRODUCTION

Direct cleavage (DC) of the zygote into three blastomeres is typically considered a negative selection marker in embryo assessment [1]. Two types of DC are recognized: rapid DC (RDC), involving two mitoses in quick succession (t3–t2 < 5h) and instant DC (IDC), where a single mitotic event results in three daughter cells via tripolar division [2]. RDC embryos tend to have better developmental outcomes, whereas IDC embryos often arrest by day 3 and are associated with high rates of chromosomal abnormalities [3]. The terminology used in the literature varies: some studies group RDC and IDC together, whereas others define IDC as a direct one-to-three cell division, with no observable two-cell stage within the acquired images (t3–t2 = 0) [1,4,5,6]. In this framework, IDC embryos are considered to have poor prognosis, and to date, no live births have been conclusively documented from embryos confirmed to undergo IDC with visible nuclei in all three blastomeres.

METHODS

A couple with over one year of primary infertility (polycystic ovary syndrome and oligozoospermia; female aged 28) underwent an intracytoplasmic sperm injection cycle in October 2022. Embryos were cultured in G-TL medium (Vitrolife, Sweden) using the EmbryoScope time-lapse system (Vitrolife, Sweden). Two blastocysts developed: one on day 5 (bl3.2.2) and one on day 6 (bl5.3.3; Figure 1G). The day-5 blastocyst failed to implant after fresh transfer. The day-6 blastocyst was frozen and transferred in a subsequent cycle, resulting in a birth of a child in August 2023.

RESULTS & DISCUSSION

We report a first case of a healthy live birth (the Apgar score was 10) following the transfer of a day-6 blastocyst that developed from a zygote exhibiting IDC with visible nuclei in all three blastomeres (Figure 1A–E). The couple returned in December 2024 to begin another IVF cycle and confirmed the healthy development of their child.

The first mitotic division of the human embryo is highly error-prone [7] and abnormal cleavage patterns can only be detected using time-lapse imaging technology. Time-lapse imaging captures embryo development at fixed 10–20-minute intervals, reliably documenting direct and rapid cleavage events, but it may miss the full dynamics of trichotomous mitosis, such as the formation of multiple cleavage furrows. The molecular and cellular mechanisms underlying tripolar mitosis remain incompletely characterized, even in model organism like Caenorhabditis elegans, where formation and potential self-repair of tripolar spindles have not been fully elucidated [8,9]. Recent work in C. elegans suggests that cells with tripolar spindles can mitigate the risk of aneuploidy through intrinsic compensatory processes, indicating that even abnormal spindle configurations may be subject to partial mechanical correction [9].

In our case, we observed asynchronous cleavage furrow formation during the trichotomous division event, which may represent an uncharacterized repair mechanism in oocytes bearing tripolar spindles, potentially leading to the inheritance of a normal chromosome number in one blastomere. Additionally, not all daughter blastomeres were incorporated into the morula (Figure 1F), which may indicate the presence of an alternative repair mechanism described in the literature as a means of removing surplus genetic material by excluding these cells from the developing blastocyst [3,6,10]. Even so, the likelihood of obtaining a viable blastocyst from instant direct cleavage embryos remains extremely low – as little as 0.43% [3].

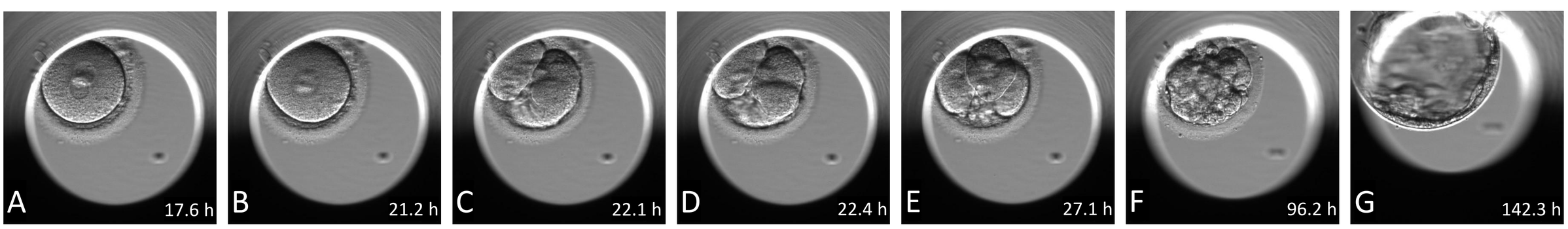

Figure 1. Instant direct cleavage from 1 to 3 cells (A–D), visible nuclei in all three blastomeres (E), partially compacted morula with excluded cells (F) and outcome on day 6 (G).

CONCLUSIONS

This clinical case supports the possibility that embryos with IDC, which are typically excluded from transfer, may reach the blastocyst stage and result in healthy live births through intrinsic self-correction mechanisms that appear to be more efficient in younger women. Therefore, we recommend not transferring IDC embryos on day 3, even if their morphological grade appears good, but rather culturing them until day 5, to the blastocyst stage.

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