



Letter to Editor

Asian Pacific Journal of Reproduction

Journal homepage: <https://journals.lww.com/apjr/>

doi: 10.4103/apjr.apjr_232_25

Revisiting blastocyst biopsy strategies in modern IVF practice: Lessons from Capalbo *et al* 2014 and 2016Thinh Ngo Van[✉], Dung Le Thi Thuy, Nhung Dang Thi Huyen, Trang Nguyen Ha

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Trophectoderm (TE) biopsy has become the preferred approach in preimplantation genetic testing, providing clear advantages over polar body and cleavage-stage biopsy. However, the optimal timing and methodology for blastocyst biopsy remain subjects of ongoing debate.

McArthur *et al* in 2005 were the first to demonstrate the safety of TE biopsy at the hatching blastocyst stage with laser-assisted opening in the zona pellucida (ZP) on Day 3, reporting 100% survival of 1050 biopsied blastocysts, all of which re-expanded, with an implantation rate of 41%[1]. Nearly a decade later, Capalbo *et al* in 2014 introduced a modified strategy, performing biopsy on fully expanded blastocysts by creating a laser-assisted ZP opening and immediately aspirating TE cells on Day 5. This strategy was considered more physiological, as intervention was delayed until complete blastocyst expansion[2]. However, it posed significant technical challenges because the procedure required advanced operator expertise, making widespread standardization difficult[3]. Several subsequent studies nonetheless suggested that Capalbo *et al*'s 2014 strategy may offer superior clinical outcomes compared with McArthur *et al*'s strategy.

In 2016, Capalbo *et al* proposed an alternative strategy: creating a ZP opening in fully expanded blastocysts and allowing natural hatching for a few hours before biopsy[4]. This strategy was easier to implement and eliminated the risk of inner cell mass (ICM) herniation reported with McArthur *et al*'s strategy. However, it introduced the potential disadvantage of exposing blastocysts twice to suboptimal culture conditions. Despite this concern, the 2016 strategy proposed by Capalbo *et al* has also been widely adopted in *in vitro* fertilization (IVF) laboratories worldwide. It should be noted, however, that no direct clinical comparison between the 2014 and 2016 strategies has yet been conducted, and current evidence remains largely theoretical.

On the other hand, several important practical issues remain unresolved. In the 2016 strategy proposed by Capalbo *et al*, if a blastocyst does not hatch within a few hours after ZP opening, embryologists face two options. One is to proceed with biopsy

immediately, which effectively combines elements of the 2014 strategy but exposes the blastocyst to an additional round of manipulation and potential stress (since waiting for the blastocyst to begin hatching, the collection of a few TE cells for biopsy may need to be performed outside regular working hours, which is not compatible with the standard workflow of IVF laboratories). The other option is to wait until the next day in the hope of natural hatching, though this delay may reduce the embryo's developmental competence. The consequences of either decision for ultimate clinical outcomes remain uncertain, as no robust evidence currently exists.

From a theoretical standpoint, Capalbo *et al*'s 2014 strategy provides the advantages of being more feasible for routine laboratory practice and reducing the need for repeated blastocyst handling. However, it is technically demanding and carries a higher risk of disturbing the ICM when performing biopsy on collapsed blastocysts[3]. In contrast, Capalbo *et al*'s 2016 strategy is easier to implement, but its effectiveness has not been validated through prospective studies. For this reason, carefully designed, randomized, multicenter trials are urgently needed to directly compare these two strategies with respect to clinical outcomes. Robust clinical evidence is essential for the IVF community to establish a standardized, evidence-based practice that maximizes the safety of blastocysts and optimizes treatment outcomes.

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How to cite this article: Thinh NV, Dung LTT, Nhung DTH, Trang NH. Revisiting blastocyst biopsy strategies in modern IVF practice: Lessons from Capalbo *et al* 2014 and 2016. *Asian Pac J Reprod* 2025; 14(6): 285-286.

Article history: Received: 17 September 2025; Revision: 21 October 2025; Accepted: 10 November 2025; Available online: 24 December 2025

Conflict of interest statement

The authors declare no conflicts of interest.

Funding

The study received no extramural funding.

Authors' contributions

Thinh Ngo Van conceptualized the study idea, conducted the literature review, drafted the manuscript, participated in detailed discussions, and revised the manuscript. Dung Le Thi Thuy, Nhung Dang Thi Huyen, and Trang Nguyen Ha contributed to the overall conceptualization, participated in detailed discussions, and critically reviewed and improved the manuscript.

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Edited by Lin LY