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Commentary

Blastocyst Rebiopsy and Clinical Outcomes: How are Biopsy Day and Embryo Grading Relevant?

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As with any assisted reproductive technology, blastocyst stage embryo biopsy for comprehensive chromosome screening continues to evolve in FET cycles as a strategy to optimize reproductive outcomes for the patient, decrease the risk of fetal loss due to whole chromosome aneuploidy, and to limit risk of transferring single gene disorders to the offspring. The concern for embryo damage with embryo biopsy has been addressed multiple times in the literature; however, embryo rebiopsy for a non-actionable original result has not been robustly investigated. Further, there is significant variation in embryo morphologic grading and quality and this can variably affect the post biopsy recovery of an embryo. This commentary outlines how biopsy day and embryo scoring, in the setting of embryo re-biopsy, have been accounted in the studies and could potentially impact the current evidence on the topic [1-3].

Evidence on embryo rebiopsy indicates thus far a variable effect on the chances of pregnancy and live birth compared to treatment with embryos biopsied once [4]. In addition, a low number of PGT cycles with rebiopsied embryos have been reported in the studies (Table 1). Zhuo and colleagues(2023) found that rebiopsied euploid embryos exhibit significantly lower odds of implantation and pregnancy compared to single-biopsied euploid embryos [1]. Since trophectoderm subsequently forms the placenta, it is proposed that the multicellular TE biopsy intervention is associated with adverse obstetrical or neonatal outcomes in single frozen-warmed blastocyst transfer [5]. Regarding blastocyst rebiopsy, there is significant variation in findings with respect to blastocyst rebiopsy and obstetric and neonatal outcomes [6-8].

In addition to significant difficulty in isolation of the intervention of rebiopsy itself from covariates and confounding variables in ART studies, such as patients specific factors and treatment [9], the intrinsic quality of blastocysts undergoing rebiopsy rely on both the biopsy day and grading. In other words, the subfertility background and embryo characteristics should not be overlooked [4]. As a common practice in IVF labs, embryos with good morphologic scoring and/or have undergone biopsy once are chosen for transfer first. Conversely embryos that have poor morpholoy and/or are biopsied more than once are typically transferred last. Embryos with poorer morphology tend to require rebiopsy at a higher percentage than good morphologically graded embryos. Thus, a tendency to rebiopsy low-grade blastocysts on day 6 rather than day 5 has been reported [1-3]. Of note, as shown in table 1, rebiopsied blastocysts have been morphologically classified using different scales between studies and the expansion grade is poorly described. Larger sample size cohort studies controlling for confounders and meta-analysis are needed to generate more precise evidence which will be clinically significant for patient care moving forward.

Author	PMID/DOI	Number of rebiopsied embryos in single FET cycles	Biopsy day	Embryo grading scale	Grades As reported in the studies	Primary outcomes
Al Hashimi., *et al*. 2024	39024926	11	5,6,7	ACE/NEQAS embryo grading scheme Balaban., *et al*. [10]	High: AA, AB, BA or BB Low: CB, BC or CC	LBR*
Guarneri., *et al*. 2024	38557804	27	5,6,7	Istanbul Consensus	A 'top-quality' blastocyst was defined as an expanded or hatched blastocyst that scored "good" for one of the inner cell mass and multicellular trophectoderm parameters, and either "good" or "fair" for the second parameter.	CPR**
Theodorou., *et al*. 2024	38718702	50	5,6	Modified Gardner Cornell's criteria	AA, AB+, B + A, AB, BA, B + B+, and AB -	LBR Birthweight
Nohales., *et al*. 2023	37432589	71	5,6	Gardner and ASE-BIR criteria	Good: A,B Poor: C	CPR
Aluko., *et al*. 2021	33516664	15	5,6,7	Gardner criteria	Good: >3 expansion stage with a BB or better Fair: C grading Poor: early blastocyst of grade 1 or 2	LBR
Neal., *et al*. 2019	DOI: 10.1016/j.fertnstert.2017.07.822	36	5,6,7	Not reported in the Methods	Good Fair Poor	CPR
Cimadomo., *et al*. 2018	30239718	49	5,6,7	Method adapted from Gardner and Schoolcraft (1999) Capalbo., *et al*. [11]	Excellent: ≥3AA Good: 3,4,5,6 AB and BA Average: 3,4,5,6 BB, AC, CA Poor: ≤ 3BB	LBR
Bradley., *et al*. 2017	29100625	30	5,6,7	Simplified Gardner criteria	Excellent: grade 1 Good: Grade 2 Poor: Grade 3	CPR

Table 1: *Data collected on blastocyst grading and biopsy day in retrospective studies addressing clinical outcomes of rebiopsied embryos in single FET cycles.*

** LBR: Live Birth Rate; **CPR: Clinical Pregnancy Rate.*

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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