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The influence of Post Thaw Embryo Culture on FET outcomes – A Meta-Analysis

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Objective:

With the advent of vitrification, a significant proportion of embryo transfers now involve frozen-thawed embryos. However, there is conflicting evidence regarding the impact of culturing thawed embryos before transfer compared to immediate transfer. This systematic review and meta-analysis aimed to evaluate the impact of post-thaw culture duration on FET outcomes across different embryonic developmental stages.

Identification of studies via databases and registers



Study Design:

The analysis investigated four distinct post-thaw culture protocols: A. Day 2 extended vs. day 2 (N=879) B. day 3 extended vs. day 3 (N=11,204) C. day 3 extended to day 5/6 vs. day 5/6 (N=1,449) and D. day 5/6 extended to day 5/6 (N=3,883). Extended culture ranged from 18 to 48 hours. We adhered to PRISMA guidelines and conducted a comprehensive search of Medline, Embase, Web of Science, Cochrane, and relevant reference lists up to December 31, 2024, including observational and randomized trials exploring the association. Studies involving slow-frozen embryos or comparing outcomes of embryos transferred at different ages were excluded. Two independent reviewers performed data extraction. Pooled relative risks (RRs) with 95% confidence intervals (CIs) and heterogeneity were calculated. Fixed or random-effects models were applied based on the degree of heterogeneity.

Results:

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Day

Fourteen studies were included after screening nearly 1,500 abstracts[1-14]. Significantly improved implantation, clinical pregnancy, and live birth rates were demonstrated in groups B and C (RR for live birth 1.07 (95% CI 1.034-1.119) and 1.229 (95% CI 1.008-1.499) respectively). In contrast, the other groups showed either no improvement or adverse outcomes.

5+



Post thaw culture day 3 to Blast (5/6)	Vs.
Blast (5/6) no PTC	

Pos HCG PTC D3-D5/6. Vs. D5/6 no PTC

Study name		Statist	ics for e	ach stud	Y		Risk ratio and 95% CI
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value		
R. Rahav-Koren 20	211.163	0.955	1.418	1.501	0.133		┼╼╋──
P. C. Aytac 2022	1.069	0.928	1.231	0.926	0.354		
G. Onalan 2023	1.354	0.946	1.937	1.655	0.098		_
X. Li 2023	1.209	0.988	1.479	1.839	0.066		
Pooled	1.140	1.036	1.256	2.680	0.007		
						0.5	1



* Total number of references screened (322)

Post thaw culture day 5/6 to ext. Blast (5/6) Vs. Blast (5/6) no PTC

Embryo loss PTC D5/6 Vs. D5/6 no PTC

Study name		Stati	stics for each	study			0	dds rat	io an	d 95%		
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value							
Herbemont 2018	16.716	2.142	130.444	2.687	0.007							
M. Ciaffaglione 2022	0.734	0.338	1.596	-0.780	0.435				∎┼─	-		
H. Ji 2023	1.182	0.696	2.006	0.618	0.537			.	_			
Pooled	1.543	0.541	4.402	0.811	0.418							
Prediction Interval	1.543	0.000	207392.230			K-						
						0.1	0.2	0.5	1	2	5	1

Favours PTC

Favours No PTC



CPR D2 to D3 PTC

Risk ratio Lower limit Upper limit Z-Value p-Value R. Rahav-Koren 20211.268 0.994 1.617 1.915 0.056 P. C. Aytac 2022 1.250 0.998 1.566 1.940 0.052 G. Onalan 2023 1.423 0.964 2.098 1.777 0.076	
R. Rahav-Koren 20211.268 0.994 1.617 1.915 0.056 P. C. Aytac 2022 1.250 0.998 1.566 1.940 0.052 G. Onalan 2023 1.423 0.964 2.098 1.777 0.076	
P. C. Aytac 2022 1.250 0.998 1.566 1.940 0.052 G. Onalan 2023 1.423 0.964 2.098 1.777 0.076	├
G Onalan 2023 1 423 0 964 2 098 1 777 0 076	
0.0141411 2020 1.420 0.004 2.000 1.111 0.010	+
X. Li 2023 1.258 0.983 1.608 1.826 0.068	
Pooled 1.275 1.121 1.451 3.684 0.000	

Meta Analysis

Study name

Risk

Meta Analysis



Meta Analysis

Clinical Pregnancy PTC D5/6 Vs. D5/6 no PTC



Live Birth PTC D5/6 Vs. D5/6 no PTC

Study name		Statist	ics for e	ach stud	y		Ris	k rati	o an	d 95%	b CI	
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value							
Herbemont 2018	1.036	0.682	1.573	0.165	0.869			-	-+-	-		
M. Ciaffaglione 2022	1.113	0.970	1.277	1.519	0.129							
H. Ji 2023	0.914	0.827	1.009	-1.780	0.075							
Pooled	1.004	0.858	1.175	0.052	0.958				•			
Prediction Interval	1.004	0.189	5.329						+		 +	
						0.1	0.2	0.5	1	2	5	1
							Favou	rs PTC		Favours	No PTC	;

Clinical miscarriage PTC D5/6 Vs. D5/6 no PTC

Study name	Statistics for each study	Risk ratio and 95% CI
	Risk Lower Upper	

Post thaw culture day 3 to 3 ext. Vs. day 3 no PTC

CPR PTC D3-D3Ext. Vs. D3 no PTC



Lower Up limit ratio P. C. Aytac 2022 1.192 0.890 1 G. Onalan 2023 1.649 0.989 2. X. Li 2023 0.828 1.138

Live Birth PTC D3-D5/6. Vs. D5/6 no PTC

1.229 1.008 1 Pooled

Statistics for each study

Meta Analysis



Study name		Statist	ics for e	ach study	<u> </u>	Odds ratio and 95% Cl
	Odds ratio	Lower lim it	Upper limit	Z-Value	p-Value	
R. Rahav-Koren 2021	0.663	0.340	1.292	-1.207	0.228	
P. C. Aytac 2022	0.395	0.237	0.658	-3.567	0.000	
G. Onalan 2023	0.491	0.076	3.165	-0.748	0.455	
Pooled	0.479	0.322	0.712	-3.644	0.000	
						0.1 0.2 0.5 1 2 5

Favours No PTC Favours PTC

Meta Analysis

Clinical pregnancy loss PTC D3-D5/6 Vs. D5/6 no PTC

oper mit	Z-Value	p-Value				Herbemont 20
.597	1.181	0.238			-	Hwang 2020
.750	1.916	0.055				M. Ciaffaglion
.563	0.795	0.427			-	H. JI 2023 Pooled
.499	2.040	0.041			•	1 Obled
			0.5	1	2	
			Favours	No PTC Favours	S PTC	Meta Analysis

Risk ratio and 95% Cl

Favours No PTC

Favours P



LBR PTC D3-D3Ext. Vs. D3 no PTC

Meta Analysis

Meta Analysis



Study name	Statistics for each study			udy name			ach study	<u> </u>	Odds ratio and 95% Cl
	Odds ratio	Lower lim it	Upper limit	Z-Value	p-Value				
R. Rahav-Koren 2021	0.695	0.346	1.396	-1.023	0.306				
P. C. Aytac 2022	1.444	0.756	2.758	1.113	0.266	┃ ┃ ┃ ↓ ■↓→			
G. Onalan 2023	0.612	0.196	1.910	-0.845	0.398				
X. Li 2023	0.877	0.296	2.595	-0.237	0.813				
Pooled	0.942	0.628	1.414	-0.288	0.773				
						0.1 0.2 0.5 1 2 5			
						Favours PTC Favours No PTC			

Meta Analysis

Conclusions

Post-thaw culture strategies should be adapted based on the embryonic stage. While day 2 embryos seem to achieve better outcomes with immediate transfer, day 3 embryos may benefit from extended culture, especially when cultured to the blastocyst stage. In contrast, blastocyst-stage embryos do not show further improvement with extended culture. These results highlight the importance of stagespecific optimization of post-thaw protocols to improve FET success rates.

Lower oppe limit Z-Value p-Value limit ratio



Favours PTC Favours No PTC

Meta Analysis

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