

Supplementary Appendix

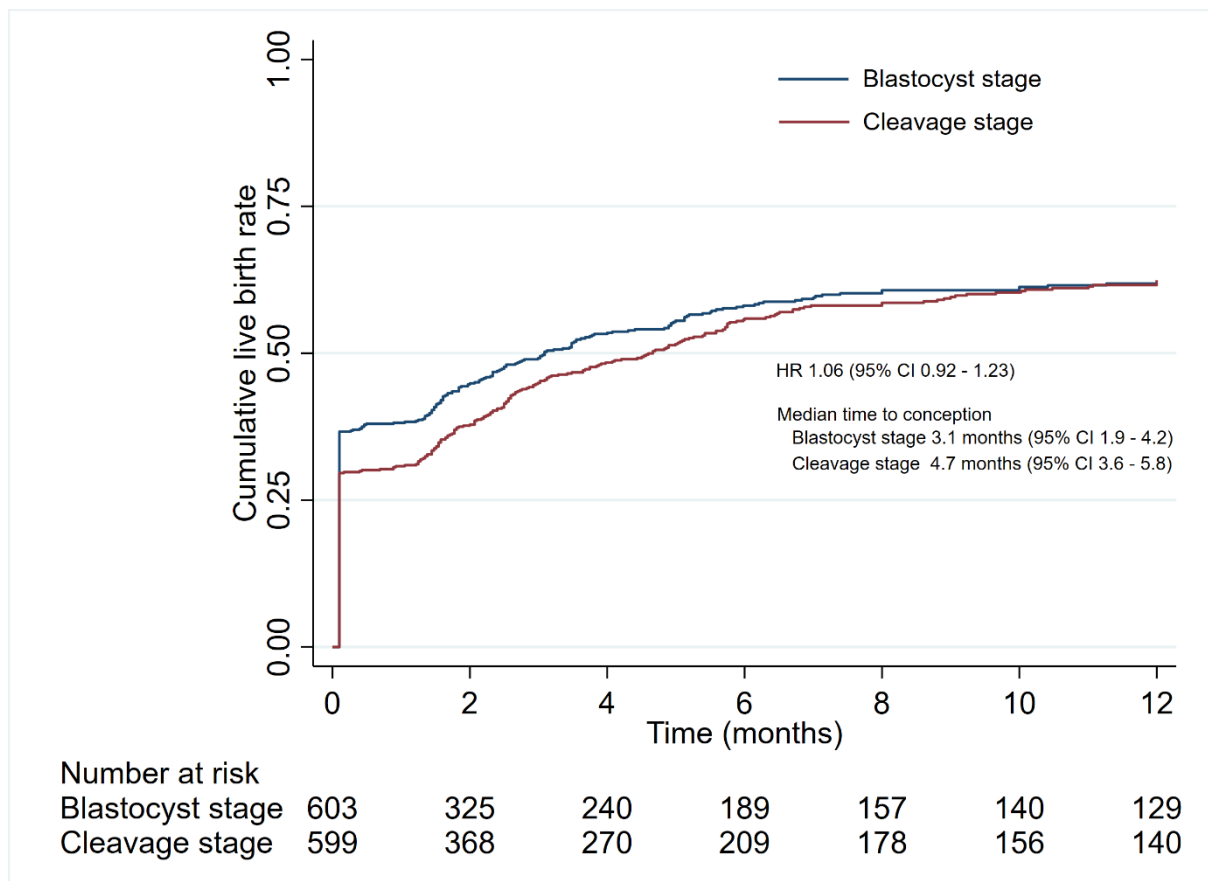
This appendix has been provided by the authors to give readers additional information about the work.

Supplement to: Cumulative live birth rate of a blastocyst versus cleavage stage embryo transfer policy during in vitro fertilisation in women with a good prognosis: multicentre randomised controlled trial.

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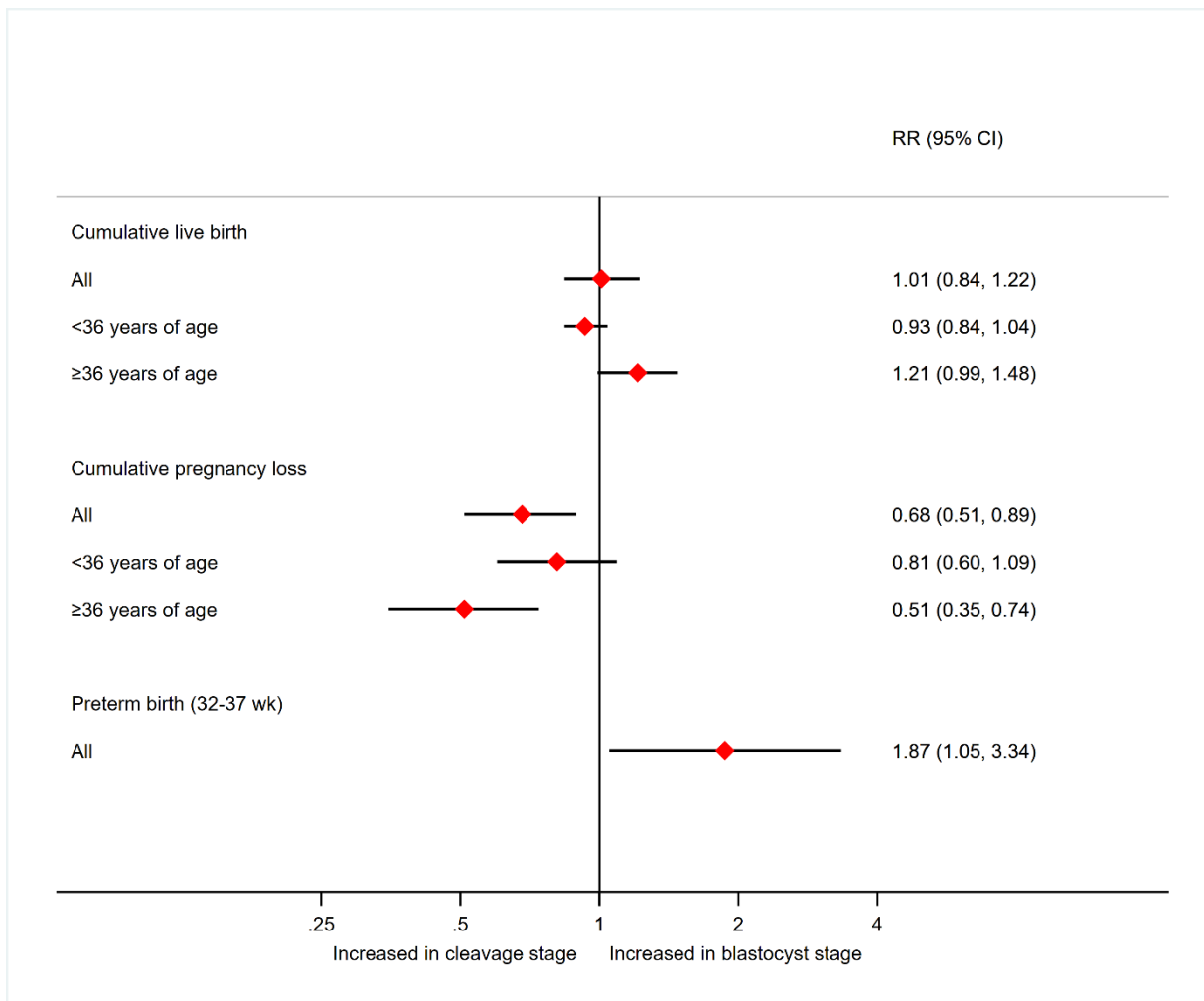
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Supplementary figure 1: Time-to-conception leading to a live birth



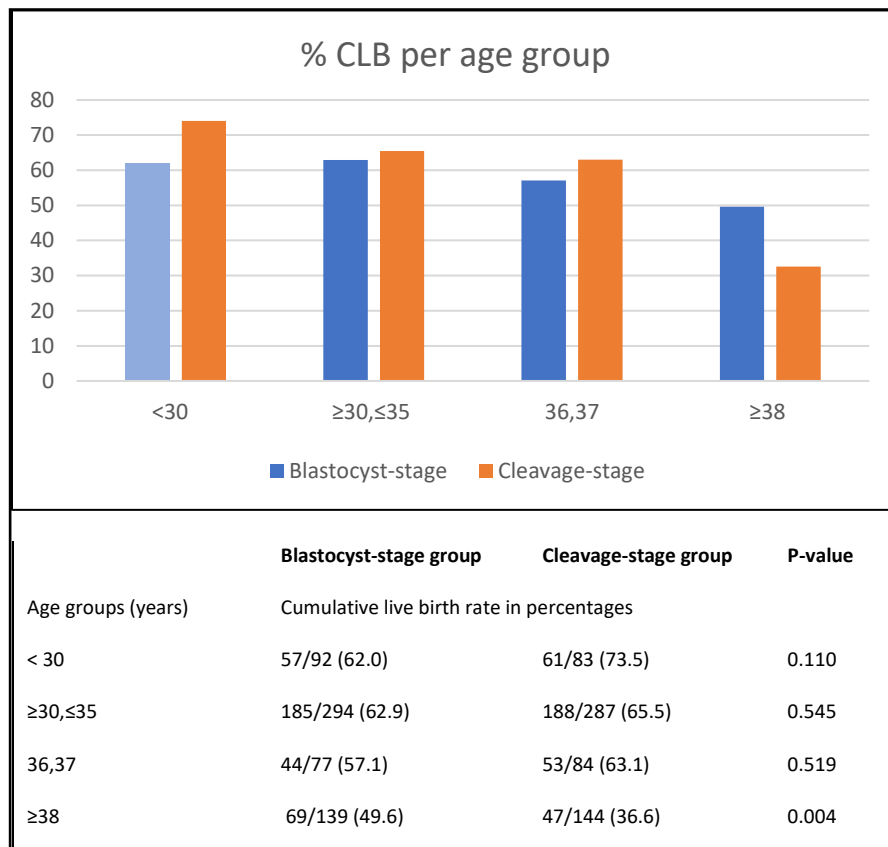
Cumulative conception leading to live birth expressed over a time horizon of 12 months. In the graph, the hazard ratio (HR) with corresponding 95% confidence interval is provided, as well as the median time-to-conception leading to a live birth. Beneath the graph, the number of patients at risk represent the number of non-pregnant patients and is given per time point. The log-rank P value for equality between the 2 graphs was 0.35 CI= confidence interval; HR=hazard ratio

Supplementary figure 2: Forest plot blastocyst-stage versus cleavage-stage transfer



Data are risk ratios (95% Confidence Interval)(see also Table 2)

Supplementary figure 3: Cumulative live birth rate per age group (subgroup analysis)



Data are n/N (%) unless otherwise stated

CLB= Cumulative live birth

Supplementary table 1: Cumulative live-birth and fresh embryo transfer results in the per protocol analysis

	Blastocyst-stage group (n=593)	Cleavage-stage group (N=556)	Absolute Difference (95% CI)	Risk Ratio (95% CI)
Cumulative results*				
Cumulative live birth rate	349/593 (58.9)	342/556 (61.5)	-2.6 (-8.2 to 3.0)	0.96 (0.80 to 1.16)
Cumulative ongoing pregnancy rate	356/593 (60.0)	346/556 (62.2)	-2.1 (-7.7 to 3.4)	0.97 (0.80 to 1.17)
Cumulative clinical pregnancy rate	372/593 (62.7)	374/556 (67.3)	-4.5 (-10.0 to 1.0)	0.94 (0.78 to 1.13)
Cumulative biochemical pregnancy	424/593 (71.5)	426/556 (76.6)	-5.1 (-10.1 to -0.1)	0.93 (0.78 to 1.12)
Cumulative pregnancy loss	98/593 (16.5)	131/556 (23.6)	-7.2 (-11.8 to -2.6)	0.70 (0.52 to 0.93)
Fresh embryo transfer results*				
Live birth rate	219/593 (36.9)	175/556 (31.5)	5.5 (0.0 to 10.9)	1.19 (0.94 to 1.49)
Ongoing pregnancy rate	223/593 (37.6)	178/556 (32.0)	5.6 (0.1 to 11.0)	1.19 (0.94 to 1.50)
Clinical pregnancy rate	239/593 (40.3)	195/556 (35.1)	5.3 (-0.3 to 10.9)	1.16 (0.93 to 1.45)
Biochemical pregnancy	280/593 (47.2)	242/556 (43.5)	3.7 (-2.0 to 9.5)	1.09 (0.88 to 1.34)
Pregnancy loss	61/593 (10.2)	67/556 (12.1)	-2.3 (-5.9 to 1.3)	0.81 (0.56 to 1.18)

Data are n/N (%) unless otherwise stated.

Biochemical pregnancy was defined as positive home pregnancy test 14–17 days after oocyte retrieval.

Clinical pregnancy was defined as the presence of at least one gestational sac 5-8 weeks after oocyte retrieval.

Ongoing pregnancy rate was defined as a viable intrauterine pregnancy with fetal heartbeat 10–12 weeks after oocyte retrieval.

Live birth rate was defined as a delivery resulting in a live born child after 24th week of gestation.

Pregnancy loss was defined as pregnancy loss after pregnancy was determined by a positive pregnancy test (<21 weeks).

Definitions for cumulative pregnancy and pregnancy loss rates were the same with the addition that at least one pregnancy or pregnancy loss occurred during the follow-up period of 1 year. Each woman could have multiple pregnancies due to the follow-up period of 1 year.

CI= Confidence Interval

*Absolute differences and risk ratios were adjusted for age group.

Supplementary table 2: Cumulative live-birth results in subgroups

	Blastocyst-stage group	Cleavage-stage group	Risk Ratio (95% CI)
Protocol			
GnRH antagonist	116/190 (61.1)	100/175 (57.1)	1.08 (0.77 to 1.51)
GnRH agonist	237/407 (58.8)	249/422 (59.0)	1.00 (0.70 to 1.25)
Fertilisation method			
IVF	154/279 (55.2)	142/271 (52.4)	1.07 (0.80 to 1.42)
ICSI	196/316 (62.0)	198/315 (62.8)	0.98 (0.76 to 1.26)
Both	5/7 (71.4)	10/13 (76.9)	0.94 (0.23 to 3.86)
Participants with single embryo transfers only	330/543 (60.8)	327/529 (61.8)	0.99 (0.81 to 1.20)
Transfer of blastocyst in blastocyst-stage group only*	349/558 (62.5)*	350/599 (58.4)	1.08 (0.89 to 1.30)
Method of cryopreservation: vitrification only	353/601 (58.7)	321/ 547 (58.7)	1.00 (0.83 to 1.21)
Per laboratory**/**			
A (2 centers)	11/17 (64.7)	10/20 (50.0)	1.25 (0.42 to 3.70)
B (4 centers)	99/162 (61.1)	91/149(61.1)	1.01 (0.70 to 1.44)
C (2 centers)	11/19 (57.9)	8/17 (47.1)	1.25 (0.41 to 3.84)
D (3 centers)	86/143 (60.1)	87/137 (64.0)	0.97 (0.66 to 1.42)
E (3 centers)	46/87 (52.9)	30/73(41.1)	1.27 (0.73 to 2.23)
F (1 centre)	1/5 (20.0)	3/5 (60.0)	0.32 (0.02 to 5.58)
G (1 centre)	18/41 (43.9)	24/55 (43.6)	1.01 (0.48 to 2.10)
H (1 centre)	10/11 (90.9)	9/11 (81.8)	1.11 (0.32 to 3.86)
I (1 centre)	18/23 (78.3)	19/33 (57.6)	1.38 (0.59 to 3.19)
J (2 centers)	33/64 (51.6)	49/67 (73.1)	0.72 (0.41 to 1.27)
K (1 centre)	22/31 (71.0)	20/33 (60.6)	1.12 (0.51 to 2.46)

Data are n/N (%) unless otherwise stated.

CI= Confidence Interval

Risk ratio was adjusted for age group.

* Participants with transfer of embryos with delayed development stage such as morula on day 5, were excluded

** A post-hoc subgroup analysis of laboratories revealed no interaction between laboratory and treatment on cumulative live birth rate (p=0.465)

*** Each laboratory always collaborated with the same centre(s). A post-hoc subgroup analysis performed with a generalised estimating model including centre as factor variable revealed a risk ratio of 1.009 (95% CI 0.918 to 1.109).

Supplementary table 3: Cumulative results according to definitions of infertility core-out come set

	Blastocyst-stage group	Cleavage-stage group	Absolute Difference* (95% CI)	Risk Ratio* (95% CI)
Cumulative results*				
Cumulative live birth rate	355/603 (58.9%)	350/599 (58.4%)	0.4 (-5.1 to 5.9)	1.01 (0.84 to 1.22)
Cumulative pregnancy loss	97/603 (16.1%)	130/599 (21.7%)	-7.9(-12.4 to -3.4)	0.67 (0.51 to 0.89)

Results according to the Standardizing definitions and reporting guidelines for the infertility core outcome set (Duffy et al 2020)¹⁰

Live birth rate was defined as a delivery resulting in a live born after 20th week of gestation.

Pregnancy loss was defined as pregnancy loss prior to 20 weeks of gestational age at delivery.

*Absolute differences and risk ratios were adjusted for age group.