

EMBRYO TRANSFER DURING OVARIAN STIMULATION CYCLE OR DURING DELAYED FET CYCLE IN NORMAL RESPONDERS: BALANCING EFFICIENCY AND SAFETY TO SHORTEN TIME TO LIVE BIRTH

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Disclosures

- Honoraria received for speaker engagements: Merck, Ferring Pharmaceuticals, MSD

Outline

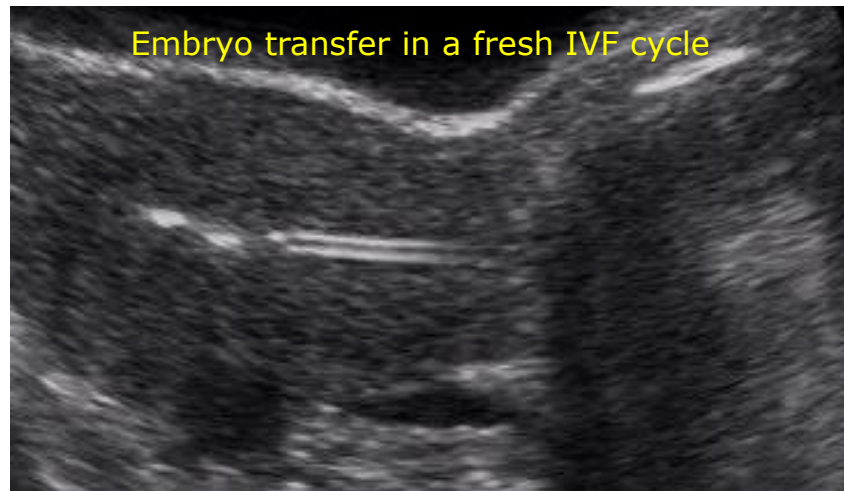
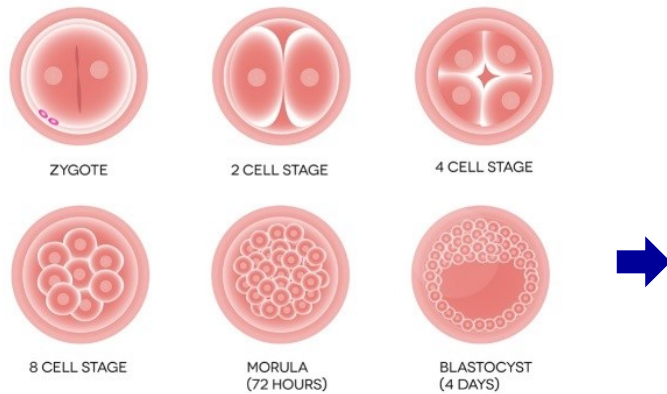
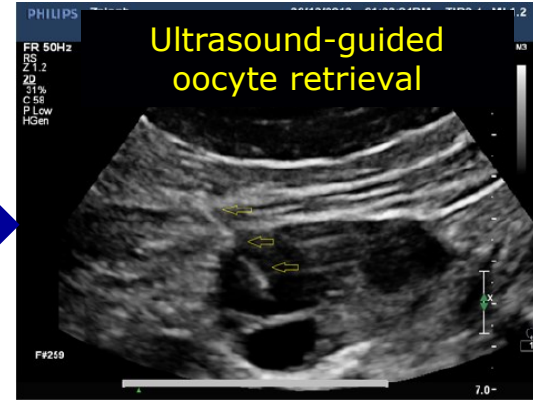
- Aim of ART
- Traditional IVF
- Fresh versus FET: clinical and safety outcomes
- Current evidence on freeze all strategy for normal responders

Aim of IVF

- Maximise success
- Healthy live birth
- Safety to the mother
- Long-term health implications of IVF conceived children



Traditional IVF



Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis

Shilpi Pandey¹, Ashalatha Shetty², Mark Hamilton¹,
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Higher risk of adverse obstetric and perinatal outcomes following IVF/ICSI compared to spontaneous conceptions

Outcome	IVF/ICSI conceptions, n	Overall effect (RR, 95% CI), fixed effect
APH	20,807	2.49 (2.30–2.69)
Congenital anomalies	4382	1.67 (1.33–2.09)
Hypertensive disorders of pregnancy	16,923	1.49 (1.39–1.59)
PPROM	14,141	1.16 (1.07–1.26)
Caesarean Section	12,950	1.56 (1.51–1.60)
Birthweight <2500 g	28,352	1.65 (1.56–1.75)
Birthweight <1500 g	27,105	1.93 (1.72–2.17)
Perinatal mortality	14,054	1.87 (1.48–2.37)
Delivery at <37 weeks	27,819	1.54 (1.47–1.62)
Delivery at <32 weeks	24,170	1.68 (1.48–1.91)
Transfer to NICU	3530	1.58 (1.42–1.77)
Gestational diabetes	13,399	1.48 (1.33–1.66)
Induction of labour	3557	1.18 (1.10–1.28)
Small for gestation age	13,207	1.39 (1.27–1.53)

GYNECOLOGY

Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology

Barbara Luke, ScD, MPH; Daksha Gopal, MPH; Howard Cabral, PhD; Judy E. Stern, PhD; Hafsatou Diop, MD, MPH

- Longitudinal cohort study
- 459,623 women with singleton live births in Massachusetts from Jul 2004–Dec 2010
 - Fertile – 441,420
 - Subfertile – 8,054
 - IVF – 10,149

Outcome	Fertility group	%	Fertile reference		Subfertile reference	
			ARR	95% CI	ARR	95% CI
Gestational diabetes ^b						
	Fertile	5.6	1.00	Reference	0.63	0.42–0.93
	Subfertile	8.5	1.60	1.08–2.36	1.00	Reference
	IVF	8.2	1.41	0.85–2.34	0.89	0.72–1.09
Pregnancy hypertension ^c						
	Fertile	8.6	1.00	Reference	0.89	0.83–0.96
	Subfertile	10.2	1.12	1.05–1.20	1.00	Reference
	IVF	12.6	1.22	1.15–1.28	1.08	1.00–1.18
Uterine bleeding						
	Fertile	0.6	1.00	Reference	0.60	0.48–0.75
	Subfertile	1.0	1.67	1.33–2.09	1.00	Reference
	IVF	2.6	3.80	3.31–4.36	1.08	1.77–2.93
Placental complications						
	Fertile	1.7	1.00	Reference	0.69	0.60–0.80
	Subfertile	2.7	1.44	1.26–1.66	1.00	Reference
	IVF	5.2	2.81	2.57–3.08	1.95	1.67–2.28

Higher risk of pregnancy complications in *subfertile* (vs fertile) women and *IVF-treated* (vs subfertile and fertile) women

Neonatal outcomes

Outcome	Fertility group	%	Fertile reference		Subfertile reference	
			ARR	95% CI	ARR	95% CI
Very low birthweight (<1500 g)						
	Fertile	0.8	1.00	Reference	0.65	0.52–0.83
	Subfertile	0.9	1.53	1.21–1.94	1.00	Reference
	IVF	1.5	2.15	1.80–2.56	1.40	1.06–1.86
Low birthweight (<2500 g)						
	Fertile	5.4	1.00	Reference	0.74	0.67–0.81
	Subfertile	5.7	1.36	1.24–1.49	1.00	Reference
	IVF	7.7	1.65	1.53–1.78	1.21	1.08–1.36
Small for gestational age						
	Fertile	8.0	1.00	Reference	1.03	0.94–1.12
	Subfertile	6.4	0.97	0.89–1.06	1.00	Reference
	IVF	7.8	1.04	0.97–1.12	1.07	0.96, 1.19
Large for gestational age						
	Fertile	9.5	1.00	Reference	0.96	0.90–1.03
	Subfertile	11.4	1.04	0.97–1.11	1.00	Reference
	IVF	9.4	0.91	0.78–1.06	0.88	0.74–1.04

Outcome	Fertility group	%	Fertile reference		Subfertile reference	
			ARR	95% CI	ARR	95% CI
Very premature (<32 wks)						
	Fertile	0.9	1.00	Reference	0.68	0.54–0.85
	Subfertile	1.0	1.48	1.18–1.85	1.00	Reference
	IVF	1.6	2.13	1.80–2.52	1.44	1.10–1.89
Premature (<37 wks)						
	Fertile	6.3	1.00	Reference	0.74	0.68–0.80
	Subfertile	7.7	1.35	1.25–1.47	1.00	Reference
	IVF	10.3	1.70	1.60–1.81	1.26	1.14–1.39
Birth defects						
	Fertile	1.6	1.00	Reference	0.82	0.70–0.97
	Subfertile	2.1	1.21	1.03–1.42	1.00	Reference
	IVF	2.1	1.25	1.09–1.44	1.03	0.84–1.27
Neonatal death (0–27 d)						
	Fertile	0.19	1.00	Reference	0.54	0.34–0.86
	Subfertile	0.24	1.85	1.16–2.95	1.00	Reference
	IVF	0.28	1.67	1.09–2.56	0.90	0.49–1.66

Adverse outcomes were > in *IVF-treated* (vs subfertile and fertile) women and in *subfertile* (vs fertile) women

Why do singletons conceived after ART have adverse perinatal outcome?

Systematic review and meta-analysis

- Underlying infertility
- ART procedures and techniques
- Epigenetic modification of embryos
 - Ovarian stimulation
 - Embryo culture
 - Cryopreservation

Perinatal outcomes after stimulated versus natural cycle IVF: a systematic review and meta-analysis

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Singleton births

Study or Subgroup	Stimulated IVF Events	Stimulated IVF Total	Natural or modified natural IVF Events	Natural or modified natural IVF Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Natural cycle IVF						
Mak 2015	73	174	59	190	61.4%	1.35 [1.03, 1.78]
Sunkara 2016	9223	96550	20	260	26.1%	1.24 [0.81, 1.89]
Subtotal (95% CI)		96724		450	87.5%	1.32 [1.05, 1.66]
Total events	9296		79			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.11$, $df = 1$ ($P = 0.74$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.35$ ($P = 0.02$)						
1.1.2 Modified natural cycle IVF with GnRH antagonist + gonadotrophin						
Bensdrop 2015	5	111	7	94	3.7%	0.60 [0.20, 1.84]
Pelinck 2010	15	161	12	158	8.8%	1.23 [0.59, 2.54]
Subtotal (95% CI)		272		252	12.5%	0.98 [0.52, 1.87]
Total events	20		19			
Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 1.09$, $df = 1$ ($P = 0.30$); $I^2 = 8\%$						
Test for overall effect: $Z = 0.05$ ($P = 0.96$)						
Total (95% CI)		96996		702	100.0%	1.27 [1.03, 1.58]
Total events	9316		98			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.94$, $df = 3$ ($P = 0.59$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.19$ ($P = 0.03$)						
Test for subgroup differences: $\chi^2 = 0.71$, $df = 1$ ($P = 0.40$), $I^2 = 0\%$						

PTB: <37 weeks

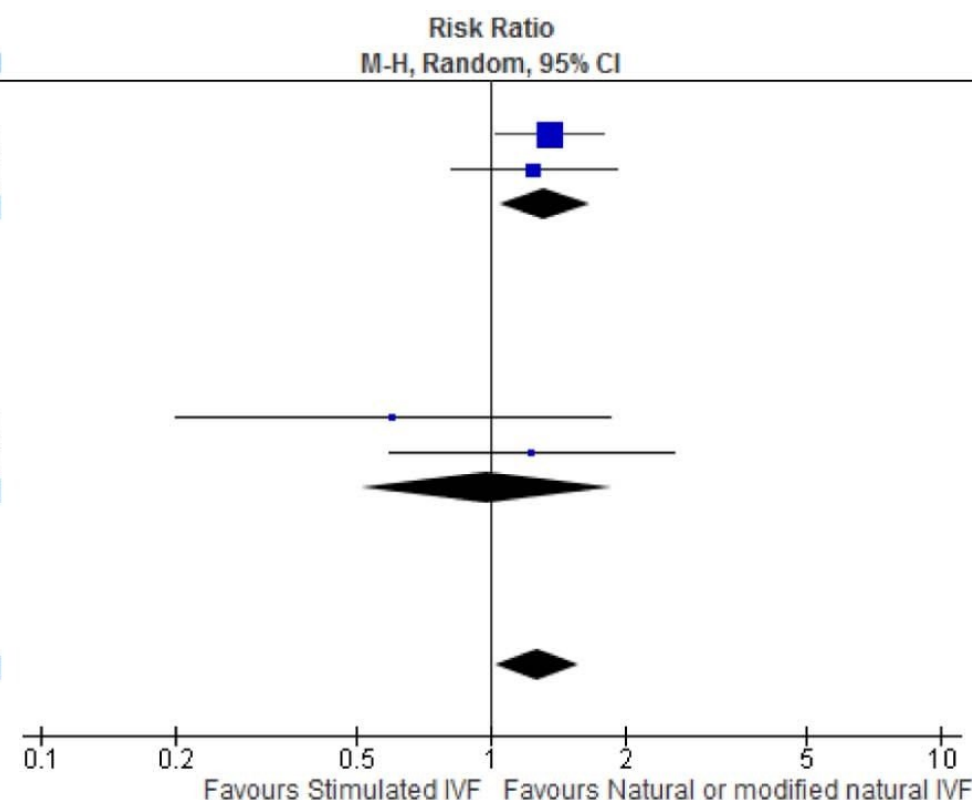
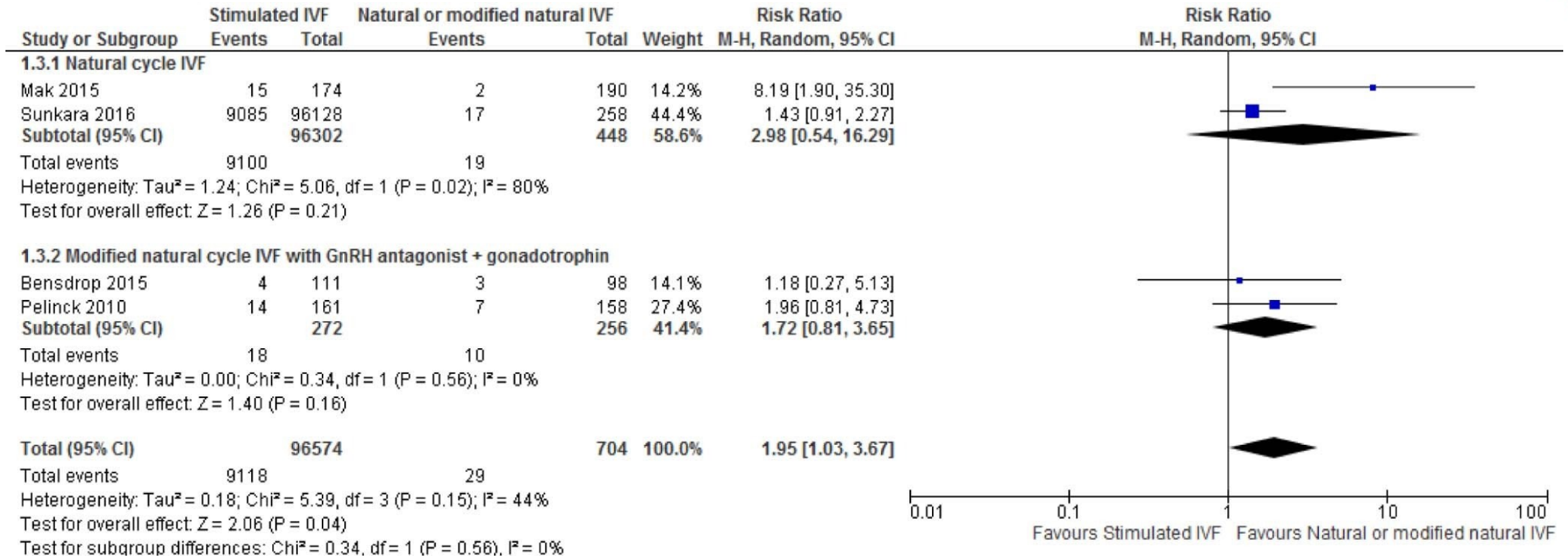


Table and figure reproduced from Kamath MS, et al. Reprod Biomed Online. 2018;36:94–101.

GnRH, gonadotropin-releasing hormone; M-H, Mantel-Haenszel model; PTB, pre-term birth.

LBW: <2500 grams



Higher risk of PTB and LBW with stimulated vs natural cycle or modified natural cycle IVF although the absolute increase in risk may be low

Ovarian response and perinatal outcomes following IVF

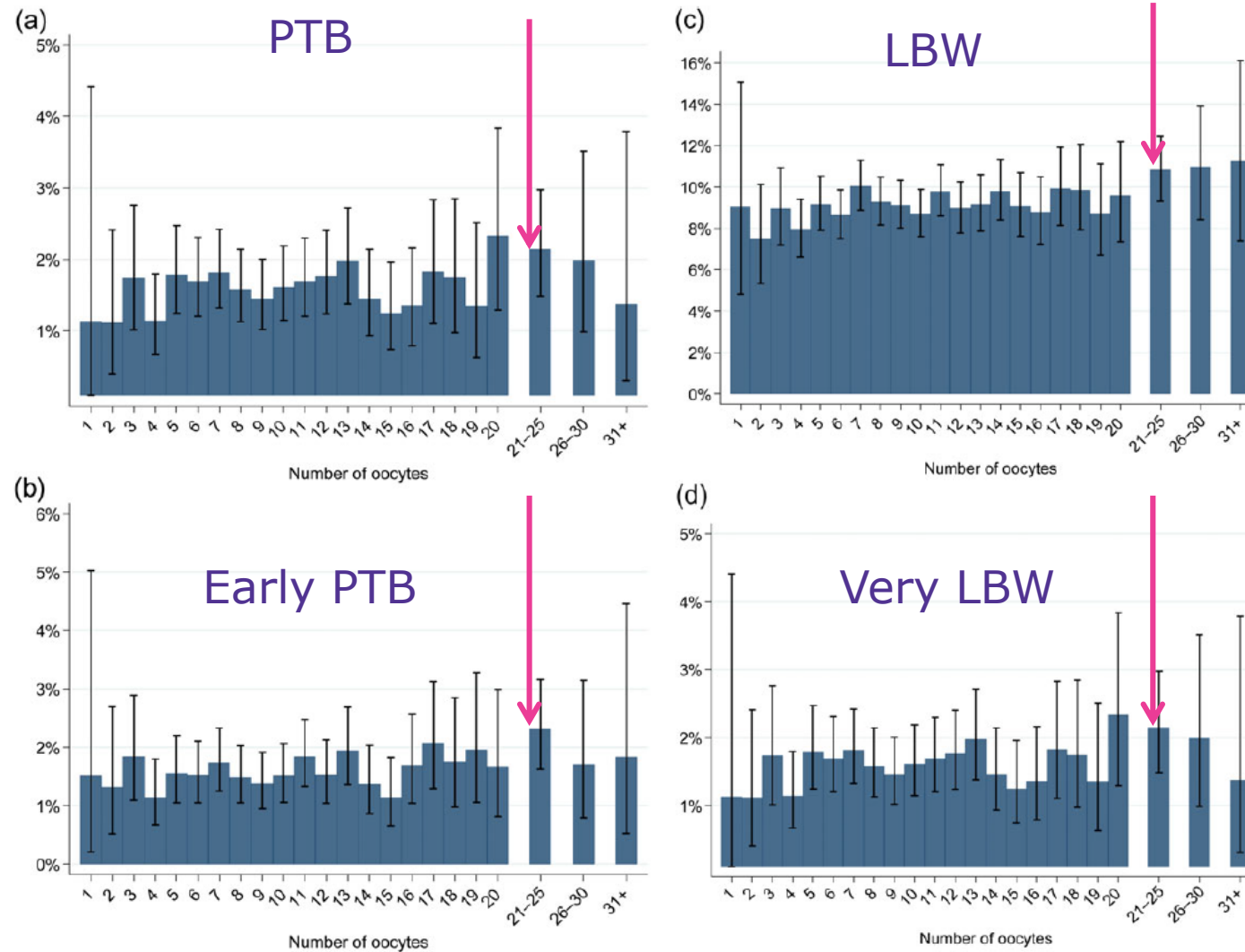


Table 1. Relationship between risk factors and preterm birth (<37 weeks) following IVF

Risk Factor	Odds Ratio	95% CI	P-value
Number of oocytes retrieved			
1–3	0.88	0.76–1.01	0.71
4–9	0.99	0.93–1.05	0.65
16–20	1.02	0.93–1.11	0.67
>20	1.15	1.03–1.28	0.01

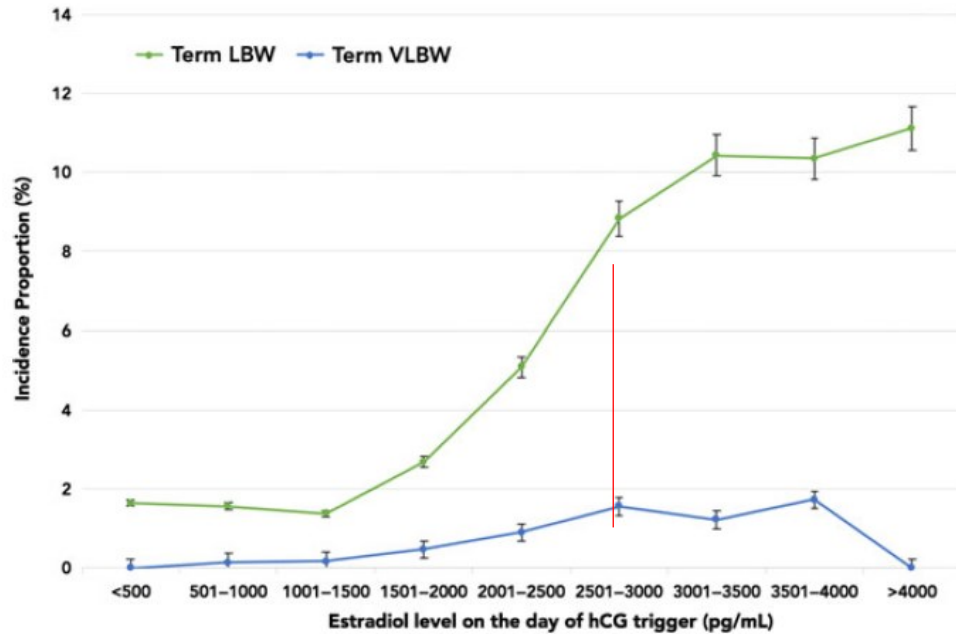
Increased risk of preterm birth and low birthweight with very high number of oocytes following IVF: an analysis of 65 868 singleton live birth outcomes

Table 2. Relationship between risk factors and low birthweight (<2500 g) following IVF

Risk Factor	Odds Ratio	95% CI	P-value
Number of oocytes retrieved			
1–3	0.92	0.79–1.06	0.24
4–9	0.99	0.93–1.05	0.76
16–20	1.02	0.93–1.11	0.72
>20	1.18	1.06–1.31	0.003

Increased risk only with >20 oocytes

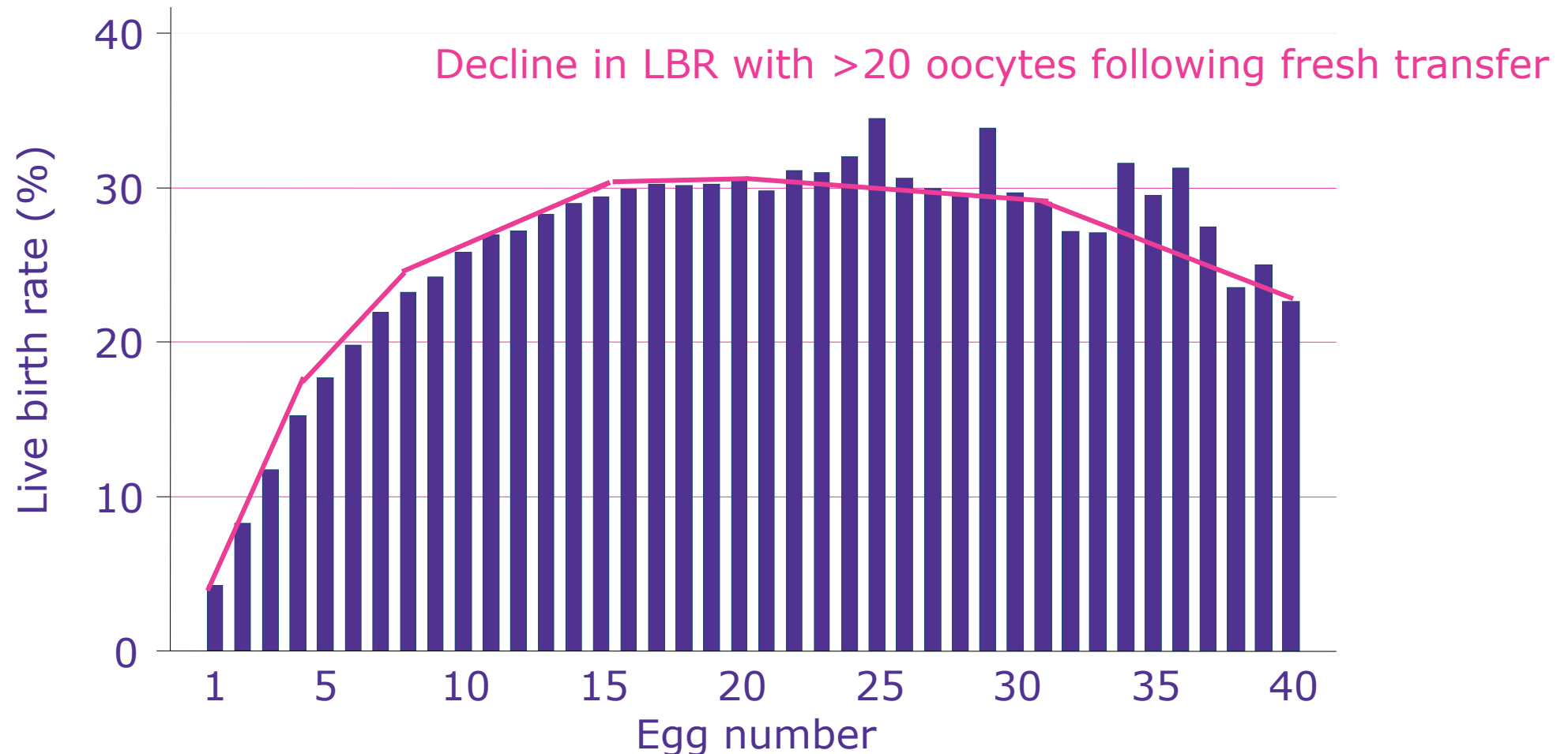
Note: Reference group of 10–15 oocytes is generally considered as the appropriate response group following IVF



Supraphysiologic estradiol is an independant predictor of low birthweight in full-term singletons born after fresh embryo transfer

Comparison	Adjusted Odds Ratio (95% CI)	P-value
Referent group E ₂ <500–1500 pg/ml (n=1929)		
E ₂ 1501–2000 pg/ml (n=858) vs referent	1.3 (0.3–2.6)	0.64
E ₂ 2001–2500 pg/ml (n=669) vs referent	3.2 (0.2–4.3)	0.21
E ₂ 2501–3000 pg/ml (n=385) vs referent	5.7 (1.6–7.6)	0.03
E ₂ 3001–3500 pg/ml (n=163) vs referent	6.7 (1.4–9.7)	0.001
E ₂ 3501–4000 pg/ml (n=58) vs referent	7.2 (1.9–9.8)	<0.001
E ₂ >4000 pg/ml (n=9) vs referent	7.8 (2.1–9.9)	<0.001

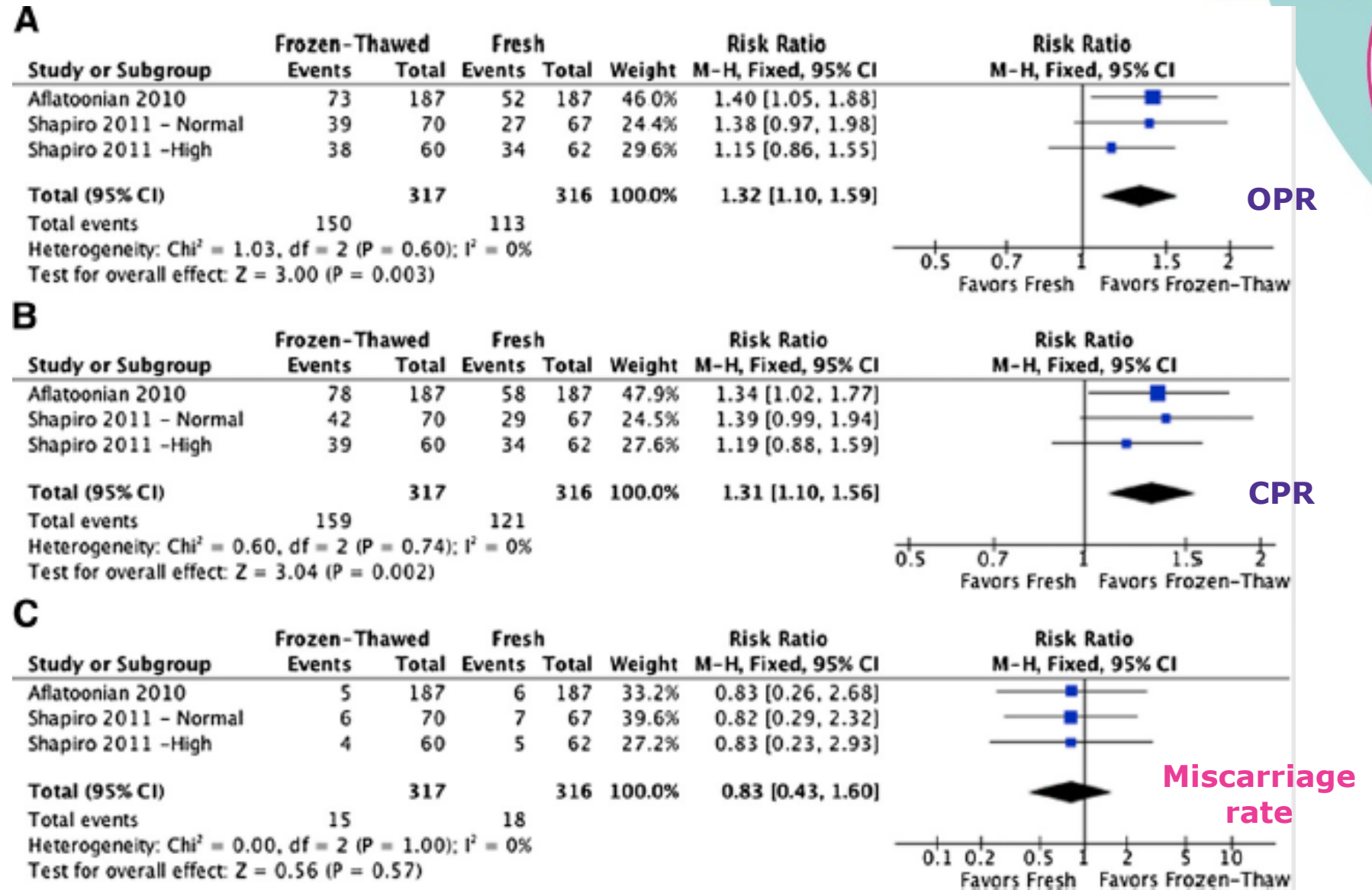
Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles



Fresh versus FET: obstetric and perinatal outcomes

- Aggregated and cumulative meta-analysis
- 26 studies with a majority of cohort studies
- **FET associated with lower risk of**
- **PTB** RR 0.90; 95% CI 0.84–0.97
- **LBW** RR 0.72; 95% CI 0.67–0.77
- **SGA** RR 0.61; 95% CI 0.56–0.67
- **FET associated with a higher risk of**
- **Hypertensive disorders in pregnancy** RR 1.29; 95% CI 1.07–1.56
- **HBW** RR 1.85; 95% CI 1.46–2.33
- **LGA** RR 1.54; 95% CI 1.48–1.61

Fresh vs FET: pregnancy outcomes



Retraction Note to: Can fresh embryo transfers be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A randomized controlled trial

Abbas Aflatoonian • Homa Oskouian •
Shahnaz Ahmadi • Leila Oskouian

Published online: 23 August 2013
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Retraction to: J Assist Reprod Genet (2010) 27:357–363
DOI 10.1007/s10815-010-9412-9

This article has been retracted at the request of the Editor and the ASRM Publications Committee, based on the results of an investigation which found serious methodological flaws in the study.

MISLEADING

Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders

Bruce S. Shapiro, M.D., Ph.D.,^{a,b} Said T. Daneshmand, M.D.,^{a,b} Forest C. Garner, M.Sc.,^{a,b}
Martha Aguirre, Ph.D.,^a Cynthia Hudson, M.S.,^a and Shyni Thomas, B.Sc.^a

^a Fertility Center of Las Vegas; and ^b Department of Obstetrics and Gynecology, University of Nevada School of Medicine, Las Vegas, Nevada

No ITT analysis!

Variable	Fresh	Cryopreservation	ITT analysis	P value
Retrievals	67	70		
Canceled transfers (rate, %)	14 (20.9)	20 (28.6)		.3280
Blastocyst transfers	53	50		
Pregnancies (rate, %)	36 (67.9)	45 (90.0)	0.2277	.0079
Clinical pregnancies (rate, %)	29 (54.7)	42 (84.0)	0.0607	.0013
Ongoing pregnancies (rate, %)	27 (50.9)	39 (78.0)	0.0878	.0072
Early pregnancy losses (rate, %)	7 (19.4)	6 (13.3)		.5481
Transferred blastocysts	95	89		
Fetal hearts (implantation rate, %)	37 (38.9)	63 (70.8)		< .0001

MISLEADING

Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfers in high responders

Bruce S. Shapiro, M.D., Ph.D.^{a,b}

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Comparison of the fresh group and cryopreservation group.

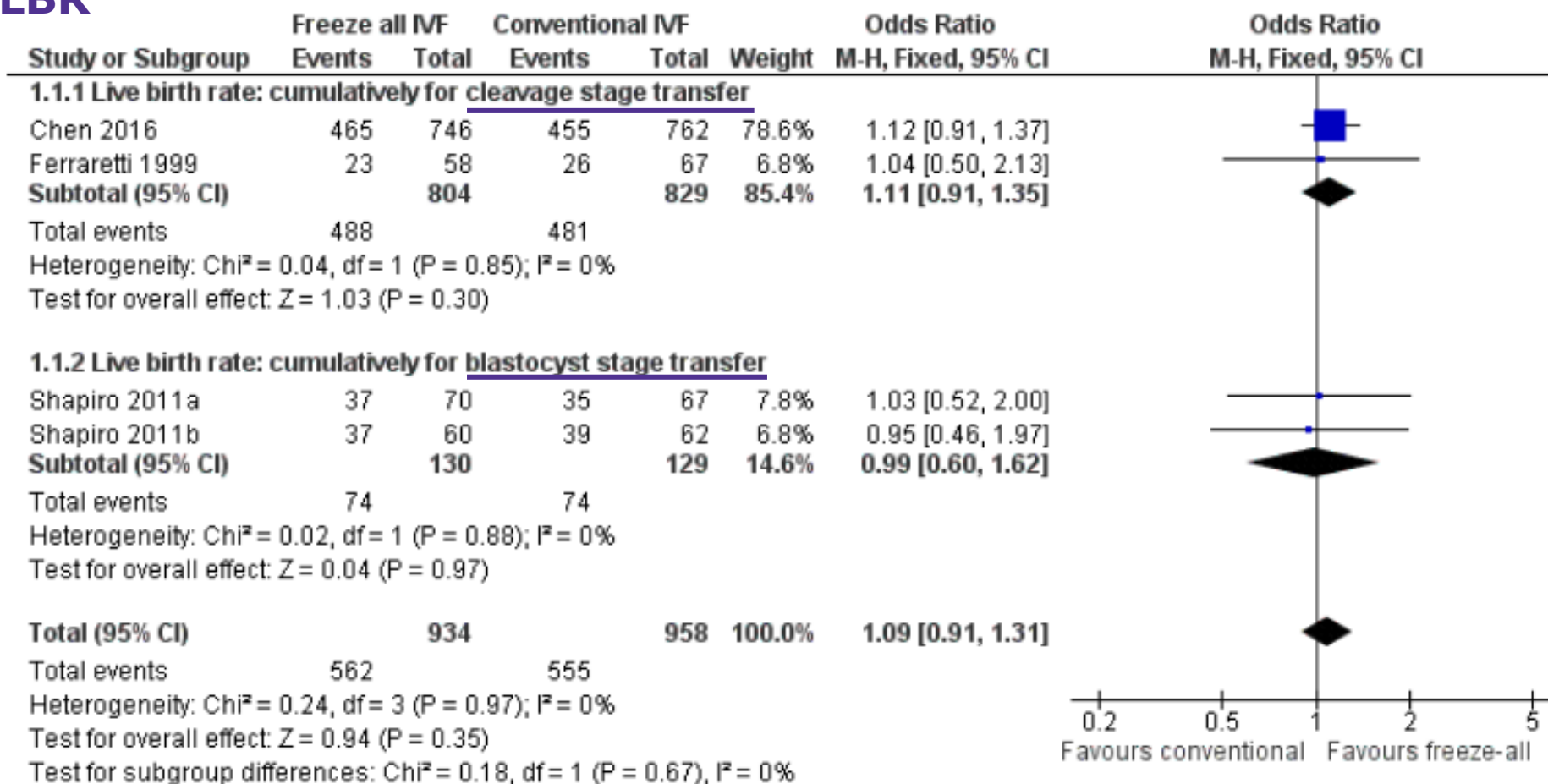
	Fresh group	Cryopreservation group	P value
Retrievals	62	60	
Cancelations (rate, %)	10 (16.1)	11 (18.3)	.8131
Blastocyst transfers	52	49	
Pregnancies (rate, %)	39 (75.0)	42 (85.7)	.2162
Clinical pregnancies (rate, %)	34 (65.4)	39 (79.6)	.1109
Ongoing pregnancies (rate, %)	34 (65.4)	38 (77.6)	.1943
Early pregnancy losses (rate, %)	5 (12.8)	4 (9.5)	.7318
Fetal hearts (implantation rate, %) ^g	60 (57.3)	63 (66.7)	.3210
Multiple pregnancies (rate, %)	25 (73.5)	23 (59.0)	.2234

No significant difference in pregnancy outcomes

Fresh versus frozen embryo transfers in assisted reproduction (Review)

Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S

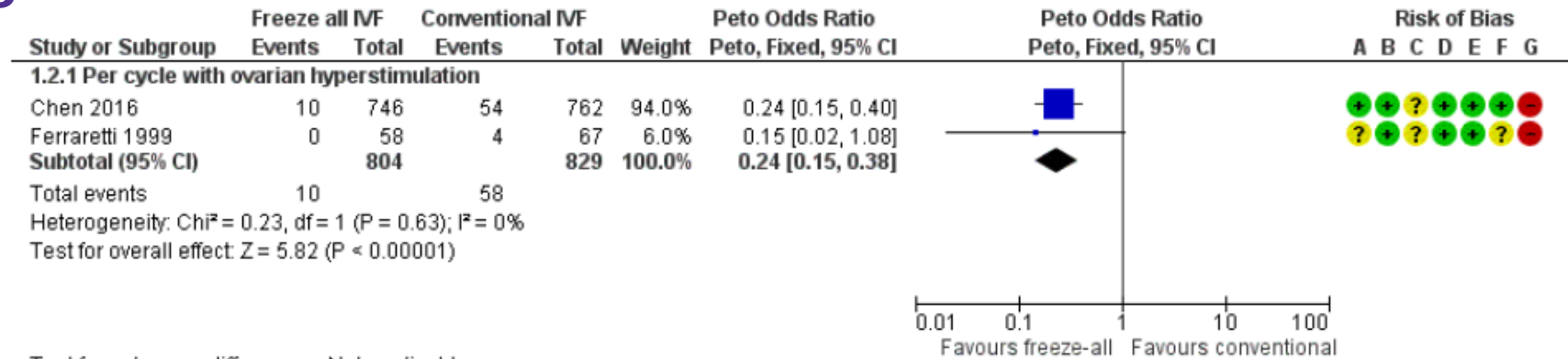
LBR



Fresh versus frozen embryo transfers in assisted reproduction (Review)

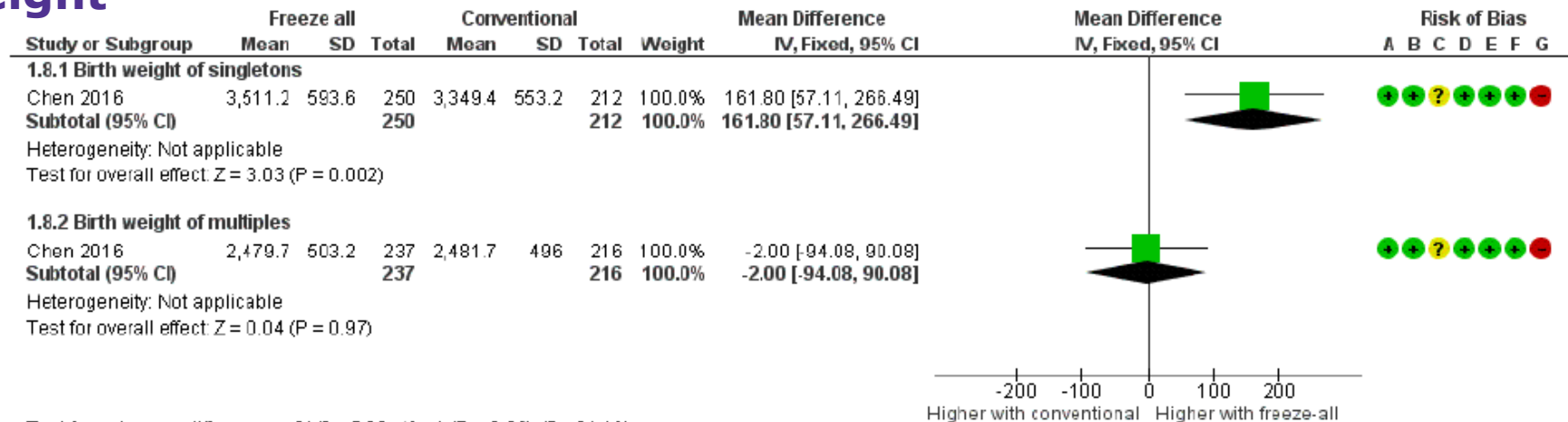
Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S

OHSS



Test for subgroup differences: Not applicable

Birthweight



Test for subgroup differences: Chi² = 5.30, df = 1 (P = 0.02), I² = 81.1%

Fresh versus frozen embryo transfers in assisted reproduction (Review)

Wong KM, van Wely M, Mol F, Repping S, Mastenbroek S

- Included 4 RCTs
- Clinical heterogeneity was observed between studies
- Pooled together studies included normal responders, hyper-responders and those with PCOS
- No sensitivity analysis based on response groups was carried out
- Further RCTs have been published,¹ providing evidence since the Cochrane review

1. See following slides for RCTs in question
PCOS, polycystic ovary syndrome; RCT, randomized controlled trial.

Fresh versus Frozen Embryos for Infertility in the Polycystic Ovary Syndrome

Z.-J. Chen, Y. Shi, Y. Sun, B. Zhang, X. Liang, Y. Cao, J. Yang, J. Liu, D. Wei, N. Weng, L. Tian, C. Hao, D. Yang, F. Zhou, J. Shi, Y. Xu, J. Li, J. Yan, Y. Qin, H. Zhao, H. Zhang, and R.S. Legro

Outcome	Frozen-Embryo Transfer (N=746)	Fresh-Embryo Transfer (N=762)	Absolute Difference between Groups (95% CI)	Rate Ratio in Frozen-Embryo Group (95% CI)	P-value
Primary outcome: live birth — no. (%) [†]	368 (49.3)	320 (42.0)	7.3 (2.3–12.4)	1.17 (1.05–1.31)	0.004
Singleton	250 (33.5)	212 (27.8)	5.7 (1.0–10.3)	1.20 (1.03–1.40)	0.02
Twin	117 (15.7)	108 (14.2)	1.5 (–2.1–5.1)	1.11 (0.87–1.41)	0.41
Triplet [‡]	1 (0.1)	0			

Transfer of Fresh versus Frozen Embryos in Ovulatory Women

Yuhua Shi, M.D., Ph.D., Yun Sun, M.D., Ph.D., Cuifang Hao, M.D., Ph.D.,
Heping Zhang, Ph.D., Daimin Wei, M.D., Ph.D., Yunshan Zhang, M.D.,
Yimin Zhu, M.D., Ph.D., Xiaohui Deng, M.D., Xiujuan Qi, M.D., Hong Li, M.D.,
Xiang Ma, M.D., Ph.D., Haiqin Ren, M.D., Yaqin Wang, M.D., Ph.D.,
Dan Zhang, M.D., Ph.D., Bo Wang, M.S., Fenghua Liu, M.D.,
Qiongfang Wu, M.D., Ze Wang, M.S., Haiyan Bai, Ph.D., Yuan Li, M.D., Ph.D.,
Yi Zhou, M.D., Mei Sun, M.D., Ph.D., Hong Liu, M.D., Ph.D., Jing Li, M.S.,
Lin Zhang, M.S., Xiaoli Chen, M.D., Ph.D., Songying Zhang, M.D., Ph.D.,
Xiaoxi Sun, M.D., Ph.D., Richard S. Legro, M.D., and Zi-Jiang Chen, M.D., Ph.D.

- Multicentre RCT
- 2,157 ovulatory women with infertility undergoing 1st IVF±ICSI
- Fresh versus FET

Characteristic		Frozen-Embryo Group (N=1077)	Fresh-Embryo Group (N=1080)
Age — yr		28.5±3.0	28.4±3.1
Body-mass index‡		22.0±3.0	22.2±3.1
Antral follicle count in both ovaries	1053	15.6±5.2	15.4±5.2
<u>No. of oocytes retrieved</u>		12.5±5.1	12.3±5.2
No. of good-quality embryos on day 3		5.0±3.5	4.9±3.5
Timing of embryo transfer — no./total no. (%)§			
Day 2		28/1028 (2.7)	35/1048 (3.3)
Day 3		944/1028 (91.8)	965/1048 (92.1)
Day 5		56/1028 (5.4)	48/1048 (4.6)
<u>No. of embryos transferred</u>			
Mean	1028	1.9±0.3	1.9±0.2

Table 3. Live Birth, Birth Weight, Pregnancy, and Pregnancy Loss.*

Outcome	Frozen-Embryo Group (N=1077)	Fresh-Embryo Group (N=1080)	Absolute Difference (95% CI) [†]	Rate Ratio for Frozen- vs. Fresh- Embryo Transfer (95% CI)	P Value
			<i>percentage points</i>		
Primary outcome: live birth — no. (%)	525 (48.7)	542 (50.2)	−1.5 (−5.7 to 2.8)	0.97 (0.89 to 1.06)	0.50
Singleton	337 (31.3)	367 (34.0)	−2.7 (−6.7 to 1.3)	0.92 (0.82 to 1.04)	0.18
Twin	187 (17.4)	173 (16.0)	1.4 (−1.8 to 4.5)	1.08 (0.90 to 1.31)	0.40
Triplet [‡]	1 (0.1)	2 (0.2)	−0.1 (−0.4 to 0.2)	0.50 (0.05 to 5.52)	1.00
Birth weight — g [§]					
Singleton					
Mean	3373±515	3380±502	−7 (−83 to 68)	—	0.85
Ongoing pregnancy — no. (%) ^{††}	540 (50.1)	573 (53.1)	−3.0 (−7.1 to 1.3)	0.95 (0.87 to 1.03)	0.18

Table 4. Maternal, Fetal, and Neonatal Adverse Events.*

Event	Frozen-Embryo Group (N=1077)	Fresh-Embryo Group (N=1080)	Absolute Difference (95% CI)	Rate Ratio for Frozen- vs. Fresh- Embryo Transfer (95% CI)	P Value
	<i>no./total no. (%)</i>	<i>no./total no. (%)</i>			
Moderate or severe ovarian hyperstimulation syndrome before biochemical pregnancy	7/1077 (0.6)	22/1080 (2.0)	−1.4 (−2.4 to −0.4)	0.32 (0.14 to 0.74)	0.005
Ectopic pregnancy among biochemical pregnancies	18/671 (2.7)	12/696 (1.7)	1.0 (−0.6 to 2.5)	1.56 (0.76 to 3.21)	0.23
Therapeutic abortion or fetal reduction due to fetal congenital anomalies at 12 to 28 wk of gestation among clinical pregnancies	3/586 (0.5)	4/615 (0.7)	−0.2 (−1.0 to 0.7)	0.79 (0.18 to 3.50)	1.00
Gestational diabetes among clinical pregnancies	18/586 (3.1)	24/615 (3.9)	−0.8 (−2.9 to 1.2)	0.79 (0.43 to 1.44)	0.43
Preeclampsia among clinical pregnancies	26/586 (4.4)	20/615 (3.3)	1.1 (−1.0 to 3.4)	1.36 (0.77 to 2.42)	0.28
Gestational hypertension among clinical pregnancies	5/586 (0.9)	7/615 (1.1)	−0.2 (−1.4 to 0.8)	0.75 (0.24 to 2.35)	0.62
Preterm delivery among clinical pregnancies	91/586 (15.5)	80/615 (13.0)	2.5 (−1.4 to 6.5)	1.19 (0.90 to 1.58)	0.21
Congenital anomalies among live newborns	16/714 (2.2)	26/719 (3.6)	−1.4 (−3.1 to 0.4)	0.62 (0.34 to 1.15)	0.12
Neonatal death among live newborns [‡]	2/714 (0.3)	4/719 (0.6)	−0.3 (−0.9 to 0.4)	0.50 (0.09 to 2.74)	0.69

IVF Transfer of Fresh or Frozen Embryos in Women without Polycystic Ovaries

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- Single centre RCT
- 782 infertile women without PCOS undergoing 1st or 2nd IVF±ICSI
- Fresh versus FET at cleavage stage (Day 3)

Characteristic	Frozen-Embryo Group (N=391)	Fresh-Embryo Group (N=391)
Age — yr	32±4	32±4
Body-mass index†	20.8±2.2	20.8±2.2
Anti-Müllerian hormone — ng/ml	5.0±3.2	5.2±3.3
No. of oocytes retrieved	13±6	13±5
No. of metaphase II oocytes	10±5	10±4
No. of two-pronuclear fertilised oocytes	8±4	9±4
No. of cleavage embryos	6±3	7±3
No. of embryos transferred	2.0±0.1	2.0±0.1

†The body-mass index is the weight in kilograms divided by the square of the height in meters; yr, year

Table 2. Fertility Outcomes and Treatment Complications after the First Embryo Transfer.*

Variable	Frozen-Embryo Group (N = 391)	Fresh-Embryo Group (N = 391)	Between-Group Difference <i>percentage points (95% CI)</i>	Risk Ratio (95% CI) [†]	P Value
Fertility outcome					
Ongoing pregnancy — no. (%) [§]	142 (36.3)	135 (34.5)	1.8 (−5.2 to 8.7)	1.05 (0.87 to 1.27)	0.65
Singleton	96 (24.6)	92 (23.5)	1.0 (−5.2 to 7.3)	1.04 (0.81 to 1.34)	0.80
Twins	46 (11.8)	43 (11.0)	0.8 (−3.9 to 5.5)	1.07 (0.72 to 1.58)	0.82
Implantation — no./total no. (%)	224/780 (28.7)	210/778 (27.0)	1.7 (−2.9 to 6.3)	1.06 (0.91 to 1.25)	0.46
Clinical pregnancy — no. (%)	173 (44.2)	163 (41.7)	2.5 (−4.6 to 9.8)	1.06 (0.90 to 1.25)	0.52
Multiple pregnancy — no. (%)	46 (11.8)	45 (11.5)	0.3 (−4.5 to 5.0)	1.02 (0.69 to 1.50)	1.00
Ectopic pregnancy — no. (%)	6 (1.5)	13 (3.3)	−1.8 (−4.2 to 0.6)	0.46 (0.18 to 1.2)	0.16
Miscarriage — no. (%)	25 (6.4)	15 (3.8)	2.6 (−0.8 to 5.9)	1.67 (0.89 to 3.11)	0.14
Live birth — no. (%) [§]	132 (33.8)	123 (31.5)	2.3 (−4.5 to 9.1)	1.07 (0.88 to 1.31)	0.54
Moderate or severe ovarian hyperstimulation syndrome — no. (%)	3 (0.8)	4 (1.0)	−0.3 (−1.8 to −1.3)	0.75 (0.17 to 3.33)	0.99

Primary outcome

Fresh versus FET: obstetric and perinatal outcomes

Variable	Frozen-Embryo Group (N = 391)	Fresh-Embryo Group (N = 391)	Between-Group Difference <i>percentage points (95% CI)</i>	Risk Ratio (95% CI)	P Value
Small for gestational age — no. (%)†	3 (0.8)	14 (3.6)	−2.8 (−5.1 to −0.5)	0.21 (0.06 to 0.74)	0.01
Large for gestational age — no. (%)‡	7 (1.8)	3 (0.8)	1.0 (−0.8 to 2.9)	2.33 (0.61 to 8.96)	0.34
Admission to neonatal intensive care unit — no. (%)	5 (1.3)	5 (1.3)	0.0 (−1.6 to 1.6)	1.00 (0.29 to 3.43)	1.00
Perinatal death — no. (%)	0	3 (0.8)			
Hypertension — no. (%)					
Pregnancy-induced	3 (0.8)	5 (1.3)	−0.5 (−2.2 to 1.2)	0.60 (0.14 to 2.49)	0.73
Preeclampsia	2 (0.5)	1 (0.3)	0.3 (−0.9 to 1.4)	2.00 (0.18 to 21.97)	1.00
HELLP syndrome	0	0			
Antepartum hemorrhage — no. (%)	0	1 (0.3)			
Gestational diabetes — no. (%)	5 (1.3)	7 (1.8)	−0.5 (−2.5 to 1.5)	0.71 (0.23 to 2.23)	0.77
Prematurity — no. (%)					
Indicated preterm birth at <32 wk of gestation	1 (0.3)	1 (0.3)	0.0 (−0.7 to 0.7)	1.00 (0.06 to 15.93)	1.00
Spontaneous preterm birth at <32 wk of gestation	4 (1.0)	2 (0.5)	0.5 (−1.0 to 2.0)	2.00 (0.37 to 10.86)	0.69
Indicated preterm birth at 32 to <37 wk of gestation	2 (0.5)	6 (1.5)	−1.0 (−2.7 to 0.6)	0.33 (0.07 to 1.64)	0.29
Spontaneous preterm birth at 32 to <37 weeks' gestation	12 (3.1)	14 (3.6)	−0.5 (−3.3 to 2.3)	0.86 (0.40 to 1.83)	0.84
Cesarean section — no. (%)					
Elective	8 (2.0)	12 (3.1)	−1.0 (−3.5 to 1.4)	0.67 (0.28 to 1.61)	0.50
Suspected fetal distress	3 (0.8)	2 (0.5)	0.3 (−1.1 to 1.6)	1.50 (0.25 to 8.93)	1.00
Nonprogressive labor	24 (6.1)	20 (5.1)	1.0 (−2.5 to 4.5)	1.20 (0.67 to 2.14)	0.64
Increased peripartum blood loss — no. (%)	0	0			
Birth weight — g					
Singleton	3253.0±413.8	3011.1±443.9	241.9 (119.7 to 364.2)		<0.001
Twins	2480.0±561.1	2382.1±537.5	97.9 (−96.7 to 292.4)		0.32

Optimal euploid embryo transfer strategy, fresh versus frozen, after preimplantation genetic screening with next generation sequencing: a randomized controlled trial

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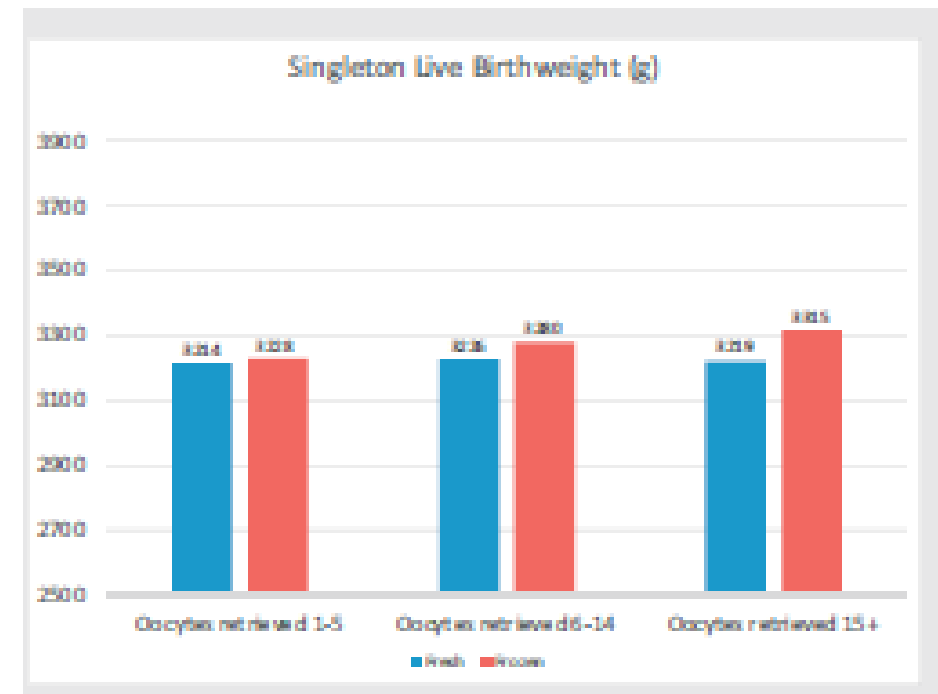
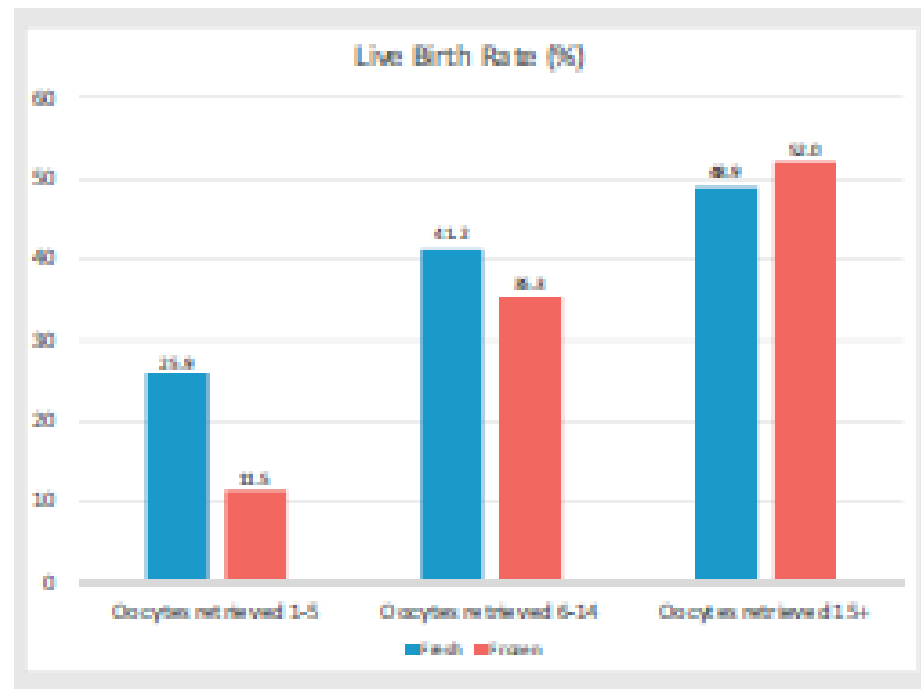
Fresh versus FET: PGS

Day 6 fresh embryo transfer vs frozen transfer of euploid embryo

Outcome in the ITT population			
Characteristics	Fresh ET (n=88)	Frozen ET (n=91)	P-value
Embryo transfer rate/cycle	61/88 (69.3)	69/91 (75.8)	0.40
No. of embryos transferred, mean (SD)	1.4 (0.5)	1.5 (0.5)	0.27
Ongoing pregnancy	36/88 (40.9)	57/91 (62.6)	<0.01
Live birth	35/88 (39.8)	56/91 (61.5)	<0.01
Implantation rate (total no. of gestational sacs/total no. of embryos transferred)	58/86 (67.4)	79/104 (76.0)	0.19

Ongoing pregnancy and LBR significantly higher in the frozen transfer group

Freezing of all embryos in in vitro fertilization is beneficial in high responders, but not intermediate and low responders: an analysis of 82,935 cycles from the Society for Assisted Reproductive Technology registry



National trends: UK

Figure 9: Number of fresh and frozen treatment cycles

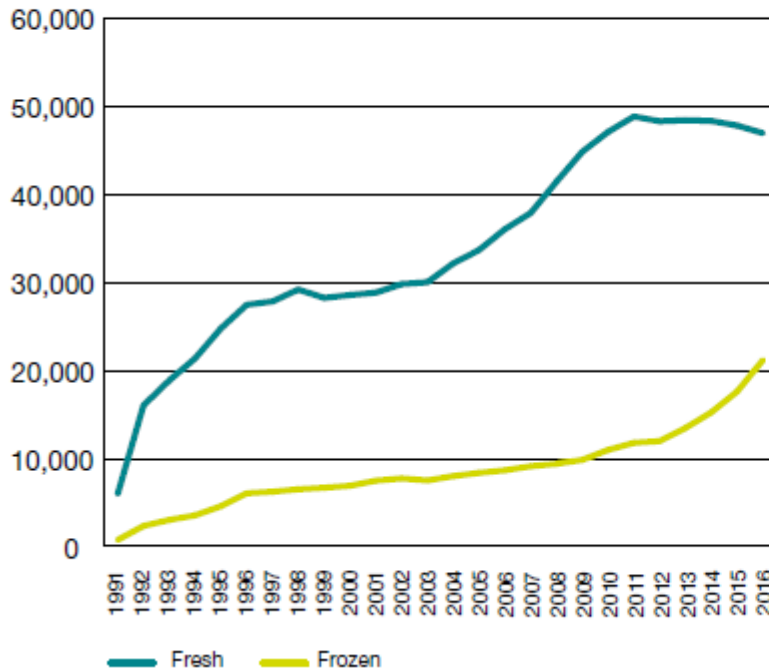
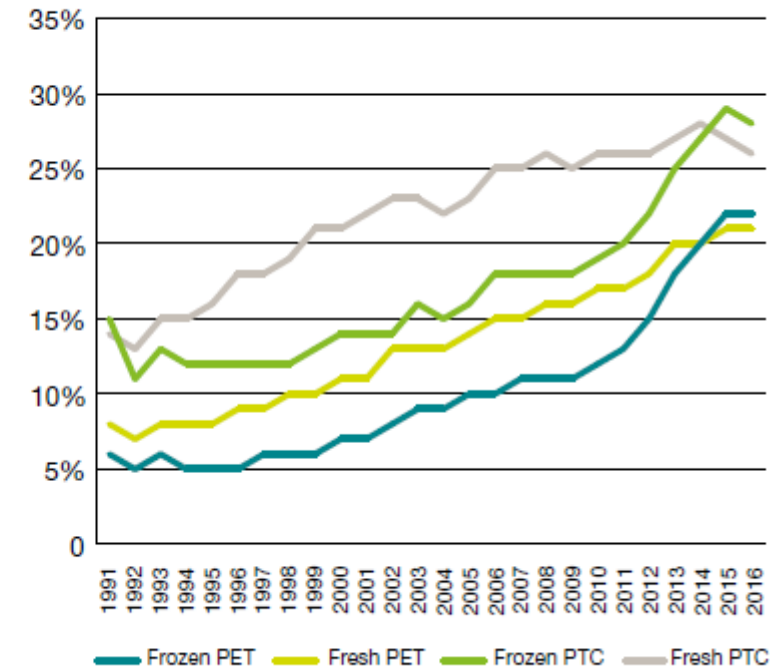


Figure 10: IVF birth rates



The increase in the use of frozen cycles is most likely due to a range of factors, including improvements in freezing processes and the increased uptake in single ET to reduce the number of multiple births

Conclusion (1)

- Increasing numbers of FET cycles worldwide
- Significantly improved cryopreservation techniques contributing to improved FET results
- Clinical outcomes when comparing fresh transfer vs FET
 - Comparable, higher LBR in normal responders with fresh transfer vs FET
 - Decline in LBR, higher risk of PTB and LBW with very high oocyte numbers in fresh cycles
 - Higher LBR with FET vs fresh transfer in women with PCOS, hyper responders
 - Significant reduction in OHSS with FET

Conclusion (2)

- Lower birth rate with fresh vs FET in the context of 2:0 PGS/PGT-A
- Higher risk of SGA and lower birth weight following fresh transfers; however, implications uncertain
- Clinical scenario, patient compliance, cost-effectiveness to be considered when deciding 1st line treatment
- Shorter TTLB with fresh transfer over FET in normal responders (when PGT-A is not used)
- Shorter TTLB with FET when PGT-A is used

Thank you

