Annex 9: Number of embryos to transfer- Evidence tables

PICO 1: Which pregnancy-related risks should be considered before the transfer of more than one embryo?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Eapen A, et al., *Fertility and sterility* 2020;114: 690-714.	Meta-analysis	60 studies	up to February 2020.	maternal and fetal outcomes	**Maternal health risk:** Antenatal hospitalisation (OR 2.6; 95%CI 1.9-3.5), caesarean section (0R 3.7; 95%CI 3.3-4.1), gestational diabetes (OR 1.2; 95%CI 1.1-1.3), preterm labour (0R 6.3; 95%CI 3.6-11.0), pregnancy-induced hypertension (OR 2.0; 95%CI 1.9-2.3), preeclampsia (OR 1.9; 95%CI 1.4-2.6), placental abruption (OR 1.3; 95%CI 1.2-1.5), placenta previa (OR 0.8 ; 95%CI 0.7-0.9) and postpartum haemorrhage (OR 2.2; 95%CI 1.2-4.1). **Fetal and neonatal risks:** Congenital anomaly (OR 1.1; 95%CI 1.0-1.2), preterm birth rate (OR 8.3; 95%CI 7.8-8.9), early preterm birth rate <32 gestational weeks (OR 3.5; 95%CI 3.1-3.9), very preterm birth rate <28 gestational weeks (OR 5.5; 95%CI 5.2-5.9), low birth weight (OR 10.6; 95%CI 9.9-11.4), NICU admission rate (OR 6.5; 95%CI 5.8-7.3), perinatal mortality rate (OR 2.4; 95%CI 2.1-2.8), and stillbirth rate (OR 2.2; 95%CI 1.8-2.6).	With twin pregnancies, the higher maternal risks, the greatly increased risk of premature delivery for infants, and the higher health care costs that results are consistent among studies throughout the world. The data are compelling that a strategy of one healthy baby at a time should be the objective of every IVF-ICSI treatment cycle.	
Sites CK, et al., *Reproductive biology and endocrinology : RB&E* 2020;18: 68.	Retrospective study	21,188 births,	singleton (12,810) and twin (8378) live-births from autologous or donor eggs from 2005 to 2012.	Risk of Preeclampsia	the transfer of multiple embryos increased the risk of preeclampsia [aRR = 1.10 (95% CI: 1.01–1.19)]. Relative risks were greatest for fresh non-donor cycles [aRR = 1.14 (95% CI: 1.03–1.26)]. Vanishing twin and number of prior ART cycles was not associated with preeclampsia among singleton births [aRR = 1.18 (95% CI: 0.91–1.53)], and aRR = 1.01 (95% CI: 0.96–	Among ART births, the transfer of more than 1 embryo for singleton gestations and more than 2 embryos for twin gestations	

					1.05)], respectively. Considering all twin births, the transfer of > 2 embryos increased the risk of preeclampsia [aRR = 1.09 (95% CI: 1.001–1.19)]. Vanishing triplet and number of prior ART cycles were not associated with preeclampsia among twin births [aRR = 0.93 (95% CI: 0.69–1264), and aRR = 0.98 (CI: 0.95–1.02)], respectively.	increased the risk for preeclampsia diagnosis.	
Luke B, et al., *Journal of assisted reproduction and genetics* 2021;38: 835-846.	Retrospecti ve study	138,435 children	Children born 2004–2013 (Texas), 2004–2016 (Massachusetts and North Carolina), and 2004–2017 (New York) were classified by ET and Fetal heartbeat FHB: [ET=1, FHB=1] was defined as the reference group; [ET=2, FHB=1] and [ET=3, FHB=1] were the excess embryos transferred groups; and [ET≥2, FHB≥2] was the excess embryos transferred and excess fetal heartbeats group. For twin births, [ET=2, FHB=2] was defined as the reference group; [ET=3, FHB=2] and [ET≥4, FHB=2] were the excess embryos transferred groups; and [ET≥3, FHB≥3] was the excess embryos transferred and excess fetal heartbeats group	Major nonchromosomal birth defect, small-for-gestational age birthweight (SGA), low birthweight (LBW), and preterm birth (≤36 weeks), by excess ET, and excess ET + excess FHB, by plurality at birth (singletons and twins).	**In singletons with [2 ET, FHB =1] and [≥3 ET, FHB=1]:** risks [AOR (95% CI)] were increased, respectively, for major nonchromosomal birth defects (OR 1.13; 95%CI 1.00–1.27 and OR1.18; 95%CI 1.00–1.38), SGA (OR 1.10; 95%CI 1.03–1.17 and OR 1.15; 95%CI 1.05–1.26), LBW (OR1.09; 95%CI 1.02–1.13 and OR1.17; 95%CI 1.07–1.27) Preterm birth OR1.06; 95%CI 1.00–1.12 and OR1.14;95%CI 1.06–1.23). With excess ET + excess FHB, risks of all adverse outcomes except major nonchromosomal birth defects increased further for both singletons and twins.	Excess embryos transferred are associated with increased risks for nonchromosomal birth defects, reduced birthweight, and prematurity in IVF-conceived births	

van Heesch MMet al., ***Acta obstetricia et gynecologica Scandinavica*** **2014;93: 277-286.**	Retrospective cohort	3041 singleton and 907 multiple pregnancies following IVF/ICSI. Groups comparable in terms of maternal age, parity, ethnicity, BMI, socio-economic status	Maternal and neonatal complications in singleton versus multiple pregnancies. Follow up till birth, mean 40 weeks.	Need for caesarean section, birthweight, gestational age, small for gestational age, NICU admission, perinatal mortality.	**Singleton vs multiple:** caesarean section 22.5% vs 41%; OR 2.49; 95%CI 2.19 - 2.84 birthweight 3362g vs 2441g gestational age in weeks 39.4 vs 36.3 Small for gestational age 11.5% vs 22.4%; OR 2.26; 95%CI 1.92 - 2.64 NICU admission 2.8% vs 12.2%; OR 5.01; 95%CI 3.80 - 6.61 perinatal mortality 0.4% vs 1%; OR 2.61; 95%CI 1.22 - 5.59	Perinatal outcomes in IVF/ICSI-conceived multiples are considerably poorer than in singletons.	
Pinborg A, et al., ***Acta obstetricia et gynecologica Scandinavica*** **2004;83: 75-84.**	Retrospective cohort	236 twin pregnancies, 634 singleton pregnancies and 566 non-IVF twin pregnancies. Groups comparable in terms of parity, social class, duration of infertility and treatment.	Maternal and neonatal complications in singleton versus multiple pregnancies. Follow up till birth, mean 40 weeks.	Pregnancy induced hypertension, pre-eclampsia, gestational diabetes, admission to hospital, caesarean section, birthweight, prematurity <37 weeks	**IVF twin vs non-IVF twin:** pregnancy induced hypertension: OR 1.0; 95% CI 0.7 - 1.6 pre-eclampsia OR 1.6 95% CI 1.1 - 2.6; gestational diabetes OR 2.0 95% CI 0.9–4.2 admission OR 1.8 95% CI 1.3 - 2.5; caesarean section 58.1% vs 44.0%; birthweight 2509g vs 2578g prematurity 52.1% vs 49.3% | **IVF twins vs IVF singletons:** pregnancy induced hypertension OR 1.3 95% CI 0.8 - 2.0 pre-eclampsia OR 2.3 95% CI 1.4–3.8 gestational diabetes OR 1.4 95% CI 0.7 - 2.7 admission OR 3.4 95% CI 2.5 - 4.7 caesarean section 58.1% vs 26.2% birthweight 2509g vs 3387g prematurity <37 weeks 52.1% vs 17.9%	Although this population study indicates that maternal risks in IVF/ICSI twin pregnancies are comparable with non-IVF/ICSI twin pregnancies, the IVF/ICSI twin mothers were more likely to be on sick leave or hospitalized during pregnancy. Furthermore, maternal risks were higher and obstetric outcome poorer in IVF/ICSI twin vs. IVF/ICSI singleton pregnancies.	
Makhseed M, et al., ***International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*** **1998;61: 155-163.**	Retrospective cohort	31 twins, 22 triplets, 5 quads, 58 singletons. No data on baseline characteristics.	Maternal and neonatal complications in singleton versus multiple pregnancies. Follow up till birth, mean 40 weeks.	Gestational diabetes, pregnancy induced hypertension, gestation at birth, birthweight, caesarean section	**Singleton vs twins vs triplets vs quads**: gestational diabetes 13.8% vs 16.1% vs 11% vs 0%; pregnancy induced hypertension 18.9% vs 16.1% vs 33.3% vs 33.3% gestational age at birth 37.1 vs 35.8 vs 30.1 vs 33.6 weeks birthweight 3086g vs 2380g vs 1300g vs 1670g prematurity <37 31% vs 67.7% vs 100% vs 100% caesarean section 74.1% vs 90.3% vs 88.9% vs 100%	There was a significantly higher maternal and neonatal complication rate in the triplet group compared to singletons and twins, including threatened miscarriage, pre-eclampsia,	

						antepartum haemorrhage, longer hospital stay and preterm labor.	
D'Souza SW, et al., *Archives of disease in childhood Fetal and neonatal edition* 1997;76: F70-74.	Retrospective cohort	278 children (150 singletons, 100 twins, 24 triplets and four quadruplets), conceived by IVF after three fresh embryos had been transferred, 278 naturally conceived singletons.	Maternal and neonatal outcomes in IVF singletons vs multiples vs natural singletons. Follow up till birth, mean 40 weeks.	Gestation at birth, birthweight, caesarean section	**IVF singleton vs IVF multiple vs Natural singletons:** gestation at birth 38.4 vs 35.2 vs 39.4; birthweight 3016g vs 2078g vs 3380g; caesarean section 26.7% vs 55.5% vs 6.8%	The outcome of IVF treatment leading to multiple births is less satisfactory than that in singletons because of neonatal conditions associated with preterm delivery and disabilities in later childhood. A reduction of multiple pregnancies by limiting the transfer of embryos to two instead of three remains a high priority.	
Gupta R, et al., *Journal of human reproductive sciences* 2020;13: 56-64.	Retrospective cohort	897 singleton and 382 twin pregnancies. Maternal age similar between groups.	Maternal and neonatal outcomes in IVF singletons vs multiples. Follow up till birth, mean 40 weeks.	Pre-eclampsia, premature rupture of membranes, antepartum haemorrhage, gestational diabetes, composite of maternal complications, gestation and birthweight at delivery	**Singletons vs twins:** pre-eclampsia OR 1.35 95% CI 0.93-1.96; premature rupture of membranes OR 2.32 95% CI 1.48-3.64 antepartum haemorrhage OR 1.94 95% CI 0.80-4.73 gestational diabetes OR 0.88 95% CI 0.34-2.26 composite maternal complications OR 1.53 95% CI 1.17-2.01 gestational age at delivery 37.2 vs 35 birthweight 2760g vs 2030g	Twin deliveries, following IVF/ICSI deliver at lower gestational age, have lower birth weight and have higher odds of stillbirth plus neonatal death as compared to singleton deliveries following IVF/ICSI	

Papers included as background information

(Kamath et al., 2020)

PICO 2. Which financial issues should be considered for couples/individuals planning a singleton or multiple pregnancy/birth?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Hernandez Torres E, et al., *Fertility and sterility* 2015;103: 699-706.	RCT	121 women (<38 years old), undergoing their first or second IVF cycles.	Women in group 1: SET + eSFET; Women in group 2: DET From January 2010 to December 2012		**cLBR:** **eSET+ eSFET group vs DET:** 38.60% vs 42.19% **MPR:** **SET+eSFET vs. DET**. 0 vs 25.9% **The mean costs/ patient:** **eSET+ eSFET vs DET** 5,614.11 vs vs 5,562.29 €,(NS)	This study does not show that eSET is superior to DET in terms of effectiveness or of costs.	
Lukassen HG, et al., *Human reproduction (Oxford, England)* 2005;20: 702-708.	RCT	107 patients with at least one good quality embryo available for transfer	2 cycles SET: 54 patients vs one cycle DET: 53 patients	Cumulative live birth rate Multiple pregnancy rate Medical cost/live birth	**cLBR/woman:** **2 consecutive SET vs DET:** 41% (95% CI: 27–54] vs 36% (95%CI 23–49), NS **MPR :** **SET vs DET:** 0% vs 37% (95% CI 15–59)(P=0.002). **Medical cost/live birth:** SET vs DET: 13 438 € vs 13 680 €.	Two cycles with SET were equally effective as one cycle with DET, and the medical costs per live birth up to 6 weeks after delivery were the same. However, if lifetime costs for severe handicaps are included, more than €7000 per live birth will be saved after implementing SET.	

Lukassen HG, et al., *Fertility and sterility* 2004;81: 1240-1246.	Retrospective cost analysis	279 pregnancies 135 Singleton pregnancies 144 twin pregnancies	No intervention Medical costs per singleton and twin pregnancy after IVF Between 1995 and 2001	Medical costs per singleton and twin pregnancy after IVF	In patients pregnant with twins, the incidence of hospital antenatal care, complicated vaginal deliveries, and caesarean sections was higher and was associated with more frequent and longer maternal and neonatal hospital admissions. Maternal and neonatal hospital admissions were the major cost drivers. **Total medical costs: singletons vs Twins: €2,549 vs €13,469.**	The medical cost per twin pregnancy was more than 10,000 higher than per singleton pregnancy. A reduction in the number of twin pregnancies by elective single ET will save substantial amounts of money.	
Kjellberg AT, et al., *Human reproduction (Oxford, England)* 2006;21: 210-216.	RCT	661 women <36y, first or second IVF cycle with at least two goo quality embryos	330 SET vs 331 DET	Maternal and Paediatric costs for health care Costs of productivity losses Quality of life	**SET vs DET (330 women):** **Total health cost:** €3069989 vs €4064837 **Mean health cost per woman:** €9309 vs €12318, p=0.002 **Difference of additional cost for DET:** €994848 **Incremental Cost-effectiveness ratio ICER:** €73307 per extra deliver live-born child **Incremental ICER + productivity:** €91701	The SET strategy is superior to the DET strategy, when number of deliveries with at least one live-born child, incremental cost-effectiveness ratio and maternal and paediatric complications are taken into consideration.	
Carpinello OJ, et al., *Applied health economics and health policy* 2016;14: 387-395.	Retrospective cohort study	Medical records of patients who conceived with IVF (n = 116)	No intervention between 2007 and 2011	Healthcare costs per cohort, extrapolated costs assuming 100 patients per cohort, and incremental costs per infant delivered	**SET vs DET vs ≥3 embryos**: **Premature singleton deliveries**: 6.3 % vs 9.1 % vs 10.0 %. **caesarean delivery** 26.7 % vs 36.6 % vs 47.1 %. **Extrapolated costs per cohort** US$718,616 vs US$1,713,470 vs US$1,227,396	Attempting to improve IVF pregnancy rates by permitting multiple embryo transfers results in sharply increased rates of multiple gestation and preterm delivery. This practice yields a greater frequency of adverse perinatal outcomes and substantially increased healthcare spending.	
Gerris J, et al., *Human reproduction (Oxford, England)* 2004;19: 917-923.	prospective observational study	367 patients: 30.9y	206/367 (56.1%) SET vs 161/367 (43.9%) DET from January 1, 2000, until December 31, 2001	LBR Neonatal costs and Maternal costs Total costs	**SET vs. DET:** **LBR**: 37.4% vs. 36.6%. **duration of pregnancy:** 39.0 ± 1.4 vs 38.3 ± 2.2 weeks; P = 0.055), **percentage prematurity:** 8.5 vs 23.8%; P = 0.033 **Percentage of neonates hospitalized:**	transfer of a single top-quality embryo is equally effective as, but substantially cheaper than, double embryo transfer in women <38 years of	

					5.7 vs 17.9%; P = 0.121 **Duration of neonatal hospitalization** 6.3 ± 2.2 vs 10.3 ± 10.1 days; P = 0.01. **Total cost**: €4700 ±3239 vs €8613± 10 105; P = 0.105) **Neonatal costs:** €451± 957 vs €3453±8154; P < 0.001 **Maternal costs:** €4250± 2882 vs €5160 ±4106; P = 0.152	age in their first IVF/ICSI cycle.	
Veleva Z, et al., *Human reproduction (Oxford, England)* 2009;24: 1632-1639.	observational study	In the DET period, 826 women had 1359 fresh and 589 FET cycles; in the eSET period, 684 women had 1027 fresh and 683 FET cycles	the DET period (fresh cycles: 1995–1999, FET cycles: 1995–2000), in which eSET was used experimentally; and the eSET period (fresh cycles: 2000–2004, FET cycles: 2000– 2005), in which eSET was more routinely practiced.		cPR/OPU: 38.2 vs 33.1%, P = 0.01 cLBR/OPU: 28.0 vs 22.5%, P = 0.002 cLBR/woman: 41.7 vs 36.6%, P = 0.04. cMPR: 8.9 vs 19.6%, P= 0.0001. **eSET vs DET**: Total costs: €3837964 vs €4865304 **Costs of the fresh cycles:** €3383250 vs €4473172 (OR 0.95 (95%CI0.91-0.97)) **Costs of the FET cycles:** €454714 vs €5890 (OR 1.03 (95%CI 0.997-1.07)) Total costs per woman: €5611 vs €5890 A term live birth in the eSET period was 19 889 euros less expensive than in the DET period.	eSET with cryopreservation is more effective and less expensive than DET and should be adopted as a treatment of choice.	
Velez MP, et al., *Human reproduction (Oxford, England)* 2014;29: 1313-1319.	Prospective comparative cohort study	7364 IVF cycles performed in Quebec	Period I: IVF treatment in Quebec during 2009, before implementation of the public IVF programme Period II: cycles performed at the same centres during 2011	utilization, pregnancy rates, multiple pregnancy rates and costs.	**2009 vs. 2011:** eSET transfer in 1.6% of the cycles vs 31.6% (P, 0.001). **CPR** 39.9% vs. 24.9% (P, 0.001), **MPR**: 29.4% vs. 6.4 (P,0.001). **Government costs per IVF treatment cycle:** CAD$3730 vs CAD$4759. **Cost per live birth** (up to 1 year post-delivery): CAD$49 517 to CAD$43 362 per baby conceived by either fresh and frozen cycles.	Universal coverage of IVF increased access to IVF treatment, decreased the multiple pregnancy rate and decreased the cost per live birth, despite increased costs per cycle.	
van Heesch MM, et al., *Human reproduction (Oxford, England)*	Retrospective study	302 multiples and 278 singletons.	children born from IVF in 2003–2005,	Hospital resource utilization Hospital costs	Multiples vs singletons: The risk of hospitalization: OR 4.9, 95% CI 3.3–7.0 Outpatient visits: OR 2.6, 95% CI 1.8–3.6 Medical procedures: OR 1.7, 95% CI 1.2–2.2	Hospital costs from birth up to age 5were significantly higher among IVF/ICSI multiple children compared with IVF/	

2015;30: 1481-1490.					The average hospital costs: -during the birth admission period: €10 018 vs €2093 (P, 0.001) -After the birth admission period to the first birthday: €1131 vs €696 (n.s.) -From the second to the fifth life year: €1084 vs €938, (n.s.) Hospital costs from birth up to age 5 were 3.3-fold higher for multiples compared with singletons (P, 0.001). Among multiples and singletons, respectively, 90.8 and76.2% of the total hospital costs were caused by hospital admission days and 8.9 and 25.2% of the total hospital costs during the first 5 years of life occurred after the first year of life.	ICSI singletons; however, when excluding the costs incurred during the birth admission period, hospital costs of multiples and singletons were comparable.	
Motohashi T, et al., *Reproductive medicine and biology* 2004;3: 159-164.	observational study	Control group: 58 singletons and 21 twins; High-order multiple group: 14 triplets and 1 quadruplets	No intervention: between 1997 and 2002	gestational ages: The average inpatient medical care cost for mother and child(ren), from maternal admissions after 12 weeks' gestation to the discharge of all family members from hospital,	gestational ages: 39.4 (singletons), 35.6 (twins), 31.9 (triplets) and 25.1 (quadruplets) weeks (P < 0.001 by ANOVA). Birthweights: 2886 ± 425 g, 2117 ± 623 g, 1430 ± 373 g, and 633 ± 77 g (mean ± SD), respectively (P < 0.001). The average inpatient medical care cost for mother and child(ren), from maternal admissions after 12 weeks' gestation to the discharge of all family members from hospital, was ¥703 279 yen (~US$5861), ¥4 903 270 (~US$40 861), ¥11 810 327 (~US$98 419), and ¥44 961 000 (~US$374 675), respectively (P < 0.001).	The present study outlined the high costs of medical care for HOM pregnancies.	
Koivurova S, et al., *Human reproduction (Oxford, England)* 2004;19: 2798-2805.	obs study	215 IVF mothers and 225 IVF neonates vs 662 control mothers and 388 control children	No intervention; 1990-1995		The total health care costs for an IVF singleton until the end of the neonatal period were 5780 euros and 15 580 euros for an IVF twin. The health care costs were 1.3-fold for IVF singletons and 1.1-fold for IVF twins compared to control singletons and twins.	The health care costs of an IVF singleton neonate were higher than those of a spontaneously conceived control neonate with similar backgrounds. For twins the health care costs were equal.	

					The costs for twins were ~3-fold compared to singletons		
Chambers GM, et al., *JAMA pediatrics* 2014;168: 1045-1053.	Retrospective population cohort study	Conceived following ART: 1% of 226 624 singleton, 15.4% of 6941 twin, and 34.7% of 285 HOM infants.	No intervention	economic and health services assessment of the frequency, duration, and cost of hospital admissions during the first 5 years of life for singleton, twin, and higher-order multiple (HOM) children Contribution of ART to the incidence and cost of multiple births	Undesirable effect Twins and HOMs > singletons Stillbirth: 3.4 and 9.6 times; Neonatal death: 6.4 and 36.7 times Preterm birth: 18.7 and 525.1 times Small for gestational age 3.6 and 2.8 times The mean hospital costs of a singleton, twin, and HOM child to age 5 years were $2730, $8993, and $24 411 (in 2009-2010US dollars), respectively.	Compared with singletons, multiple-birth infants consume significantly more hospital resources, particularly during the neonatal period and first year of life.	
Fiddelers AA, et al., *Human reproduction (Oxford, England)* 2006;21: 2090-2097.	observational study Cost analysis of a RCT (Van Montfoort et al., 2006)	308 couples, first IVF cycle with at least two embryos (2PN) available	154 SET vs 154 DET; January 2002 to December 2004	cost-effectiveness of one fresh cycle eSET versus one fresh cycle DET	Successful pregnancy rates were 20.8% for eSET and 39.6% for DET. Societal costs per couple were significantly lower after eSET (€7334) compared with DET (€10 924). The ICER of DET compared with eSET was €19 096, meaning that each additional successful pregnancy in the DET group will cost €19 096 extra.	One cycle eSET was less expensive, but also less effective compared to one cycle DET.	
Stillman RJ, et al., *Fertility and sterility* 2009;92: 1895-1906.	retrospective study	Infertile women undergoing 15418 consecutive IVF; good prognosis patients.	eSET: 583 autologous + 201 donor cycle vs DBT: 3300 autologous+ 783 donor cycle; January 2002 to December 2007		**eSET vs. DET:** **PR:** 65% vs. 63% **MPR** (Twin rate) 1% vs. 44%. **Donor cycles** **PR** 63% vs. 74% **MPR:** 2% vs. 54%. There was no decrease in overall pregnancy rates: 1.5% to 8.6% of all autologous transfers and 2.0% to 22.5% of all transfers to donor oocyte recipients	Selective eSET use among good-prognosis patients can significantly reduce twin pregnancies without compromising pregnancy rates. Patients are more likely to choose eSET when freed from financial pressures to transfer multiple embryos.	

Papers included as background information

(Collins et al., 2002), (Gleicher and Barad, 2006), (Ryan et al., 2004), (Lemos et al., 2013), (Sitler et al., 2019), (Polinder et al., 2008), (Monteleone et al., 2018).

PICO 3: Which psychosocial issues should be considered for couples/individuals having a singleton or multiple pregnancy/birth?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Wenze SJ. et al., *Archives of women's mental health* 2015;18: 163-176.	Systematic review	27 papers (between 1989-2014). More than 40.000 patients. parents of multiples vs parents of singletons	No intervention	mental health outcomes in the postpartum and early childhood periods: symptoms of depression, anxiety, and parenting stress		mental health outcomes in the postpartum and early childhood periods are, in general, worse for parents of multiples versus parents of singletons, and may be worse in the case of higher-order multiples versus twins. In contrast, we found no clear evidence for differences in mental health outcomes in the antenatal period between women expecting singletons versus multiples. Postpartum (but not early parenthood) outcomes may be worse for parents of multiples resulting from ART versus NC multiples, while maternal antenatal depressive symptoms may be higher among women with NC multiples versus ART.	
van den Akker O. et al., *Reproductive biomedicine online* 2016;33: 1-14.	Systematic review	8 papers, 1732 mothers.	No intervention	-depression, anxiety or stress of assisted reproductive technology twins/multiple birth mothers versus assisted reproductive technology singleton birth mothers;		Mothers of assisted reproductive technology multiple births exhibit significantly more stress and depression compared with mothers of assisted reproductive technology singleton births.	

				-depression, anxiety or stress of assisted reproductive technology twins/multiple birth mothers versus natural conception twins/multiple birth mothers.			
Porat-Zyman G. et al. *Women & health* 2018;58: 72-91.	Systematic review	2001-2012: 561 mothers	No intervention	maternal mental health (MMH) 1-month post-partum changes in MMH over 4 years in relation to birth circumstances (singleton/twins, full-term/pre-term infant/s, first/non-first child), internal resources (adult attachment styles), and external resources (marital quality and maternal grandmother's support) at 1 month post-partum.		Shortly after birth, mothers at risk for poorer MMH were those who gave birth prematurely or were characterized by insecure attachment styles, lower marital quality, younger age, or a higher level of education. The mothers with a good prognosis for improvement in MMH were those who had given birth prematurely or were younger, more highly educated, or multiparous. Women with insecure attachment or lower marital quality reported lower MMH one month after delivery that did not improve over time, and the MMH of older or less educated mothers deteriorated over time. Marital quality mitigated or exacerbated the effects of birth circumstances and insecure attachment style on MMH shortly after giving birth.	
Noy A, et al. *Women & health* 2014;54: 317-335.	Observational study	274 mothers. Of these, 127 were mothers of singletons and 147 mothers of twins.	No intervention	Mother's well-being and distress		being a mother of a singleton or twins did not contribute to the explanation of variance in well-being or distress. Marital quality provided the strongest explained variance for both well-being and distress. Mother's health, attachment anxiety and self-differentiation also explained significant amounts of the variance.	

De Roose M, et al. *Women and birth : journal of the Australian College of Midwives* 2018;31: e197-e203.	Observational study	151 singleton mothers and 101 twin mothers	No intervention	parenting stress levels		Coparenting seems to be a significant coping strategy reducing the level of parenting stress in singleton and twin mothers, irrespective of their personal and obstetric characteristics.	
Spinelli M, et al. *Journal of family psychology : JFP : journal of the Division of Family Psychology of the American Psychological Association (Division 43)* 2013;27: 873-883.	Observational study	125 mothers and their preterm infant	No intervention	Parenting stress and maternal interaction quality during play were measured at 4, 24, and 36 months corrected age.		Mothers of multiples and infants with more medical risks and shorter hospitalization, and mothers with lower education and more depressive symptoms, reported more parenting stress at 4 months of age. Parenting stress decreased over time for mothers of multiples and for mothers with lower education more than for mothers of singletons or for mothers with higher educational levels. Changes in parenting stress scores over time were negatively associated with maternal behaviours during mother-infant interactions.	
Boivin M, *Journal of child psychology and psychiatry, and allied disciplines* 2005;46: 612-630.	Observational study	Parents (2122 mothers and 1829 fathers) of 5-month-old infants, and parents of 5-month-old infant twins (510 families)	No intervention	parenting perceptions and behaviours: parental self-efficacy, perceived parental impact, parental hostile-reactive behaviours and parental overprotection genetic-environmental aetiology analysis			
Anderson KN et al., *Family process* 2017;56: 997-1011.	Observational study	57 families with eighty 6- to 12-year-old MAR twin and singleton children	No intervention	Parent-child relationships and interactional behaviours twins vs singletons			

Golombok S, et al., *Human reproduction (Oxford, England)* 2007;22: 2896-2902.	Observational study	10 families with triplets and matched groups of 15 families with twins and 30 families with singletons.	No intervention	Standardized measures of the mother's psychological well-being (parenting stress, depression and quality of marriage) and standardized measures of the child's psychological development (emotional/behavioural problems and general development) were completed by the mother.		The birth of triplets or twins does appear to cause difficulties for parents in the early years, however, the children themselves do not seem to experience markedly raised levels of psychological or developmental problems.	

PICO 4. Which personal, regulatory and reimbursement factors are expected to affect the decision for number of embryos to transfer? (Narrative)

Evidence Table (not applicable, narrative chapter)

PICO 5. Should the number of previous unsuccessful ART treatments be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, what is the cut off?

Evidence Table

Reference	**Study Type**	**Patients Include: No. of patients Patient characteristics + group comparability**	**Interventions (+comparison) Include: Study duration / follow-up**	**Outcome measures Include: Harms / adverse events**	**Effect size**	**Authors conclusion**	**Comments**

Monteleone PA, et al., Reprod biomed. online 2016;33: 161-167.	retrospective study	234 patients, 18-38 y, first or second IVF cycle, at least four oocytes found, At least 2 surplus top quality blastocyts available for cyropreservation after transfer	fresh eSET (234), and those who failed to conceive (n= 58 (24,8%)) underwent a second vitrified-warmed embryo transfer: eDFET (n = 102) or eSFET (n = 40), D5 transfer	Implantation rate, CPR and MPR	No difference in CPR , MPR was lower for eSET: eSFET: CPR: 42.5% & MPR 5.9% vs eDFET : CPR 35.3% & MPR 22.2%.	For patients with a good prognosis who failed to conceive in the first fresh eSET, no advantage was found in undergoing an eDET compared with eSET in a second frozen cycle.	there is no published evidence on how many repeated implantation failures could potentially justify DET instead of SET

Papers included as background information

(McLernon et al. 2016), (Roberts et al. 2010), (Strandell et al. 2000), (Templeton et al. 1996), (Thurin et al., 2005)

PICO 6. Should the duration of infertility be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, what is the cut off?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Monteleone PA, et al., Reproductive biomedicine online 2016;33: 161-167.	retrospective study	234 patients, 18-38 yo, first or second IVF cycle, at least four oocytes found, At least 2 surplus top quality blastocyst available for cryopreservation after transfer	234 underwent eSET in a fresh cycle, and those who failed to conceive (n= (24,8%) underwent a second vitrified-warmed embryo transfer: eDFET (n = 102) or eSFET (n = 40). Embryos were transferred and vitrified on day 5 of development.	CPR MPR	**eSFET vs DET:** **CPR:** 42.5% (17) vs CPR 35.3% (36) **MPR:** 5.9% vs 22.2%	for patients with a good prognosis who failed to conceive in the first fresh eSET, no advantage was found in undergoing an eDFET compared with eSFET in a second cycle.	

Yilmaz N, et al., Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2013;29: 600-602.	retrospective study	404 women: age: 20–35 years.BMI: 18 and 29 kg/m2. time periods of 1 year before and after the new law (6 March 2010).	Group 1: n = 281 SET with group 2: n = 123 DET.	CPR, Abortion rate, LBR, MPR, gestational age, birth weight, pregnancy outcome, neonatal care unit admissions	SET (281) vs DET (123): MPR: 0 vs 12 (P= 0.001); LBR/ clinical pregnancy 74.16% vs 76.19%; LBR/transfer: 31.7% vs 26%; Gestational age: 38 (28-41) vs 37 (25-40), (P= 0.001), Perinatal fatal morbidity/ongoing pregnancy: 7.9% vs 59.4% (P= 0.001)	Under the SET legislation, multiple pregnancy rates and perinatal complications are significantly reduced without causing a significant decline in the pregnancy rates.	SET vs. Multiple ET

Papers included as background information

(McLernon et al. 2016), (Hunault et al. 2004), (Leridon,Spira 1984)

PICO 7. Should a previous pregnancy/live birth from ART treatment be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Luke B, et al. American journal of obstetrics and gynecology 2015;212: 676.e671-677.	Other (Logistic regression modelling study)	SET at cycle 1: 33065 cycles DET at cycle 1: 126921 cycles. Fresh SET at cycle 2: 8682 cycles Thawed SET at cycle 2: 6747 cycles. Women with no previous conceptions or live births (nulligravid).	SET over 2 cycles with DET in 1 cycle. cycles from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System for 2006-2012 were used	LBR; cLBR. MBR	The cumulative LBR over 2 cycles with SET was similar to or better than the LBR with DET in a single cycle	The cLBR is as good or better with SET over 2 cycles than with DET in 1 cycle, while greatly reducing the probability of a multiple birth	This study did not compare outcomes in women with previous Live birth and therefore could not answer the question on whether the number of previous births should be considered a factor in

							deciding to apply DET instead of SET

Papers included as background information

(Engmann et al. 2001), (Kupka et al. 2003), (Molloy et al. 1995), (Simon et al. 1993), (Bhattacharya et al. 2013), (Lintsen et al. 2007), (McLernon et al. 2016), (Roberts et al. 2010), (Templeton,Morris 1998), (Strandell et al. 2000).

PICO 8. Should female age be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, what is the cut off?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comment
Couples/individuals undergoing ART with own oocytes							
Ma S, et al. Reproductive biology and endocrinology: RB&E 2022;20: 20.	Systematic review and meta-analysis	14 RCTs and 71 observational studies	Studies published through to February 2021. SET vs DET; single IVF cycle with own oocytes	CPR, LBR, MPR, miscarriage rate, Preterm birth rate, gestational age at birth, low birth weight rate, Perinatal mortality, birth defect, NICU admission., caesarean section, gestational diabetes, PE, antepartum haemorrhage, Apgar score 1 <7.	**LBR:** **Patients aged <35y:** DET > SET (OR 0.71, 95%CI 0.61-0.84, I2= 85%, 12 studies) **Patients aged 35-40y:** DET >SET (OR 0.80, 95%CI 0.69-0.94, I2= 69%, 6 studies), **Patients aged ≥40 years:** No difference (OR 0.87, 95% CI 0.54–1.40, I2=69%, P=0.565, 4 studies). **MPR:** **Patients aged <35y**: DET > SET (OR 0.03; 95%CI 0.03-0.05, I2= 0%, P<0.0001, 11 studies) **Patients aged 35-40y**: DET>SET (OR 0.04, 95%CI 0.03-0.06, I2= 0%, P<0.001, 5 studies) **Patients aged ≥40 years**: No difference (OR 0.34, 95%CI0.06-2.03, I2= 0%, P=0.236, 3 studies). **Preterm birth:** **In all age categories:** DET >SET (9.9% vs 31%, OR 0.25, 95%CI 0.21-0.30, I2=0%, P<0.001, 13 studies)	In women aged <40years or if any GQE is available, SET should be incorporated into clinical practice. While in the absence of GQEs, DET may be preferable. However, for elderly women aged ≥40 years, current evidence is not enough to recommend an appropriate number of embryo transfer;	

Kamath MS, et al., *The Cochrane database of systematic reviews* 2020;8: Cd003416	Cochrane review	17 RCTs, 2505 women most women included in the studies were under 36 years of age, with a good prognosis.	A single cycle of SET was compared with a single cycle of DET in 13 studies, 11 comparing cleavage-stage transfers and three comparing blastocyst-stage transfers. One study reported both cleavage and blastocyst stage transfers.	Primary outcomes: LBR and MPR Secondary outcomes: CPR and Miscarriage rate.	**LBR:** DET>SET (RR 0.67, 95% CI 0.59 to 0.75; I2 = 0%; 12 studies, 1904 participants; low-quality evidence). **MPR:** DET>SET (Peto OR 0.16, 95% CI 0.12 to 0.22; I2 = 0%; 13 studies, 1952 participants; moderate-quality evidence).	Although DET achieves higher live birth and clinical pregnancy rates per fresh cycle, the evidence suggests that the difference in effectiveness may be substantially offset when elective SET is followed by a further transfer of a single embryo in fresh or frozen cycle, while simultaneously reducing multiple pregnancies, at least among women with a good prognosis.	
Mejia RB, etal. *F&S reports* 2021;2: 50-57.	retrospective study	49333 patients aged 21 to 45 years; with initial oocyte retrievals cycles Age categories: <35, 35–37, 38–40, and>40y; Gravidity: 0; Parity: 0	Initial eSET (n=17576) vs DET (n= 31757) January 2014 – December 2015 + subsequent frozen embryo transfers occurring through December 2016 that used embryos from the initial retrieval (n=725)	Primary outcomes: LBR, cLBR, Secondary outcomes: MPR, Preterm birth, cycle to pregnancy, infant birthweight, and perinatal mortality	**eSET vs. DET:** **cLBR:** **In all age categories:** 74% vs 57 % (AOR 1.32, 95% CI 1.26-1.38). **< 35y**: AOR 1.31, 95% CI 1.24-1.39 **35-37y**: AOR 1.27, 95% CI 1.15-1.40 **38-40y:** AOR 1.06; 95%CI 0.90-1.24 **>40y**: AOR 1.36; 95%CI 0.91-2.04 **MPR:** **In all ages categories:** 8% vs 34% (AOR 0.13; 95%CI 0.12-0.14) **<35y: AOR 0.14; 95%CI 0.12-0.17** **35-37y**: AOR 0.10, 95% CI 0.06-0.16 **38-40y:** AOR 0.12; 95%CI 0.11-0.13 **>40y**: AOR 0.31; 95%CI 0.07-1.39 **Preterm birth**: 1.2 % vs 2.8%. **Perinatal mortality**: 0.5% vs 1.2%.	The association of initial eSET with a higher cLBR and markedly improved perinatal outcomes outweigh the relatively minor increase in time to pregnancy, reinforcing the guidance for eSET in initial transfer cycles, particularly in younger patients with a good prognosis.	
Veleva Z, et al., Human reproduction (Oxford, England) 2006;21: 2098-2102.	retrospective study	women 36-39 years	eSET vs. DET: 1224 fresh cycles; 828 frozen embryo transfer (FET): 335 eSET of top-quality embryo, 110 eSET of non-top-quality embryo (nt-eSET), 194 compulsory single embryo (cSET) and 585 DET	LBR and cLBR	**eSET of top-quality embryo and nt-eSET of non-top-quality embryo vs. DET:** **LBR:** 26% and 15.5% vs. 21.9% **cLBR** 41.8% and 29.1% vs 26.7% **MPR**: 1.7% and 2.8% vs. 16.6%	The eSET policy can be applied also to patients aged 36–39 years, reducing the risk of multiple birth and increasing the safety of assisted reproduction technique (ART) in this age group.	
Niinimaki M, et al., Human reproduct	retrospective	628 women 40-44 years. The characteristics	women treated between 2000-2009. eSET (n= 264) vs. DET (n=364)	LBR and cLBR MPR and cMPR (twins rate in fresh cycle and the cumulative	**eSET vs. DET:** **LBR:** 11 vs 13.6% **cLBR**: 13.2 vs 22.7%	An eSET policy can be applied with gratifying cumulative clinical pregnancy and live birth rates in older	

ion (Oxford, England) 2013;28: 331-335.	coh ort	of the two patients' groups are not comparable	In the subsequent frozen-thawed embryo transfer cycles, SET/DET was performed in both groups according to the number of embryos available and the opinion of the couple.	twins rate in subsequent cycles)	**MPR:** fresh cycle: 0% vs. 7.5% **cMPR:** 6.7% vs 8.3% All of the twin pregnancies in the eSET group resulted from frozen and thawed DET embryo transfer cycles.	women (40 –44 years) with a good prognosis.	
Tannus S, et al., Reproductive biomedicine online 2017;35: 733-738.	retr osp ecti ve stud y	411 women aged 41- 43y.	SET vs DET in fresh blastocyst transfer cycles. eSBT	LBR, MPR, cLBR, cMPR	**eSET vs. DET; Fresh cycles:** **LBR:** 19.3% vs. 26.5%. **MPR**: 0% vs 17.5% **eSET vs DET; frozen cycles:** **LBR**: 9.4% vs. 13.7 %; cLBR: 28% vs 31.1%. **cMPR:** 0% vs. 14.9%, p= 0.03.	Women aged 40-43y, when fully expanded blastocysts are achieved, maternal age is not a predictor for live birth, and elective single blastocyst transfer can be performed without compromising cLBRs.	
Lawlor DA, Nelson SM. Lancet (London, England) 2012;379: 521-527.	pros pect ive stud y	124,148 IVF cycles; Age categories: 18-34 (53821); 35-37 (32178); 38-39 (18874); 40-42 (15145); 43-44 (3200); 45-50 (930)	between January 2003, and December 2007. SET (14749; 10.5%), DET (117378 (83.3%) or TET (8772 or 6.2%)	Outcomes: LBR, MPR, low birthweight (<2.5 kg), preterm birth (<37 weeks), and severe preterm birth (<33 weeks) in women younger than 40 years and those aged 40 years or older.	**<40 years; SET vs. DET** **LBR:** OR 2.33, 95% CI 2·20–2.46 **MPR:** OR 20.6; 05%CI 14.14-29.93 **Preterm birth:** OR 2.25; 95%CI 1.91-2.66 **Severe preterm birth:** OR 2.33; 95%CI 1.68-3.24 **≥40 years; SET vs. DET** **LBR:** OR 3.12, 95% CI 2.58-3.77 **MPR:** OR 4.32; 05%CI 1.57-11.9 **Preterm birth:** OR1.27; 95%CI 0.72-2.23 **Severe preterm birth:** OR1.02; 95%CI 0.35-2.89	Transfer of three or more embryos at any age should be avoided. The decision to transfer one or two embryos should be based on prognostic indicators, such as age and the number of embryos successfully fertilised	
Arab S, et al., Reproductive sciences (Thousand Oaks, Calif) 2020.	retr osp ecti ve stud y	1140 FET cycles; 818 women aged up to 39y and 97 women aged 40y or older.	FET cycles between January 2008 and December 2019 in women aged ≤ 39y: 744 SET vs 74 DET; women ≥40y: 63 SET vs 34 DET	CPR, LBR and MPR	**≤ 39y: SET** (n=744) **vs. DET** (n=74) **LBR:** 20.21% vs 12,16% **MPR**: 1.63% vs 6.7% **≥40y: SET** (n=63) **vs DET** (n= 34) **LBR:** 6.34% vs 0 **MPR:** 0% vs 0%.	Single embryo transfer should be offered even in women ≥ 40 years of age or transferring lower quality embryos since transferring more did not increase outcomes in this group, and SET is likely the safest path.	
Mancuso AC, et al. Fertility and sterility 2016;106:	retr osp ecti ve coh ort	USA, 464 centres, Patient ages <35 and 35–37 years old	during 2013, eSET vs DET	LBR and MBR.	No significant differences in clinic level LBR for each age group (<35 y vs 35-37 y). There was a linear decrease in MBR with increasing eSET rate and no significant difference in clinic-level LBR for each age group. Cycle-level analysis found slightly higher LBR with DET, but this was mainly observed in women aged	A linear reduction in MPR, and important, little to no effect on clinic-level LBR with increasing rates of eSET -->eSET is effective in decreasing the high MPR associated with IVF and suggests that eSET should be used	

1107-1114.					35–37 years or with four or more embryos available for transfer and confirmed the marked reduction in MBR with eSET.	more frequently than is currently practiced.	
Couples/individuals undergoing ART with donor oocytes							
Merserea u J, et al Fertility and sterility 2017;108: 750-756.	retr osp ecti ve coh ort	281660 patients age categories: 18-29; 30-34; 35-37; 38-40 and 41-43y;	2004-2013; SET vs DET. 181523 women with autologous fresh first cycle; 37,658 with fresh second cycles, and 35,446 with frozen thawed second cycles. **27,033 with fresh first oocyte donor cycles**	LBR and MBR after SET DET were measured.	there was little to no effect of maternal age. **LBR (in all age categories)** No embryo cryopreserved, CST: SET vs DET: 20.1% vs. 41.7%; BT: 45.6% vs. 57.6% ≥1 embryos cryopreserved: CST: SET vs DET: 38.5% vs. 53.1%; BT: 56.1% vs. 66.6% **MPR (in all age categories)** No embryo cryopreserved, CST: SET vs DET: 4.3% vs.27.4 %; BT: 0.9% vs. 38.1% ≥1 embryos cryopreserved: CST: SET vs. DET: 0% vs 35.3%; BT: 1.7% vs. 49.4%	This study reports a 10%-15% reduction in live birth rate and a 47% decrement in multiple birth rate with SET compared with DET in the setting of favourable patient prognostic factors.	

Papers included as background information

(Baird et al., 2005), (Min et al. 2010), (Scotland et al. 2011), (ASRM 2021), (Rodriguez-Wallberg et al. 2019), (Jeve et al. 2016), (Jacobsson et al., 2004), (Kenny et al., 2013), (Lean et al., 2017), (Reddy et al., 2006), (Yogev et al., 2010).

PICO 9. Should ovarian response (i.e. low, normal or high) be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, what is the appropriate transfer strategy for low, normal or high responders?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments

Moustafa MK, et al. Reprod Biomed Online. Jul;17(1):82-7. 2008	RCT	81 patients: eSET (n=40) vs. DET (n=41). ≤30 years old, at least 1 good quality embryo on day of transfer (grade I-II). ET day 2-3. Slow freezing	eSET vs DET in fresh and frozen cycle	Primary outcome: LBR Secondary outcome: MPR ET on day 2- day 3; Number of oocytes retrieved: 10.23 (SET) vs 9.80 (DET); NS	**Fresh cycles: eSET (n=40) vs DET** (n=41): fresh cycles **LBR: 30.00% vs. 31.71%** **MPR: 0% vs. 12.20%** **Frozen cycles: eSET (n=10) vs. DET (n=16)** **LBR** 42.86% vs. 37.5% MPR: 0% vs 18.75% Summary of the results of all the cycles performed: **cLBR (%/number of women):** 45.00% vs 46.34% **cLBR (%/cycle):** 33.33% vs. 33.33% **cMPR (%/cycle):** 0% vs 14.04%	Elective SET should be the first line of choice; No difference between the DET and eSET in LBR. Higher MPR in DET group in fresh cycles. In frozen cycles no significant differences in LBR and MPR.	very low quality (high risk of selection, performance, and attrition biases): The study by Moustafa and co-workers did not compare outcomes in low or high responder patients and therefore could not answer the question on whether ovarian response should be considered a factor in deciding to apply DET instead of SET

Papers included as background information

(Templeton et al. 1996), (Bancsi et al. 2002), (Broer et al. 2013a), (Broer et al. 2013b), (Oehninger et al. 2015), (Arce et al. 2013), (Soldevila et al. 2007), (Shaker et al. 1992), (Faber et al. 1998), (Surrey,Schoolcraft 2000), (Veleva et al. 2005), (The ESHRE Guideline group on ovarian stimulation, 2020).

PICO 10. In a fresh cycle, should endometrial criteria be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, what is the appropriate cut off?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Huang X et al., The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal	Retrospective study (prediction model)	Prediction model: 2478 patients undergoing fresh cleavage DET Sensitivity, specificity and	SET vs DET For the prediction model: From January 2015 to December 2015	LBR Twin LB probability TLBP	**SET vs. DET LBR**: 62.0% vs. 39.0% a 1 mm increase in endometrial thickness was associated with an increased risk of twinning (OR 1.4; 95%CI 1.1-1.7).	Female age, endometrial thickness, the number of transferred top embryos and previous embryo transfer times were critical variables for the twin live birth prediction model	

Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2020: 1-8.		usefulness of the model: 300 fresh cleavage DET and 550 cleavage SET	For testing the sensitivity and specificity of the model: January 2016 to March 2016				

Papers included as background information

(Craciunas et al. 2019), (Shakerian et al. 2021), (Liao et al., 2021).

PICO 11. In FET, should endometrial characteristics be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART (with own gametes or with donated oocytes/embryos) (hormonal substitution vs. ovulatory cycle)? If yes, what is the appropriate cut off?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
El-Toukhy T, et al., Fertility and sterility 2008;89: 832-839.	Retrospective study	768 consecutive FER cycles The mean endometrial thickness recorded on the day of P supplementation was 9.3 ± 2.1 mm(range, 5–20 mm)	FER cycle between 1997 and April 2006	Implantation, clinical pregnancy, ongoing pregnancy, and LBR.	the clinical pregnancy rate in group B SET cycles (9-14mm) was double that in group A SET cycles (7-8mm) (19.5% vs. 9.5%, respectively; P= 0.1) but similar to the clinical pregnancy rate achieved in group A cycles where more than one embryo was replaced (n = 315; 19.4%; P=.87).	In medicated FER cycles, an endometrial thickness of 9–14mmmeasured on the day of P supplementation is associated with higher implantation and pregnancy rates compared with an endometrial thickness of 7–8 mm.	

Papers included as background information

(El-Toukhy et al. 2008)

PICO 12. Should a different embryo transfer strategy be applied for patients undergoing ART with donor oocytes and donated embryos?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments

Jeve YB, et al., *BJOG : an international journal of obstetrics and gynaecology* 2016;123: 1471-1480.	Systematic review and meta-analysis	11 studies, (n= 81752). From 1 January 1980 to 31 January 2015	SET vs DET, Donor cycles vs autologous cycles	Primary outcome: hypertensive disorders in pregnancy	**Donor pregnancies (DO) vs autologous pregnancies: hypertensive disorders (10 studies):** 35% (341/970) vs 17% (1831/10569); OR 3.92; 95% CI 3.21–4.78. **Small for gestational age (6studies):** 9% (58/630) vs 5% (594/11262); OR 1.81; 95%CI 1.26-2.60 **Caesarean section (6 studies):** 88% (435/690) vs 33% (3452/10283); OR: 2.71; 95%CI 2.23-3.30 **Preterm delivery (9 studies):** 19% (194/1011) vs 9% (1078/11651); OR 1.34; 95%CI1.08-1.66 **No difference in:** **Risk for IUD (2 studies):** 1.3% (4/303) vs 0.8% (3/346); OR 1.39; 95%CI 0.32-6.15 **Gestational diabetes risk (5 studies):** 11% (58/524) vs 10% (52/519), OR 1.25; 95%CI 0.68-2.30	Donor oocyte pregnancy acts as an independent risk factor for pregnancy complications, including hypertensive disorders, small for gestational age, and preterm delivery	
Rodriguez-Wallberg KA, et al., *JAMA pediatrics* 2023;177: 149-159.	Cohort study	115863 singleton births 30713 after SET 5123 after DET From 2007 to 2017	Singletons conceived through SET vs DET	Adverse outcomes in singletons: Gestational hypertension Preclampsia Gestational diabetes Bleeding during pregnancy Placental abruption	A higher risk of neonatal death was found in singletons after DET vs SET (OR, 2.67; 95%CI, 1.28-5.55]; ARD,0.2 percentage points [95%CI,0.0-0.4 percentage points]). Frozen embryo transfers: DET was associated with a higher risk of low birthweight (OR, 1.64	These results indicate a higher risk of adverse outcomes following DET, even when the result is a singleton birth, vs singletons born after SET. Adverse outcomes were mainly observed in singletons following DET using frozen embryos and blastocysts.	

				Prelabor rupture of membranes Caesarean section Induced delivery Infant death within 0-27d Gestational age at delivery Low birthweight Apgar score Congenital malformation	[95%CI, 1.19-2.25]; ARD, 2.0percentage points [95%CI,0.5-3.5 percentage points]). Blastocyst transfers: DET was associated with very preterm birth (relative risk ratio, 2.64 [95%CI, 1.50-4.63]; ARD, 1.8 percentage points [95%CI,0.3-3.4 percentage points]) and low birthweight (OR, 1.83 [95%CI, 1.29-2.60]; ARD, 3.2 percentage points [95%CI,0.9-5.5 percentage points]).		
Acharya KS, et al. ***Fertility and sterility*** **2016;106: 603-607.**	Retrospective cohort study	13393 donor-recipient cycles 3,157 donor cleavage-stage transfers and 10,236 donor blastocyst transfers. from 2011 to 2012	Embryos transferred in donor IVF cycles SET vs DET	Pecentage of compliant cycles with the ASRM guideline 2009 MPR according to the number embryos transferred	**Cleavage-stage**: SET (n=249) vs DET (n=2538): CPR: 41.4% (103) vs 55.0% (1397) LBR: 33.3% (83) vs 45.8% (1163) Singletons: 98.9% (93) vs 67.0% (884) MPR: 1.1% (1) vs 33.0% (436) HOM: 0% (0) vs 0.7% (9) Miscarriage rates: 19.4% (20) vs 16.1% (226)	The majority of donor cleavage-stage transfers are compliant with current guidelines, but the transfer of two embryos results in a significantly higher MPR compared with single-embryo transfer. The majority of donor blastocyst cycles are noncompliant, which appears to be driving an unacceptably high MPR in these cycles.	
Peigné M, et al., ***Fertility and sterility*** **2023;119: 69-77.**	Retrospective study	73 singletons with donated embryos (exposed) 136 singletons after autologous FET (nonexposed) From 2003 tp 2018			HDPs (24.6% vs. 11.9%) were significantly more frequent among the donated-embryo pregnancies, mostly in its severe forms (17.5% vs. 4.6%). In contrast, their respective isolated hypertension frequencies were comparable (7.0% vs. 7.3%). Multivariate analysis retained increased severe HDP risk with donated embryos (odds ratio 2.08 [95% confidence interval:	Even for young women, the risk of severe HDP was 4 times higher for donated-embryo pregnancies than for autologous-FET pregnancies. The HDP risk must be acknowledged to inform donated-embryo recipients and provide careful pregnancy monitoring.	

					1.08-4.02]). No significant effect of endometrial preparation was observed. C-sections were more frequent for donated-embryo pregnancies (47.3% vs. 29.2%). Newborns from embryo donation or autologous FET were comparable for prematurity, birth weight and length, Apgar score, small for gestational age, large for gestational age, neonatal malformations, and sex ratio.		

Papers included as background information

(Rodriguez-Wallberg et al., 2019)

PICO 13. Should a different embryo transfer strategy be applied for gestational carriers?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Namath A, et al., Fertility and sterility 2021;115: 1471-1477.	Retrospective study	583 frozen embryo transfer cycles with vitrified high-grade blastocysts (grade BB or higher) to GCs	One or 2 embryo frozen embryo transfers with and without PGT-A. From 2009 to 2018		SET vs. DET: LBR: 36.8% vs. 51.3% MPR: 1.9% vs. 20.0% Preterm Birth (<37w): 13.4% vs. 40% Very preterm (<32 w): 0.6% vs. 6.3% Extremely preterm (<28w): 0.6% vs 3.8%	frozen embryo transfer cycles in GCs with DET were associated with more preterm births and lower birth weights compared with those of SET. Intended parents and GCs should be counselled that DET is associated with greater risks of adverse pregnancy and perinatal outcomes, which mitigates higher live birth rates.	

Wang AY, et al. The Australian & New Zealand journal of obstetrics & gynaecology 2016;56: 255-259.	observational study	557 surrogacy cycles: 169 intended parents' cycles and 388 gestational carrier cycles The age range of intended parents (females: 20–58 years; males: 26–70 years) compared to 22–45 years for gestational carriers.	557 surrogacy cycles during 2004–2011; SET (248; 68.9%) vs. DET (110; 30.5%). 1 January 2014 to 31 December 2011	CPR, LBR, Twin rate, preterm birth rate and low birth rate.	SET vs. DET: CPR: 27.4% vs. 24.5% LBR: 19.0% vs 19.1% MPR (twins): 0% vs. 22.7% Preterm birth: 12.8% vs 30.8%.	To avoid adverse outcomes for both carriers and babies, SET should be advocated in all gestational surrogacy arrangements.	retrospective large size

Papers included as background information

(Swanson et al., 2021); (Shenfield et al., 2005).

PICO 14. . In fresh transfer, should embryo criteria be considered a factor in deciding to apply DET instead of (e)SET at cleavage-stage for couples/individuals undergoing ART? If yes, which criteria are appropriate?

Evidence Table

Reference	**Study Type**	**Patients Include: No. of patients Patient characteristics + group comparability**	**Interventions (+comparison) Include: Study duration / follow-up**	**Outcome measures Include: Harms / adverse events**	**Effect size**	**Authors conclusion**	**Comments**
Couples/individuals undergoing ART with their own oocytes							
Martikainen H, et al., Human reproduction (Oxford, England) 2001;16: 1900-1903.	RCT	144 patients underwent randomization, Inclusion criteria: ≥ 4 good quality embryos (<20% fragmentation, even-sized	Fresh cycles: SET (74 patients) vs. DET (70 patients).	IPR CPR: confirmed on ultrasound. cLBR	**Fresh SET (74) vs. DET (70):** **CPR**: 32% (24) vs 47%(33) **LBR:** 92%(22) vs 85%(28) **MPR:** 5% vs. 39% **Frozen SET (84) vs. DET (56):** **CPR:** 47.3% vs. 58.6%	No difference in terms of cumulative live birth rate between two groups. Multiple pregnancy rate increased in DET group (assessed in fresh embryo transfer, P=0.01).	no specific data if fresh or frozen unclear detection and possible bias

		blastomeres at day 2); 1° cycle; different age according to centres. ET day 2.			**<u>cLBR per patient</u>**: 39% vs. 51%, NS **<u>Twins:</u>** 1 vs. 0 Power calculations to show diff of 10%: 360 patients should have been needed : only 144 were in the trial.		
Thurin A, et al. New England journal of medicine 2004;351: 2392-2402.	RCT	661 pt underwent randomization, 330 pt in eSET group and 331 pt in DET group. Inclusion criteria: < 36y, 1°-2° cycle, ≥ 2 good quality embryos (<20% fragm, 4-6 cells at day 2, 6-10 cells at day 3). ET day 2 (90%). Slow freezing?	eSET fresh + eSET frozen vs DET fresh (eSET in frozen embryo transfer).	Primary outcome: cLBR Secondary outcomes: pregnancy, implantation, multiple birth, spontaneous abortion and ectopic pregnancy rates.	**SET vs. DET:** **LBR:** 27.6% vs. 42.9% **MPR:** 0.8% vs. 33.1% **cLBR (fresh and frozen SET cycles):** 38.8% vs. 42.9%	A fresh eSET followed (if there was no live birth) by the transfer of one thawed embryo, results in a marked reduction in the multiple pregnancy rate (P<0.001) but not in a reduction of live birth rate (P=0.30)	relative low number of patients
Fauque P, et al., Fertility and sterility 2010;94: 927-935.	prospective non-randomized study	151 couples women<36 years with adequate ovarian function, in their first or second IVF or intracytoplasmic sperm injection (ICSI) attempt with ejaculated sperm, with at least 4 mature oocytes and 2 fertilized top-quality embryos.	2005 and 2007 eSET (53 patients) vs. DET (98 patients)	Cumulative delivery rate, twin delivery rate, obstetrical and neonatal outcome	**Fresh eSET vs. DET:** **<u>CPR:</u>** 49.1% vs. 51.0% **<u>LBR:</u>** 41.5% vs 41.8% **<u>MPR:</u>** 0% vs. 48.0% **<u>Miscarriage rate:</u>** 7.7% vs. 12.0% **Cumulative outcomes after Frozen Embryo transfer; eSET vs. DET** **<u>cCPR:</u>** 69.8% vs. 64.3% **<u>cLBR:</u>** 54.7% vs. 49.0% **<u>cMPR:</u>** 3.5% vs. 37.5%	In a selected population, the elective transfer of one embryo with high implantation potential helped to avoid twin pregnancies without decreasing delivery rate.	low no of patients; Prospective nonrandomized study

Hatırnaz S, et al., Fertility and sterility 2016;106: 1691-1695.	Retrospective study	159 women with PCOS SET patients were: - statistically younger (24.1±4.2y vs. 32.4±3.5) -have shorter duration of infertility (4.4 ±2.1 vs. 9.2±4.5y) -Fewer previous ART cycles (<2 prior attempts, 6% vs. 39.5%; >2 prior attempts, 0 vs. 60.5%) -Fewer collected oocytes (12.6±3.8 vs. 15.1±4.6) -Fewer metaphase II oocytes (5.7±2.9 vs. 9.0±4.1) -Fewer fertilized oocytes (3.6±2.3 vs. 8.2±3.7) None of the patients had any surplus good quality embryos available for cryopreservation (Embryo of grade 1, 2 or 3).	SET (83 patients) vs. DET (76 patients); September2007 and May 2014.	LBR Twin pregnancy rate Implantation rate CPR Obstetrical and neonatal risks	**Fresh SET vs. DET:** **Implantation rate:** 47.0% (39) vs. 27.0% (41) **CPR:** 44.6% (37/83) vs. 44.7% (34/76) **LBR**: 34.9% (29/83) vs. 34.2% (26/76); OR 1.2; 95% CI 0.4-3.8 **MPR:** 2.4% vs. 9.2% **Perinatal death according to the number of transferred embryos:** 5.4% (2/37) vs. 5.9% (2/34)	In vitro maturation is a successful assisted reproduction technique that can be an alternative to conventional in vitro fertilization in women presenting with PCOS-related infertility. Our observations suggest that SET is a feasible option to prevent multiple pregnancies	specific case IVM specific population, embryo quality. The study was terminated before the target sample size was reached due to the high twin pregnancy rate in the eDET group.
Aldemir O, et al., Geburtshilfe und Frauenheilkunde 2020;80: 844-850.	Retrospective study	2298 cycles of women aged ≤ 40 years who had their first, second or third cycles with SET or DET.	fresh IVF/intracytoplasmic sperm injection (ICSI) cycles with two good quality embryos (group A; n=324), one good and one poor quality embryo (group B; n=127), and single good quality embryo (group C; n=887)	CPR LBR Miscarriage rate Obstetric outcomes	**Group A vs. group B vs. group C:** **LBRs:** 27.5% vs. 26.8% vs. 24.5% **MBR:** 22.8% vs. 13.0% vs. 3.4% **Preterm birth rate:** 7.0% vs. 7.1 %vs. 3.6%	DET with mixed quality embryos results with lower clinical pregnancy and live birth rates compared with DET with two good quality embryos at the blastocyst stage. At cleavage stage transfer, there is no difference in live birth rates between the two groups.	
Couples/individuals undergoing ART with donor oocytes							

Clua E, et al., *Reproductive biomedicine online* 2015;31: 154-161.	Pilot RCT	65 patients The number of cryopreserved embryos, was higher in the eSET group (6.4 ± 2.1 versus 4.9 ± 2.1 in eDET; P = 0.0055) due to the study design	eSET (34 patients; 52.3%) vs. eDET (31; 47.7%)	Cumulative CPR cLBR MPR	**eSET vs. eDET:** **CPR**: 47.1% (16/34) vs. 61.3% (19/31) **LBR**: 44.1% (15/34) vs. 54.8% (17/31) **MPR**: 0% vs. 47.1% (8/17) **cumulative CPR:** 73.5% vs. 77.4%; RR: 0.95; 95% CI: 0.72–1.25) **cLBR:** 58.8% vs. 61.3%; RR: 0.96; 95% CI: 0.64–1.42 **MPR:** 0% vs. 47.7%	When considering cumulative success rates, eSET and eDET are similar in terms of efficacy. However, eDET involves an increased and unacceptable twin pregnancy rate. The only prevention strategy is single embryo transfer.	

Papers included as background information

(Ebner et al., 2003), (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011), (Glujovsky et al., 2022), (Hviid et al., 2018), (Chang et al., 2009), (Liu et al., 2018), (Busnelli et al., 2019).

PICO 15: In fresh embryo transfer at blastocyst stage, should embryo criteria be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, which criteria are appropriate?

Evidence Table

Reference	**Study Type**	**Patients** **Include: No. of patients** **Patient characteristics + group comparability**	**Interventions (+comparison)** **Include: Study duration / follow-up**	**Outcome measures** **Include: Harms / adverse events**	**Effect size**	**Authors conclusion**	**Comments (if excluded, list exclusion criterion)**

Abuzeid OM, et al., *Facts, views & vision in ObGyn* 2017;9: 195-206.	RCT	100 patients All women were <35 years and had favorable reproductive potential. Randomization criterion was two good quality blastocysts on day 5. Patients who did not get pregnant or who miscarried underwent subsequent frozen cycles with transfer of two blastocysts (if available) in both groups.	50 patients with SBT (Group 1) and 50 patients with DBT (Group 2)	CPR, cumulative CPR Delivery rate and cumulative delivery rate Implantation rate Miscarriage rate Ectopic pregnancy rate MPR	**SET vs. DET:** **CPR:** 61.2% vs 80.0% **LBR:** 49.0% vs 70.0% **Implantation rate** 59.2% vs 54.0% **Miscarriage**: 13.3% vs. 10.0% **Ectopic pregnancy rates:** 3.3% vs. 2.5% **MPR:** 0% vs. 35.0% When fresh and first frozen cycles were combined, **cumulative CPR:** 77.6% vs 96.0%, P=0.007 **Cumulative LBR:** 65.3% vs 86.0%, P=0.016	In patients with favorable reproductive potential, although e-SBT appears to reduce clinical pregnancy and live-birth rates, excellent pregnancy outcomes are achieved	
Aldemir O, et al., Geburtshilfe und Frauenheilkunde 2020;80: 844-850.	Retrospective study	2298 cycles of women aged ≤ 40 years who had their first, second or third cycles with SET or DET.	fresh IVF/intracytoplasmic sperm injection (ICSI) cycles with two good quality embryos (group A; n=324), one good and one poor quality embryo (group B; n=127), and single good quality embryo (group C; n=887)	CPR LBR Miscarriage rate Obstetric outcomes	**Group A vs. group B vs. group C:** **LBRs:** 27.5% vs. 26.8% vs. 24.5% **MBR:** 22.8% vs. 13.0% vs. 3.4% **Preterm birth rate:** 7.0% vs. 7.1 %vs. 3.6%	DET with mixed quality embryos results with lower clinical pregnancy and live birth rates compared with DET with two good quality embryos at the blastocyst stage. At cleavage stage transfer, there is no difference in live birth rates between the two groups.	
Hill MJ, et al., *Fertility and sterility* 2020;114: 338-345.	Retrospective cohort study	Patients with DET were 2.5 years older than those who received SET (P<.01). Patients with DET also had lower serum estradiol level on the day of trigger and fewer oocytes were retrieved. Patients in this primary analysis had no supernumerary	4640 autologous fresh IVF cycles SET vs. DET from 2013 to 2015 There were 889 double-embryo transfers with one good-quality blastocyst and a second poorer-quality embryo. Of those secondary embryos, 205 were a fair or poor blastocyst,	LBR MPR	The primary analysis: **SET vs. DET** **LBR** was 6% higher with transferring a second poor-quality embryo (44% vs. 50%, OR 1.28; 95% CI 1.28–1.90). MPR 1% vs. 16% DET with a second lower-quality embryo (P<.01).	Addition of a lower-quality embryo does not have a detrimental effect on a good-quality blastocyst and results in a small increase in live births. However, this is at the expense of a marked increase in the likelihood of multiple gestations.	

		blastocysts for vitrification	455 were early blastocyst, and 229 were a morula to transfer. There were 3,751 controls with a good-quality blastocyst SET.		The singleton live birth rate: 43.5% in SET vs. 42% in the second lower-quality cohort (P=0.35)		
Theodorou E, et al., *Acta obstetricia et gynecologica Scandinavica* 2021;100: 1124-1131.	Cphort study	2145 women under the age of 40 years	2346 fresh blastocyst transfers between January 2013- June 2019 grade B for TE and ICM was further subcategorized into a B+ and a B− score based on both cell number and package. According to this, blastocysts graded as AA, AB+, AB−, B+A, B−A, B+B+ were classified as high-quality blastocystsHBQ, whereas blastocysts graded B−B+, B+B- or lower were considered low-quality blastocysts (LQB).	LBR MPR Miscarriage rate Outcomes were compared between single embryo transfers with a high-quality blastocyst (SET-H), double embryo transfers with two HQBs (DET- HH), and transfers with one high- quality and one low-quality blastocyst (DET- HL). Outcomes were also assessed between SET and DET when only low- quality blastocysts were available (SET-L vs. DET LL).	**eSET-H vs. DET-HH:** **LBR:** 51.0% vs. 61.0%; OR 1.8; 95%CI 1.4-2.2 **MPR** 1.9% vs. 42.5%; OR 49.3; 95%CI 24.7-98.3. **eSET with mixed-quality DET** **LBR**: 51.0% vs. 47.0%; OR 0.9; 95%CI 0.7-1.1), **MPR:** 1.9% vs. 28.7%; OR 20.9; 95%CI 10.2-42.9. **SET-H with at least one or more high-quality blastocyst available to freeze vs. SET-H with no other HQB available:** **LBR:** aOR 1.69; 95%CI 1.17-2.45 **SET-L vs. DET-LL with no high-quality blastocysts available:** **LBR:** aOR 3.20; 95%CI 1.78-7.703 **MPR**: aOR 3.72 $*10^{10}$	When there is one HQB available, transferring an additional low- quality blastocyst would only slightly increase the LBR, but significantly increase the twin rate, therefore SET should be recommended. When two or more HQBs are available, ET-H would have a reasonably good chance of success without the very high twin rate associated with DET- HH. DET- LL when compared with SET- L, would increase the LBR, but increase the risk of multiple gestation.	

Papers included as background information

(Ebner et al., 2003), (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011), (Glujovsky et al., 2022), (Hviid et al., 2018), (Chang et al., 2009), (Liu et al., 2018), (Busnelli et al., 2019), (Shebk et al., 2021), (Wang et al., 2019), (Rodriguez-Wallberg et al., 2023).

PICO 16. In FET, should embryo criteria be considered a factor in deciding to apply DET instead of SET at cleavage-stage for couples/individuals undergoing ART? If yes, which criteria are appropriate?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments
Thurin A, et al. New England journal of medicine 2004;351: 2392-2402.	RCT	661 pt underwent randomization, 330 pt in eSET group and 331 pt in DET group. Inclusion criteria: < 36y, 1°-2° cycle, ≥ 2 good quality embryos. ET day 2 (90%).	eSET fresh + eSET frozen vs DET fresh (eSET in frozen embryo transfer, natural or hormone-stimulated cycle).	Primary outcome: cumulative live birth rate. Secondary outcomes: pregnancy, implantation, multiple birth, spontaneous abortion and ectopic pregnancy rates.	**Frozen SET vs. DET:** **LBR:** 16.4% **(SET)** **MPR:** 0.8% (1) **cLBR (fresh and frozen SET cycles):** 38.8% vs. 42.9%	A fresh eSET followed (if there was no live birth) by the transfer of one thawed embryo, results in a marked reduction in the multiple pregnancy rate (P<0.001) but not in a reduction of live birth rate (P=0.30)	
Martikainen H, et al., Human reproduction (Oxford, England) 2001;16: 1900-1903.	RCT	144 patients underwent randomization, Inclusion criteria: ≥ 4 good quality embryos (<20% fragmentation, even-sized blastomeres at day 2); 1° cycle; different age according to	Fresh cycles: SET (74 patients) vs. DET (70 patients). (NO eSET in frozen embryo transfer). Natural cycles or Stimulated cycles: GnRH agonist (d21–23 of the previous cycle).	IPR CPR: confirmed on ultrasound. cLBR	**Fresh SET (74) vs. DET (70):** **CPR**: 32% (24) vs 47%(33) **LBR:** 92%(22) vs 85%(28) **MPR:** 5% vs. 39% **Frozen SET (84) vs. DET (56):** **CPR:** 47.3% vs. 58.6% **cLBR per patient**: 39% vs. 51%, NS **Twins:** 1 vs. 0 Power calculations to show diff of 10%: 360 patients should have been needed : only 144 were in the trial.	No difference in terms of cumulative live birth rate between two groups. Multiple pregnancy rate increased in DET group (assessed in fresh embryo transfer, P=0.01).	no specific data if fresh or frozen unclear detection and possible bias. The replacement of frozen embryos was not subjected to any protocol policy related to the present study.

		centres. ET day 2.	Oestradiol valerate (4 mg/day; on d3) + Vaginal progesterone 600 mg daily d3 before ET. Slow freezing protocol with 1,2-propanediol.				
Moustafa MK, et al. Reprod Biomed Online. Jul;17(1):82-7. 2008	RCT	81 patients: eSET (n=40) vs. DET (n=41). ≤30 years old, at least 1 good quality embryo on day of transfer (grade I-II). ET day 2-3.	eSET vs DET in fresh and frozen cycle A slow-freezing protocol with 1.5 M 1,2-propanediol	Primary outcome: LBR Secondary outcome: MPR ET on day 2- day 3; Number of oocytes retrieved: 10.23 (SET) vs 9.80 (DET); NS	**Fresh cycles: eSET (n=40) vs DET** (n=41): fresh cycles **LBR: 30.00% vs. 31.71%** **MPR: 0% vs. 12.20%** **Frozen cycles: eSET (n=10) vs. DET (n=16)** **LBR** 42.86% vs. 37.5% MPR: 0% vs 18.75% Summary of the results of all the cycles performed: **cLBR (%/number of women):** 45.00% vs 46.34% **cLBR (%/cycle):** 33.33% vs. 33.33% **cMPR (%/cycle):** 0% vs 14.04%	Elective SET should be the first line of choice; No difference between the DET and eSET in LBR. Higher MPR in DET group in fresh cycles. In frozen cycles no significant differences in LBR and MPR.	very low quality (high risk of selection, performance, and attrition biases): The study by Moustafa and co-workers did not compare outcomes in low or high responder patients and therefore could not answer the question on whether ovarian response should be considered a factor in deciding to apply DET instead of SET
Hydén-Granskog C, et al., *Human reproduction (Oxford, England)* 2005;20: 2935-2938.	obs study	1647 frozen embryo transfer cycles eSET criteria: 2-3 cryopreserved embryos and >1 embryo fulfilled the transfer criteria (an embryo with a blastomere survival rate > 75%.	From 1998-2003 eSET vs DET vs cSET in frozen transfer. 1647 frozen embryo transfers carried out during 1998–2003 775 SET (eSET +cSET) cycles and 872 DET cycles. Cryopreservation day 2-3 with 1,2-propanediol	CPR, Multiple pregnancy, delivery and multiple delivery rates.	CPR/ frozen embryo transfer was 30.7% the delivery rate 22.6%. **SET vs. DET** **LBR**: 19.2% vs. 25.7; P < 0.01). **MPR**:2.0% vs. 21.9%, P < 0.0001. eSET vs. DET **LBR**: 28.6 and 25.7%. **MPR:** 0% vs. 21.9%, P<0.0001.	SET can be used in frozen cycles to reduce multiple delivery rates.	

Salumets A, et al., *Human reproduction (Oxford, England)* 2006;21: 2368-2374.	Retrospective study	2064 embryos transferred in 1242 frozen embryo transfers Cryopreservation day 2 only embryo with grade 1-3A. The mean age (±SD) of a woman at IVF/ICSI treatment was 34 ± 4.3 years	SET vs DET in frozen transfer. (No eSET) 420 pt SET and 822 pt DET. a slow freeze protocol using 1 -,2-propanediol. natural or down-regulated hormone replacement cycle	Clinical and biochemical pregnancy rate, Number of Gestational sacs, miscarriage and delivery rates.	**SET vs DET:** **LBR (delivery rate)** 14.3% vs 18.7%, P≤0.05.	the delivery rate after frozen embryo transfer was dependent on both the woman's age and the quality of embryos transferred, at the same time being unaffected by IVF/ICSI treatment: (1-2 vs 3A OR 1.56 95%CI 1.01-2.40).	
Le Lannou D, et al., *Reproductive biomedicine online* 2006;13: 368-375.	obs study paired case-control study	428 pt, 138 in the eSET group and 290 in DET group. Case-control study population: 130 pt eSET vs 130 pt for fresh transfer, 96 pt eSET vs 89 DET for frozen transfer. Inclusion criteria: <38y, 1° cycle, ≥ 2 good quality embryos. ET day 3.	eSET fresh vs DET fresh (eSET in frozen embryo transfer). eSET: embryos frozen singly in straws, DET: up to two embryos were placed in each straw. Stimulation with oestradiol valerate (6mg/day) and intravaginal micronized progesterone (600 mg/day).	Pregnancy, implantation, live birth multiple pregnancy and cumulative live birth rates.	**<u>SET vs DET:</u>** **cLBR**: 43% vs 45%, No difference **MPR:** 3.5% vs 34%, p<0.01.	while twin pregnancies are not totally adverse outcomes in IVF–ICSI, it is possible to reduce their occurrence considerably by pursuing a policy of single embryo transfer that can be applied to a large majority of patients, but only if it is accompanied by widespread embryo cryopreservation.	
López Regalado ML, et al., Journal *of assisted reproduction and genetics* 2014;31: 1621-1627. .	Retrospective cohort study	221 pt included, 105 pt in DET-FET group, 60 pt in cSET-FET group and 41 pt in eSET-FET group. Inclusion criteria: < 38 y, BMI 19-29 kg/m2, FSH < 15mUI/ml, 1°-2°	eSET (cumulative) vs DET vs cSET in frozen transfer. From January 2010 to June 2013 Cryopreservation day 3 using ethylene glycol and 1,2-	Clinical, multiple pregnancy, miscarriage, ongoing pregnancy, live birth and cumulative live birth rates.	**<u>eSET vs DET:</u>** **cLBR**: 34.1% vs 30.0% **<u>MPR:</u>** 0% SET vs 32.5% DET, p<0.05.		

		cycle, no pregnancy in their fresh cycles and ≥ 2 vitrified embryos A/B quality.	propanediol in HTF culture medium fluid				
Racca A, et al., Gynecological endocrinology: the official journal of the International Society of Gynecological Endocrinology 2020;36: 824-828.	Retrospective cohort study	3601 pt included, 1936 pt in SET group, 16665 pt in DET group. Criteria for cryopresevation: ≥ 6 blastomeres and < 20% fragmentation.	SET (n= 1936) vs DET (n=1665) in frozen transfer. Natural or artificial cycle estradiolvalerate and micronized vaginal progesterone	Live birth and multiple birth rates.	Overall, 657/3601 (18.24%) had a live birth. **SET vs DET:** **LBR:** cleavage [100/757 (13.1%) versus 153/1032 (14.8%), p=.33] o blastocyst stage FET [256/1179 (21.7%) versus 148/633 (23.4%), p¼.4). **OPR**: 359/1936 (18.5%) vs. 316/1665 (18.9%) **MPR:** 7/359 (1.9%) vs. 53/316 (16.7%) p<.001.	the number of embryos transferred in the frozen cycle was not related to LBR. both SET and DET may result in similar LBR, albeit multiple pregnancy rates are significantly lower in case of SET.	
Zhu Q, et al., *Frontiers in physiology* 2020;11: 930.	Retrospective cohort study	26676 women 1st FET Inclusions: Autologous oocytes Each women included only 1 time in the study Exclusion: Women with previous fresh or FET Patients receiving mixes cleavage and blastocyst transfer	Between Jan 2011 – Dec 2017 Information on IVF/ICSI procedure, embryo culture, evaluation and freezing see other papers of this group. Embryos cultured until day 3 or day 5/6. Cleavage embryos: Grade I and grade II: 4cell on day 2 or 6 to 8 cells on day 3 with <20% fragmentation. Grade III or IV: 2cell on day 2 or <6 cell on day 3, >20%	LB: infant born alive after 24 weeks of gestation surviving more than 28 days per FET (see remark) 2 major groups: cleavage vs blastocyst. 5 subgroups: SET-GQE SET-PQE DET-2GQE DET-GQE+PQE DET-2PQE	24613: FET using cleavage stage embryos 2063: FET using blastocyst cleavage stage embryos Blastocyst FET vs cleavage stage FET: LBR for SET: 38.64% vs. 24.72% LBR DET: 56.08% vs. 45.01% MPR for SET: 0.81% vs. 0.29% MPR for DET: 21.69% vs. 13.76% LBR was higher in blastocyst vs. Cleavage n all 5 subgroups. Cleavage stage FET DET2GQE: LBR:45.73%-MPR: 14.22% DET-GQE+PQE: 37.25%-MPR:8.7% DET-2PQE: 32.89%-MPR:6.14% SET-GQE: 25.55%-MPR:0.31% SET-PQE: 12.16%-MPR:0% LBR is significantly reduced in SET-PQE (OR: 0.49 (0.28-0.84) p=0.009 and significantly higher in DET-2GQE OR 1.62 (1.40-1.51) p=<0.001 and in DET-GQE+PGE OR1.25 (1.04-1.51) p=0.018. No sign diff for LBR in DET-2PQE vs SET-GQE. Blastocyst stage FET	DET with GQE+PQE increases the LBR for cleavage stage FET but not for blastocyst FET for the 1st FET. DET with GQE+PQE increases MPR for both cleavage stage and blastocyst stage FET. Although DET with GQE + PQE leads to increasing LBR, but it leads to increased MPR in cleavage stage FET. For blastocyst FET, DET with GQE+PQE does NOT increase LBR, it only increases MPR. MPR is higher in DET vs. SET regardless of the transferred embryo quality and developmental stage of the embryo.	Results are expressed per ET or per warming? Is not described in the study – however in the discussion it is stated: per transfer

			fragmentation (=poor quality). Blastocysts: Day 5/6: Gardner score Good quality >=3BB Poor quality <3BB Embryo grading by 2 embryologists and verified by senior embryologist. Vitrification on day 3 or day5/6: cryotop (Kitazato), 15% ethylene glycol 15% DMSO, 0.5mol/l sucrose. Warming: 1.0, 0.5, 0.0 mol/l sucrose solutions at room temp, except the first warming step at 37°C. Endometrial prep: natural cycles for patients with regular cycles, hormone therapy cycle or stimulation cycle for patients with irregular cycles. Prog suppl. Provided until 8 weeks of gestation. preparation,		DET2GQE: LBR 60.31%-MPR:26.20% DET-GQE+PQE: LBR 53.76-MPR:17.29% DET-2PQE: LBR 46.25%-MPR/ 14.37% SET-GQE: LBR 42.99-MPR:0.79% SET-PQE: LBR 29.56%-MPR:0.83% LBR is significantly reduced in SET-PQE (OR: 0.62 (0.46-0.83) p=0.001 and significantly higher in DET-2GQE OR 1.76 (1.20-2.57) p=0.003. No sign diff for LBR in DET-GQE+PQE and DET-2PQE vs SET-GQE.	SET with GQ blastocyst =preferred recommendation. LBR with SET-GQE in blastocyst is higher than DET with cleavage stage with mixed quality and DET-2PQE.	

			endometrial thickness. OR; 95%CI are reported. Stat v12 was used.				

Papers included as background information

(Wyns et al. 2021), (Guerif et al., 2002), (Glujovsky et al., 2022), (Wong et al., 2014) (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group Embryology, 2011), (Blake et al. 2007), (Papanikolaou et al. 2008), (Gardner et al. 1998)

PICO 17: In FET, should embryo criteria be considered a factor in deciding to apply DET instead of SET at blastocyst stage for couples/individuals undergoing ART? If yes, which criteria are appropriate?

Evidence Table

Reference	**Study Type**	**Patients** **Include: No. of patients** **Patient characteristics + group comparability**	**Interventions (+comparison)** **Include: Study duration / follow-up**	**Outcome measures** **Include: Harms / adverse events**	**Effect size**	**Authors conclusion**	**Comments**
Park DS, et al., *J Obstet Gynaecol Res* 2019;45: 849-857.	Propensity score matching study	Age between 35 and 39y Exclusion: donor oocytes IVM protocol Women with endo <7mm Uterine anomalies PS matching: Maternal age, BMI, infertility duration, number of	Jan 2014 – Dec 2015 643 patients included. Vitrified- warmed cycles n:643 included 3 groups: GG= DFET of two good Q embryos GP= DFET of good and poor GS= SFET 1 good embryo Good quality ≥3BB	IPR= number of sacs/total number of transferred embryos. CPR= presence of fetal heartbeat. LBR MPR Prematurity <37 weeks (cycles) Anomaly	GG (reference) vs GSET (n=102) IPR: 43.1% vs 43.1 (NS) OR (95%CI) : 1 (0.62-1.62) CPR: 64.7% vs 41.2% (p=0.001) OR: 0.38 (0.22-0.67) LBR: 54.9% vs 32.4% (p=0.001) OR: 0.39 (0.22-0.69) MPR: 33.3% vs 4.8% (p<0.001) OR: 0.10 (0.02-0.45) Premat: 23.2% vs 9.1% (p=0.094) OR: 0.33 (0.09-1.26) Anomaly: 1.3% vs 2.9% (NS) GP (reference) vs GSET (n=93)	The optimal number of blastocysts to transfer according to grade for FET: LBR is higher in GG, then GS, MPR is also higher in GG and GP. No diff in LBR between GG and GP although higher CPR in GG than in GP. DFET with 1 good and	No data on cLBR, It is not stated in the paper if the SET is eSET or compulsory SET because only 1 embryo was there -> agreed by group to take SET along

		previous attempts, tubal factor, ovulatory factor, endometriosis, male factor, stimulation protocol, freeze-all, ICSI, endometrial thickness.	EQ graded by 3 embryologists Vitrification d5 or d6+ artificial shrinkage by laser. 7.5%ethylene glycol + 7.5% DMSO+0.5M sucrose. Gold grid using fine glass pipette. Vit Master. Warming: 0.5-0.25-0.125-0.0625M sucrose for 2.5min with 20%HSA. Culture overnight after warming. All patients: natural cycles: dominant follicle collapse during d10-d12 of cycle. Luteal sup: crinone gel 8 or utrogestan 600mg. Propensity score matching to minimize bias. Matching resulted in matched pairs: GG vs GP: 166 GG vs GS: 102 GP vs GS: 93		IPR: 25.3% vs 44.1 (p=0.001) OR (95%CI) : 2.33 (1.38-3.95) CPR: 45.2% vs 43% (p=0.768) OR: 0.79 (0.43-1.44) LBR: 38.7% vs 33.3% (p=0.445) OR: 0.79 (0.43-1.44) MPR: 21.4% vs 2.5% (p=0.009) OR: 0.09 (0.01-0.78) Premat: 19.4% vs 12.9% (p=0.471) OR: 0.61 (0.16-2.33) Anomaly: 0% vs 3.1% (NS)	1 poor quality embryo should be avoided = no advantage.	
Park DS, et al. Taiwanese journal of obstetrics & gynecology 2020;59: 398-402.	Retrospective cohort study	1410 vitrified blastocyst transfer cycles Inclusion criteria: Women age: <40y, endometrial thickness >7mm using non-donor oocytes Exclusion criteria: Donor	Between 2014 and 2015 1306 cycles SET or DET Three groups: 3 groups: GG= DFET of two good Q blastocyts (n=628) GP= DFET of good and poor-quality blastocysts (n=401) GS= SFET 1 good	IPR= number of sacs/total number of transferred embryos. CPR= presence of fetal heartbeat. LBR MPR Prematurity <37 weeks (cycles) (PTB) Ectopic pregnancy rate Miscarriage	GG (n=628) vs GP (n=401) vs GS (n=277) (reference) IPR: 46.0% (578/1256; OR 0.74; 95%CI 0.57-0.96) vs 33.5% (269/802; OR 0.44; 95%CI 0.34-0.59) vs 53.4% (148/277) (p<0.001) CPR: 65.9% (414; OR 1.60; 95%CI 1.20-2.13) vs 48.4% (194; OR 0.92; 95%CI 0.67-1.24) vs 50.5% (140) (p<0.001) LBR: 55.3% (347; OR 1.57; 95%CI 1.18-2.09) vs 39.4% (158; OR 1.02; 95%CI 0.75-1.93) vs 40.1% (111) (p<0.001);	Both CPR and LBR were the highest in group GG, but not significantly different between group GP and GS. MPR was higher in GG followed by GP and the lowest MPR was in the GS group. Single LBR was the highest in group GS.	No data on cLBR, It is not stated in the paper if the SET is eSET or compulsory SET because only 1 embryo was there -> agreed by group to take SET along

		oocytes or embryos, or only poor-quality blastocysts or from other hospitals; endometrial thickness <7mm; Uterine anomaly	blastocyst (n=277) Good quality ≥3BB EQ graded by 3 embryologists Vitrification d5 or d6+ artificial shrinkage by laser. 7.5%ethylene glycol + 7.5% DMSO+0.5M sucrose. Gold grid using fine glass pipette. Vit Master. Warming: 0.5-0.25-0.125-0.0625M sucrose for 2.5min with 20%HSA. Culture overnight after warming. All patients: natural cycles: dominant follicle collapse during d10-d12 of cycle. Luteal sup: crinone gel 8 or utrogestan 600mg.		MPR: 25.6% (161; OR 21.39; 95%CI 7.82-85.28) vs 13.5% (54; OR 11.48; 95%CI 4.11- 32.03) vs 1.4% (4) (p<0.001). Ectopic pregnancy: 1.8% (11; OR 1.92; 95%CI 0.54-6.79) vs 2.0% (8; OR 1.62; 95%CI 0.41-6.31° vs 1.4% (4). Miscarriage rate: 16.2% (67/414; OR 0.74; 95%CI 0.44-1.24) vs 18.0% (35/194; OR 0.78; 95%CI 0.50-1.21) vs 20.7% (29/140) PTB: 27.4% (95/347; OR 3.91; 95%CI 2.18-7.08) vs 20.3% (32/158; OR 3.00; 95%CI 1.60-5.65) vs 9.0% (10/111) (p=0.775)		
Liu L, et al., *J Huazhong Univ Sci Technolog Med Sci* 2014;34: 750-754.	Retrospective study	Inclusion: Age 21-40y BMI≤23 Intrauterine morphology= normal (under hysteroscopy) In case of DET: both blastocysts were frozen on d5or d6 and had the same morphology score. Exclusion: Uterine malformations	July 1, 2012 – 31 December 2013 Frozen-thawed transfer cycles (n=741) In total: 1391 blastocysts were transferred: 91 cycles SFET 650 cycles DFET Vitrified on d5/d6. Vitrified before day 6, scored ≥4CC SET: S-ICM B /TE B (n=91) DET: D-ICM B/TE B (n=579) D-ICM B/TE C (n=35) D-ICM C/TE B (n= 36)	HCG levels: 12d after FET CPR: presence of gestational sac 4 weeks after FET. Biochemical preg: bHCG>5mU/ml and no sac identified on ultrasound. IR= number of gestational sacs/ number of embryos transferred.	D-ICM B/ TE B vs S-ICM B/TE B CPR: 74.94% vs 46.15% (p<0.001) IPR: 57.43% vs 47.25% NS MPR: 48.62% vs 2.38% p<0.001 Biochemical pregnancy: 7.25% vs 14.29% p=0.023	ICM plays a decisive role in CPR outcomes. Pregnancy rate in de SFET group is acceptable. SFET can also effectively reduce the amount of multiples.	SET, but no info if it is eSET. No LBR

		Uterine fibroids Abortion in history	Vitrification on d6 ≥4CC Kizatato vitrification kit / cryoloop Warming: 1 mol/L sucrose for 2.5min, than successive steps: 0.5, 0.25, 0.125 mol/L for 2.5min each. After warming: 2h incubation in triple gas Routinely 2 blastocysts were transferred. If only 1 blastocyst survived, then SET. Transfer on d6 Endometrium preparation: Oral estradiol valerate (Bayer) on d2 of menstrual period and adjusted according to endo thickness and hormone levels. When endo ≥7mm and ≥10d if drug admin. : hormone levels check: E2>200pg/ml and <1.5ng/ml-> prog was given for endometrial transformation. Luteal sup: progesterone oil: 60-80mg/day				
Van Landuyt L, et al., *Human reproduction (Oxford, England)* 2011;26: 527-534.	Observational study	759 warming cycles Female age: Mean 31.5y (range 22-42y). 921/1185 embryos survived (70.0% survival rate).	Blastocyst warming between April 2008 and February 2010 Vitrifcation on d5/d6 in CBS high sec straw using Irvine scientific freeze kit (DMSO – EG) and warming using the Irvine scientific thawing kit. No artificial shrinking	Clin.preg/FRET= intrauterine gestational sac at least at 5 weeks after FRET. Ong preg/FRET= clinical preg with fetal heartbeat at ≥12 weeks Impl rate per transferred embryo.	SET n= 759, DET n=156. Clin preg/ET SET FRET= 16.4% Clin preg/ET DET FRET= 24.4% (p<0.05). Ong preg/ET SET FRET= 14.2% Ong preg/ET DET FRET= 20.5% (NS) 1 monozygotic twin after SET (1.3%) MPR/DET FRET= 21.9% (p<0.01) Impl/embryo transferred:	Overall ongoing pregnancy rate per transfer after SET (14.3%) vs DET (20.5%) was not significantly diff. MPR after DET FRET was 21.9% with random choice of embryo being warmed. The MPR	This paper was on showing the potential of a closed HS device. No data on LBR and no data if SET is eSET or not

		Embryos were frozen on day 5 and day 6. SET FRET 530 cycles DET FRET 156 cycles	was applied. Cryopreservation: early blastocysts or expanded with A/B ICM/TE, on d6 only full expanded blastocysts A/B. Vitrification 1 by 1. Warming on the day of FRET, 1 by 1, randomly selected. Choice of SET or DET based on MD. SET in patients <36y in first warming cycle after 1st IVF. If blastocyst were severely or completely damaged: another blastocyst was warmed. If fully intact or moderate damage: expansion and re-expansion was assessed 1-2h later. FRET was conducted with embryos that had good survival and expansion or-re-expansion. Outcome parameters were compared using Chi-square		SET FRET= 14.3% DET FRET= 12.8% Looking at quality parameters for SET pregn: Early blastocysts vs bl3/4: Clin preg/FRET= 12.2.% vs 20.3% (p<0.05) Fetal heart beat/FRET= 10.6% vs 17.5% (p<0.05).	occurred in cycles where excellent or fully expanded blastocysts that were fully intact after warming were transferred.	
Zhu Q, et al., *Frontiers in physiology* 2020;11: 930.	Retrospective cohort study	26676 women 1st FET Inclusions: Autologous oocytes Each women included only 1	Between Jan 2011 – Dec 2017 Single centre China Information on IVF/ICSI procedure, embryo culture, evaluation and freezing: see other papers of this group.	LB: infant born alive after 24 weeks of gestation surviving more than 28 days per FET (see remark) 2 major groups: cleavage vs blastocyst.	24613: FET using cleavage stage embryos 2063: FET using blastocyst cleavage stage embryos Blastocyst FET vs cleavage stage FET: LBR for SET: 38.64% vs. 24.72% LBR DET: 56.08% vs. 45.01% MPR for SET: 0.81% vs. 0.29%	DET with GQE+PQE increases the LBR for cleavage stage FET but not for blastocyst FET for the 1st FET. DET with GQE+PQE increases MPR for both cleavage stage	Results are expressed per ET or per warming? Is not described in the study – however in the discussion it is stated: per transfer

		time in the study Exclusion: Women with previous fresh or FET Patients receiving mixes cleavage and blastoycst transfer	Embryos cultured until day 3 or day 5/6. Cleavage embryos: Grade I and grade II: 4cell on day 2 or 6 to 8 cells on day 3 with <20% fragmentation. Grade III or IV: 2cell on day 2 or <6 cell on day 3, >20% fragmentation (=poor quality). Blastocysts: Day 5/6: Gardner score Good quality >=3BB Poor quality <3BB Embryo grading by 2 embryologists and verified by senior embryologist. Vitrification on day 3 or day5/6: cryotop (Kitazato), 15% ethylene glycol 15% DMSO, 0.5mol/l sucrose. Warming: 1.0, 0.5, 0.0 mol/l sucrose solutions at room temp, except the first warming step at 37°C. Endometrial prep: natural cycles for patients with regulare cycles, hormone therapy cycle or stimulation cycle for patients with irregular cycles. Prog suppl. Provided until 8 weeks of	5 subgroups: SET-GQE SET-PQE DET-2GQE DET-GQE+PQE DET-2PQE	MPR for DET: 21.69% vs. 13.76% LBR was higher in blastocyst vs. Cleavage n all 5 subgroups. Cleavage stage FET DET2GQE: LBR:45.73%-MPR: 14.22% DET-GQE+PQE: 37.25%-MPR:8.7% DET-2PQE: 32.89%-MPR:6.14% SET-GQE: 25.55%-MPR:0.31% SET-PQE: 12.16%-MPR:0% LBR is significantly reduced in SET-PQE (OR: 0.49 (0.28-0.84) p=0.009 and significantly higher in DET-2GQE OR 1.62 (1.40-1.51) p=<0.001 and in DET-GQE+PGE OR1.25 (1.04-1.51) p=0.018. No sign diff for LBR in DET-2PQE vs SET-GQE. Blastocyst stage FET DET2GQE: LBR 60.31%-MPR:26.20% DET-GQE+PQE: LBR 53.76-MPR:17.29% DET-2PQE: LBR 46.25%-MPR/ 14.37% SET-GQE: LBR 42.99-MPR:0.79% SET-PQE: LBR 29.56%-MPR:0.83% LBR is significantly reduced in SET-PQE (OR: 0.62 (0.46-0.83) p=0.001 and significantly higher in DET-2GQE OR 1.76 (1.20-2.57) p=0.003. No sign diff for LBR in DET-GQE+PQE and DET-2PQE vs SET-GQE.	and blastocyst stage FET. Although DET with GQE + PQE leads to increasing LBR, but it leads to increased MPR in cleavage stage FET. For blastocyst FET, DET with GQE+PQE does NOT increase LBR, it only increases MPR. MPR is higher in DET vs. SET regardless of the transferred embryo quality and developmental stage of the embryo. SET with GQ blastocyst =preferred recommendation. LBR with SET-GQE in blastocyst is higher than DET with cleavage stage with mixed quality and DET-2PQE.	

			gestation. Anova / chi-square / Multivariate logistic regression to understand the different ET strategy on the LBR after controlling for maternal age, maternal BMI, type of infertility, parity, duration of infertility, causes of infertility, number of 2PN, endometrial preparation, endometrial thickness. OR; 95%CI are reported. Stat v12 was used.				
Wang W, et al., *Reproductive biology and endocrinology : RB&E* 2020;18: 97.	Retrsocpective CCS	Retrospective Propensity score matching (PSM) FET Exclusion: d7 blastoscysts and blastocysts derived from frozen cleavage embryo or vitrified oocytes. Cycles with data missing were excluded. PS matching on: Maternal age, paternal age, maternal BMI, parity, gravity, duration of infertility, cause of infertility, baseline FSH,	Between Jan 2012 – May 2019 FET with blastocysts Group G= SET with GQE Group GP= DET with GQE+PQE IVF and ICSI cycles. IVF: COC+ 1.5 - 3x105 PR sperm for 4h. ICSI: oocyte denuded 2h after pickup – ICSI performed 4h after pickup. Cook sequential medium in 20µl droplets. Gardner on day5/6. Good quality (GQE)= expansion ≥3 with AA, BA, AB and BB. Poor quality (PQE)= expansion ≥3 with AC, CA, BC, CB and CC. Top quality= grade ≥4 with AA, BA and AB. ≤4CC or blast 1 or 2	Outcomes: LBR - MPR - CPR - MR Group G: 4484 patients Group GP: 553 patients. After PSM: 520 cycles. After matching no diff in patient characteristics.	Outcomes GP vs G (OR; 95%CI) after PSM (n=520): CPR: 57.3% vs. 47.3%; OR 1.51 (1.18-1.93) p=0.001 LBR: 47.9% vs. 41%; OR 1.33 (1.04-1.7) p=0.024 MPR: 30.5% vs. 2.4%; OR 17.49 (7.49-40.81). P<0.001 MR: 15.4% vs. 13.4%; OR 1.18 (0.73-1.9). NS Outcomes in women <35y (n=419): CPR: 58% vs 50.2%; OR 1.38 (1.05-1.82) p=0.02 LBR: 48.7% vs 43.9%; OR 1.22 (0.93-1.59) NS MPR: 31.7% vs. 1.9%; OR 23.81 (8.54-66.43). P<0.001 MR: 14.8% vs. 11%; OR 1.42 (0.81-2.48). NS Outcomes in women ≥35y (n=81) CPR: 56.8% vs. 38.3%; OR 2.17 (1.15-4.1) p=0.017 LBR: 48.1% vs. 27.2%; OR 2.56 (1.3-5.03) p=0.006 MPR: 26.1% vs. 3.2%; OR 10.87 (1.4-84.62). P=0.023	Transfer of an additional PQE along with a GQE did not have a detrimental effect on GQE: DBT GQE+PGE achieved higher CPR, LBR in women over 35y. For women <35y: only CPR was higher, no diff in LBR. In both groups: MPR was significantly higher in GP vs. G. For blastocyst FET: it is not harmful to add a lower quality blastocyst in a GQE FET // but it results in significant higher MPR.	

		antral follicle count, stim protocol, insemination method, endometrial prep, endometrial thickness, number of blastocysts vitrified, number of cycles of ET, day of blastocyst transferred, proportion of top quality blastocysts.	were not considered for vitrification. Vitrification: Cryotop –3-5 min 7.5%DMSO + 7.5% ethylene glycol (ES)/ 20-40s, 15%DMSO, 15% ethylene glycol, 10mg/ml Ficoll-70, 0.6M sucrose (VS). Warming: 1M sucrose 37°C, 1 min (TS), equilibrated each step for 3 min: 0.5M, 0.25M, 0M sucrose. Warming and FET on the same day Endometrial preparation and FET: Natural cycle, hormone replacement cycle with or without GnRH downregluation. Luteal support until 10 weeks of pregn. SPSS V22: continuous variables: Mann-Whitney U Categorical variables: Chi-square test Propensity score matching on maternal age, paternal age, maternal BMI, parity, gravidity, duration of infertility, cause of infertility, baseline FSH, AFC, ovarian stimulation protocol, insemination methods, endometrial prep, endometrial thickness, number of blastocysts vitrified,		MR: 15.2% vs. 29%; OR 0.45 (0.15-1.37). NS		

			cycles of ET, day of blastocyst transferred and the proportion of top quality blastocysts. 1:1 nearest neighbour matching between group G and GP with a caliper equal to 0.03. GEE (generalized estimating equations) model was used.				
Arab S, et al., *Reproductive sciences (Thousand Oaks, Calif)* 2020.	Retrospective cohort study	Retrospective cohort study 1104 FET single center 856 patients All frozen on day 5/6 Gardner score Exclusion: Transfer of a blastocyst of AA, BA and AB. Cycles with mixed quality of fresh and frozen blastocysts. Blastocyst ≤4BB was defined medium to poor quality and included in the study.	Jan. 2008 – Dec 2019. ET: 969 vs DET: 135. Blastocysts scored by 3 trained embryologists with 10-25 years of experience in embryology. 1104 FET: 915 own oocyte, 189 donor oocytes None of the FET were with blastocysts with lower grade than CC. All embryos were grade 4 or 5. Data was stratified according to age: Own oocytes: 97 cycles in patients ≥40y and 818 cycles in women <40y. Vitrification: 7.5% DMSO, 7.5 ethylene glycol RT 3min – vitrification medium: 15%EG, 15% DMSO, 0.5M trehalose solution 1min. Vitri straw (Sci tech). Warming: submerge straw in 1ml 37°C	Outcomes: CPR – MPR – LBR per cycle (ET) CPR = intrauterine gestational sac with or without a fetal heartbeat using ultrasound. MPR= more than 1 fetus an ultrasound 6 weeks. LBR= 1 or more live-born infants at > 24 weeks.	Own oocytes ≥40y SET (n=63) vs. DET (n=34) CPR: 11.11% vs. 11.76% NS LBR: 6.34% vs. 0% NS MPR: 0% vs 0% NS Own oocytes <40y SET (n=744) vs DET (n=74) CPR: 33.46% vs 32.43% NS LBR: 20.21% vs 12.16% NS MPR: 1.6% vs. 6.8% p= 0.004 Oocyte donor cycles SET (n=162) vs DET (n=27) CPR: 25.92% vs. 29.62% NS LBR: 11.72% vs. 22.22% NS MPR: 3.12% vs 7.40% NS Outcomes related to EQ: Not written down (see remark). Also low amounts in cycles		Data on DET based on blastocyst quality is poor: DET with BB (n=118) is the only cycles that has pregnancies, DET with BC (n=11), CB (n= 4) (n=2) or CC have 0% pregnancy

			warming solution 1M trehalose 1min – DS 1 (0.5M trehalose 3min – 0.25M trehalose 3 min – 2 washes. Time from warming to transfer was 3-4h. Warming and FET on the same day. Blastocysts with greater than 50% intact blastomeres survived. Survival rate up to 98% - grading of the blastocyst was on day of warming 30 min before FET. Hormonal treated and natural frozen cycles, luteal support: 200mg of vaginal progesterone 3x/day (98% of the cycles) or 100mg intramuscular prog daily for 14d (only 2% of the cycles). SPSS v23. Continuous data: One-Way Anova Categorical data: Chi-squared.				
Dobson SJA, et al., *Fertility and sterility* 2018;110: 655-660. .	Prospective observational study	Prospective observational study. 1st FET: 1009 cycles All own oocytes. Women with gynaecological pathologies like fibroids, endometrial	Between 2010 – 2016. All blastocyst FET TQE= AA, BA, AB, BB PQE= AC, CA, BC, CB, CC SET or DET decided together with patient. FET day 5 embryos (383/1009, 38%) FET day 6 embryos (583/1009, 57.8%)	CPR: intrauterine pregnancy at 4 week scan. Ongoing viable pregn: 12 weeks ultrasound. LBR: viable infant born after 24 weeks of gestation. Twin live birth was considered 1 live birth per cycle. MR: pregn lost before 24 weeks.	**DET TQE+PQE vs. SET TQE** **LBR**: 24.2% vs. 32.7% OR 0.75 (0.48-1.2) NS **MPR:** 7.1% vs. 2.6% OR 2.4 (1.2-4.9) p <0.05.	There is no benefit to LBR with the addition of a PQE, but it carries an increased risk for multiple PR. This study does not support DET when there is only 1 TQE and a PQE. -> do not put them together, you will only increase MPR.	Paper has data both on fresh ET and FET

		polyps, hydrosalpinx and large ovarian cysts were treated before commencing IVF. If not treated, they were excluded. 1 cycle per patient was included.	FET day 7 embryos (21/1009, 2.1%) Mixture of day5/6 (13/1009, 1.3%) Mixture of day 6/7 (9/1009, 0.9%) Artificial hormone therapy cycles using E2 valerate at dose 6mg/d from d1 of natural cycle or withdrawal bleed and continued same dose. Endometrial thickness ≥7mm, Prog. Pessaries (400mg 2x/day) were started on d15. Blastocyst ET was done on d6. Luteal supp: progesterone pessaries (utrogestan or cyclogest 400mg) used vaginally 2/day. SPSS v16: continuous data analyzed by Student's T or Mann Whitney U. categorical data analyzed by chi Square. OR were calculated after controlling for age			DET with PQE+TQE at blastoycst stage does not increase LBR but increases MPR compared to SET TQE.	
Chen S, et al., *BMC pregnancy and childbirth* 2020;20: 655.	Retrospective single-center	Prospective observational study. Women age :20-42y Own oocytes FSH<10mIU/ml 1st IVF/ICSI with freeze-all and 1st FET SET or DET day 5 blastocyst	Between January 2016 an October 2018: Total 3.362 patients included Lost to follow up: 22 pregnant patients Women were divided in 5 groups depending on quantity and quality of day 5 blastocyst: Group A (n=1569): SET GQE	CPR: ultrasound visualization of gestational sac 4-5 weeks after ET LBR: viable infant born after 28 weeks of gestation. Low birth weight: birth weight <2500g Very low birth weight: birth weight<1500g	**<35y** **LBR** A SET GQE: 54.25% (P<0.05 to B, C,D) B DET 2GQE: 64.57% C mDET GQE+PQE: 64.08% D DET 2PQE: 48.63% E SET 1PQE: 36.67% (P>0.05 D vs E) **MPR** A SET GQE: 3.52% (P<0.05 to B, C,D) B DET 2GQE: 62.38% C mDET GQE+PQE: 49.66% D DET 2PQE: 50%	Results show that when good quality blastocysts are available, SET should be incorporated because of the reduced risk of MPR without significantly impacting the LBR. DET was associated with higher MPR and adverse neonatal outcomes when	Low birth weight is not on prematurity (PICO) hence this data is not mentioned in the text of the guideline. Zero still births in all the babies born.

		Endometrium ≥7mm Reasons for freeze-all: prevention of OHSS, increased Prog on HCG day, untreated hydrosalpinx, personal reasons. Exclusion: Donated oocytes, PGT cycles, uterine anomalies, untreated hydrosalpinx, stage III-IV endometriosis or adenomyosis, uncontrolled endocrine and/or immune disorders or other systemic diseases.	Group B (n=1113): DET 2GQE Group C (n=313): mixed DET GQE+PQE Group D (n=222): DET 2PQE Group E (n= 145): SET 1PQE Stratified by age **<35y** Group A (n=1425): SET GQE Group B (n=844): DET 2GQE Group C (n=206): mixed DET GQE+PQE Group D (n=183): DET 2PQE Group E (n= 120): SET 1PQE **≥35y** Group A (n=144): SET GQE Group B (n=269): DET 2GQE Group C (n=107): mixed DET GQE+PQE Group D (n=39): DET 2PQE Group E (n= 25): SET 1PQE **All blastocyst FET** GQE= min 4 A/B ICTM/TE PQE= 4CC, or blast 3. Endometrial preparation for FET: natural cycle with ET on day 6 after ovulation or hormone replacement therapy (estradiol valerate tablets) from day 3 to		E SET 1PQE: 0% (P>0.05 D vs E) **≥35y** **LBR** A SET GQE: 42.36% (P<0.05 to B) B DET 2GQE: 59.48% C mDET GQE+PQE: 48.60% D DET 2PQE: 30.77% E SET 1PQE: 24.06% **MPR** A SET GQE: 6.25% (P<0.05 to B, C,D) B DET 2GQE: 49.24% C mDET GQE+PQE: 42.62% D DET 2PQE: 31.25% E SET 1PQE:10%	compared to SET, suggesting that SET is also preferred in these patients regardless of age.	

			day 4 after menstruation with ET on day 6 of progesterone injection (60mg/day). Luteal support: progesterone until 10 weeks after conception. SPSS v22: continuous data analyzed by ANOVA or Student's T test. Categorical data analyzed by chi Square or Fisher Exact.				

Papers included as background information

(Wyns et al. 2021), (Guerif et al., 2002), (Glujovsky et al., 2022), (Wong et al., 2014)

PICO 18: Can TL morphokinetics be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART? If yes, which criteria and what is the appropriate cut off?

Evidence Table

Reference	**Study Type**	**Patients** **Include: No. of patients** **Patient characteristics + group comparability**	**Interventions (+comparison)** **Include: Study duration / follow-up**	**Outcome measures** **Include: Harms / adverse events**	**Effect size**	**Authors conclusion**	
Fishel S, et al., *Reproductive biomedicine online* 2017;35: 407-416.	Retrospective study	Patients' or 'non-recipients' (n = 21,466 cycles) comprised those who used all their own oocytes (n = 20,664) and patients who were also oocyte-share donors (n = 802); 'recipients' comprised those women undergoing oocyte	IVF included. Algorithm from Vitrolife. January 2010-January 2015 ; 21,235 treatment cycles in the standard treatment group	LBR MPR Standard treatment vs Embryoscope	**Embryoscope vs. standard treatment:** **LBR:** Patient <38years: 19% increase with EmbryoScope and morphokinetic algorithm embryo selection **Recipients** >37years: 37% increase **SET after embryoscope vs. DET after standard treatment, blastocyst transfer:** **Non-recipients**	Incidence of live birth after embryo transfer using morphokinetic algorithms during uninterrupted culture to select embryos was increased by 19% compared with conventional morphology and standard incubation in	the distinction of the use of algorithms generated by TLI compared with any benefits ac-cruing from the sole use of closed incubation systems.

		donation (n = 2296 cycles).	2527 in the EmbryoScope treatment group EmbryoScope treatment in which a single blastocyst is transferred was compared with standard treatment in which two blastocysts were transferred		< 38 years: OR 0.854; 95% CI 0.735 to 1.000. >38 years: OR 0.603; 95% CI 0.478 to 0.748. **Recipients:** **LBR:** Recipients aged over 37 years did equally well in live birth outcome **> 38 years:** OR 0.981, 95% CI 0.557 to 1.750). **MPR:** Increased risk of a multiple pregnancy in the DET group by about 30– 40%. highly elevated risk of multiple pregnancy in all groups when two embryos were transferred	women younger than 38 years and an Increase of 37% for oocyte recipients aged over 37 years.	

Papers included as background information

(Pribenszky et al., 2017), (Apter et al., 2020), (Kieslinger et al., 2023).

PICO 19. Can the outcome of PGT-A testing of blastocysts be considered a factor in deciding to apply DET instead of (e)SET for couples/individuals undergoing ART?

Evidence Table

No evidence found

Papers included as background information

(Theobald et al. 2020), (Wyns et al. 2021), (Forman et al. 2013), (Grifo et al. 2013), (Scott et al. 2013); (van Montfoort et al., 2021); (ASRM, 2021)

PICO 20- In any patient undergoing ART, should the transfer of more than two embryos be applied considering the risks of the higher order pregnancies?

Evidence Table

Reference	Study Type	Patients Include: No. of patients Patient characteristics + group comparability	Interventions (+comparison) Include: Study duration / follow-up	Outcome measures Include: Harms / adverse events	Effect size	Authors conclusion	Comments (if excluded, list exclusion criterion)
Elizur SE et al. Reproductive biomedicine online 2005;10: 645-649.	observational study	1928 women; Mean age: 32.7 ± 5.9 years. A total of 235 women (12.3%) were older than 40 years. IVF cycles per woman: 2.8 ± 2.3 (range 1–28). Retrieved and fertilized oocytes: 10.7 ± 7.3 (ovarian stimulation cycles) and 6.0 ± 4.3 (frozen embryo transfer cycles) Number of transferred embryos was 3.5 ± 1.6. ICSI was performed in 2795 cycles (52.6%).	From 1 January 1995 to 30 June 2001, 5310 consecutive IVF cycles in a single IVF unit. From 1995 to 2001	Delivery success rate Multiple pregnancy rate MPR	**Delivery rate** (n=5310) **Age:** 17-25 years: 41.0% (80/195) 26-30 years: 48% (273/569) 31-35 years: 36.7% (183/499) 36-40 years: 31% (116/374) 41+: 12.3% (29/235) Unknown: 14.3% (8/56) **Number of embryos** **SET:** 4.4% (22/495) **DET**: 11.4% (93/816), AOR: 1.97 (95%CI 1.20-3.23) **TET**: 17.1% (224/1309); AOR 2.69 (95%CI 1.20-3.23) ≥4 embryos: 15.8% (346/2184); AOR 2.14 (1.29-3.54) Unknown: 0.8% (4/506) Twins rate: DET: 21.5% (17/79) TET: 27.7% (57/206) ≥4 embryos: 33.1% (107/323). Triplet: TET: 5.3% (11/206)	the best live birth results following IVF treatment were achieved when the maternal age was 26–30 years, in couples with male factor infertility undergoing ICSI, and when two embryos were transferred.	transferring three embryos was not significantly superior to two embryos. Moreover, following a three-embryo transfer, the multiple delivery rates were significantly higher (P < 0.01) compared with transferring two embryos.

					≥4 embryos: 6.2% (20/323) Choice of embryo: No: 7.8% (109/1404) Yes: 17.0% (574/3371); AOR 1.96 (1.46-2.64) Unknown: 1.1% (6/535)		
Heijnen EM, et al., *Reproductive biomedicine online* 2006;13: 386-393.	RCT	45 patients ≥ 38 years Patients had an indication for an IVF or IVF/ICSI treatment either for the first time or after a previous IVF or IVF/ICSI childbirth	DET over a maximum of four cycles (DET group): 23 patients (66 cycles) TET over a maximum of three cycles (TET group): 22 patients (46 cycles) in the period October 2001 to December 2003	cLBR MPR	cLBR: 47.3% after 4 cycles in the DET group vs 40.5% after 3 cycles in the TET group. The difference between the DET and the TET group was 6.8% in favour of the DET group (95% CI –25 to 38). MPR in the DET and TET group were 0% (95% CI 0 - 24) and 30% (95% CI 7 - 65) respectively (P = 0.05). Mean number of treatment cycles: 2.9 (DET) vs 2.1 (TET), P = 0.01.	In women of 38 years and older, DET after IVF may result in similar cumulative term live birth rates compared with TET, provided that a higher number of treatment cycles is accepted	
Salha, et al. J Assist Reprod Genet, 2000. 17(6): p. 335-43.	obs. study	1448 women having their first IVF treatment cycle (4004 embryos) At least six embryos were available for transfer.	7-year period from 1991 to 1998; DET or TET depending on the patients' age, the availability and quality of the embryos.	Clinical pregnancy rate CPR Live birth rate LBR Multiple birth rate MPR	**≤35 years old vs >35 years old**: **CPR/cycle**: 41.6% vs 30.1% **LBR/cycle**: 32.8% vs 24.5% **Singletons**: 63.7% vs 89.9% **Twin pregnancy:** 30.8% vs 8.9% **Triplet pregnancy:** 5.4% vs 1.3% **DET vs TET:**	The presence of good-quality supernumerary embryos can be used as a reference to determine the optimal number of embryos to transfer and as indicator of the probability of success of an individual couple in a given cycle. Optimal pregnancy rates and simultaneous reduction of multiple	Recommends 3 embryos if >35, or not good qual embryos

					Quality embryos available CPR: 45.2% vs 50.5% LBR: 35.7% 38.9% **Twin birth rate**: 11.9% vs 12.5% **Triplets birth rate**: 0% vs 2.9% **Quality embryos not available** **CPR**: 28.8% vs 39.3%, p=0.04 **LBR**: 19.4% vs 32.7%, p=0.01 **Singleton birth rate**: 14.4% vs 20.8%, p=0.3 **Twin birth rate**: 5% vs 9.8%; **Triplet birth rate:** 0% vs 2.1%	gestation can be achieved with a flexible embryo replacement policy that is based on embryo quality, maternal age, and the presence or absence of surplus quality embryos.	
Ng, et al. J Obstet Gynaecol Res, 2001. 27(6): p. 329-35.	obs. study	863 cycles were initiated: 1998: 453 cycles 1999: 410 cycles	cycles initiated in 1998 and in 1999, DET vs TET	Pregnancy rate PR Implantation rate IR Multiple pregnancy rates MPR: Twins and triplets rates	**DET vs TET:** **PR/ transfer:** 21.6% (84/388) vs 24.8% (86/347), NS **IR:** 14.6% (113/776) vs 18.6% (142/762), p=0.038 **MPR**: 15.5% (13/84) vs 31.4% (21/86), p=0.023 **Twin**: 15.5% (13/84) vs 24.4% (21/86), NS **Triplet:** 0% (0/84) vs 7.0% (6/86), p=0.04 **eDET vs DET:** **PR:** 29.2% (57/195) vs 19.1% (29/152), NS **IR:** 24% (99/413) vs 12.3% (43/349), p<0.001 **MPR**: 29.8% (17/57) vs 34.5% (10/29), NS **Twin**: 26.3% (15/57) vs 20.7% (6/29), NS	transfer of 2 embryos instead of 3 will not compromise pregnancy rate but will reduce the multiple pregnancy rate in an assisted reproduction unit.	Patients should be advised to have 2 embryos replaced without jeopardizing the pregnancy rates in the fresh cycles. The risk of multiple pregnancy is significantly increased when 3 embryos are transferred instead of 2.

					Triplets: 3.5% (2/57) vs 13.8% (4/29), NS **eTET vs TET:** **PR:** 29.2% (57/195) vs 19.1% (29/152), NS IR: 24.0% (99/413) vs 12.3% (43/349), p<0.001 **MPR**: 29.8% (17/57) vs 34.5% (10/29), NS **Twin**: 26.3% (15/57) vs 20.7% (6/29), NS **Triplet**: 3.5% (2/57) vs 13.8% (4/29), NS		
Ruhlmann, et al., JBRA Assist Reprod, 2017. 21(1): p. 7-10.	retrospective study	Group A (N = 219), Group B (N = 357) Group C (N = 208); Age and previous attempts were comparable in the 3 groups.	784 consecutive fresh day-5 embryo transfers From 2007 to 2015, Group A: received the only 2 embryos that reached a transferable stage. Group B: received 2 selected embryos among several that reached a transferable stage. Group C: received the only 3 developing embryos.	Clinical pregnancy rate: CPR Implantation rate: IR Multiple pregnancy rate MPR	**Group A vs Group B vs Group C:** Oocyte recovery: 10.7 ± 5.6 vs. 14.7 ± 8.0 vs. 13.8 ± 6.6 Fertilization rate: 75.97% vs. 81.60% vs. 83.29%) Embryos reaching transferable stage on day 5: 39.98% vs. 63.99% vs. 60.97%), CPR: 42.92% vs. 61.06% vs. 58.17% IR: 21.09% vs. 40.98% vs. 36.97%. MPR:11.70% vs. 31.19% vs. 37.19%. HOM (> 2): 1.06% vs. 0.92% vs. 14.05%.	In patients with 3 or more day 5 developing embryos, delivery rates are similar if 2 or 3embryos are transferred. The transfer of 3 embryos carries an unacceptable increase in the risk of high order multiple pregnancy, with its known consequences. According to our data, we should not exceed the number of 2 day-5 fresh embryos transferred.	If only 3 embryos develop
Combelles, et al., Fertil Steril, 2005. 84(6): p. 1637-42.	obs. study	863 Women aged > 40 years undergoing a fresh cycle with a day-3 ET	between January 1998 and July 2003 IVF	Pregnancy, chemical pregnancy, miscarriage rates, number of viable fetuses at 12 weeks' gestation, live birth rates, and number of babies delivered	**<5 embryos vs 5 embryos vs >5 embryos transferred**: **Total pregnancies** (%ET): 19.1% (75/392 vs 40.1% (57/142) vs 47.4% (156/329 **Total pregnancy loss:**	The present study demonstrates that in women aged >40 years, five embryos is the optimum number to transfer, and transferring more than five does not confer any additional benefit to clinical outcome.	In women > 40 years, 5 embryos is the optimum number to ET, and transferring more than five does not confer any additional benefit to clinical outcome.

					80% (60/75) vs 47.4% (27/57) vs 59.6% (93/156) **Live birth rate:** 4.3% (15/347) vs 22.6% (30/133) vs 22.3% (63/282) **Singletons:** 86.7% (13/15) vs 63.3% (19/30) vs 76.2% (48/63) **Twins**: 13.3% (2/15) vs 36.7% (11/30) vs 23.8% (15/63) **Triplets:** 0%		
Setti, et al., Reprod Biomed Online, 2005. 11(1): p. 64-70.	retrospective study	1028 assisted reproductive technology cycles	In the first period (2002), 262 cycles in women <36 years old were studied, 3 embryos transferred, followed by 157 cycles in women ≥36 years, 4 embryos were transferred. In the second period (2003), 332 cycles were evaluated in women <36 years and 277 cycles in women ≥36 years old, reducing the number of embryos transferred to two and three respectively.	Clinical pregnancy rate CPR Implantation rate IR (mean ± SD) Singleton rate Twins rate Clinical abortions Ectopic pregnancies	Women <36 years old: DET vs TET: 42.5% (141) vs 55.7% (146) IR: 26.1 ± 33.9 (173) vs 24.6 ± 28.0 (205) Single: 75.2% (106) vs 65.1% (95) Twins: 24.8% (35) vs 28.1% (41) Triplets: 0 vs 6.8% (10) Clinical abortions: 121% (17) vs 11.0% (16) Ectopic pregnancies: 2.1% (3) vs 1.4% (2) women ≥36 years old: TET vs 4 embryos: CPR: 28.5% (79) vs 39.55% (62) IR (mean ± SD): 13.1± 23.9 (109) vs 14.1± 21.0 (89) Singletons: 64.6% (51) vs 64.5% (40) Twins: 29.1% (23) vs 24.2% (15	the reduction in the number of embryos transferred, from three to two in women <36 years of age, and from four to three in women ≥36 years of age, without any selection other than pre-transfer morphological score, adversely affects the outcome of treatment, without a significant reduction in twin gestation	reduction in no. of embryos ETd, from 3 to 2 in women < 36y, and from 4 to 3 in women >36y, adversely affects the outcome of treatment, without a significant reduction in twin gestation rate.

					Clinical abortions: 13.9% (11) vs 11.3% (7) Ectopic pregnancies: 3.8% (3) vs 3.2% (2) Elective transfer: eDET vs eTET vs elective 4-embryos transfer Singletons: 75.2% (106) vs 69% (146) vs 64.5% (40) Twins: 24.8% (35) vs 28.4% (64) vs 24.2% (15) Triplets: 0% vs 6.7% (15) vs 11.3% (7)		
Berin, et al., Fertil Steril, 2010. 93(2): p. 355-9.	retrospective study	145 patients aged <35 ; and 93 patients aged 35 to 39	transfer of two or three embryos in FET cycles between January 2004 and December 2005	Clinical pregnancy rate (PR), multiple clinical pregnancy rate (MPR), and live birth rate (LBR).	DET vs TET group **In patients aged <35:** **CPR:** 55.7% vs 56.4% **MPR:** 9.4% vs 41% **LBR**: 39.8% vs 56.4% **In patients 35-39 years old:** **CPR:** 43.8% vs 44.4% **MPR**: 14.6% vs 8.9% **LBR**: 42.4% vs 44.4%	Transfer of two instead of three frozen embryos in patients <35 years old resulted in a significant decrease in MPR without compromising PR or LBR. Transferring additional embryos when a patient had an unsuccessful fresh cycle was not warranted. In the age group 35–39 years, transferring two instead of three embryos did not decrease PR or LBR, and had no effect on the risk of high-order multiples.	In the age group 35–39 years, transferring two instead of three embryos did not decrease PR or LBR, and had no effect on the risk of high-order multiples

Sun, et al., J Assist Reprod Genet, 2012. 29(5): p. 417-21.	retrospective study	776 patients <35 years; 169 patients aged 35 to 39 years; 35 patients > 40	980 FET cycles performed between January 2007 and October 2010. Transfer DET: 785 cycles TET: 195 cycles	Clinical pregnancy rates (CPR), implantation rates (IR) and live birth rates (LBR).	**DET vs TET:** **<35 years:** CPR: 41.2% vs 44.83% MPR: 24.23% vs 44.62% **35-39 years old:** CPR: 37.98% vs 40% MPR: 6.12 vs 43.75% **>40 years old:** CPR: 28% vs 30% MPR: 0% vs 0%	Transferring two instead of three multicellular embryos in patients under 40 years old significantly decreases the risk of MPR without compromising PR, IR and LBR. In the age group above 40, transferring two instead of three multicellular embryos did not decrease PR, IR, MBR or LBR. Transferring more embryos when a patient had more unsuccessful cycles was not warranted in all patients.	china - In <40y, ET of two instead of three multicellular embryos did not decrease PR, IR, MBR or LBR.
Richter, et al. Fertil Steril, 2016. 106(2): p. 354-362.e2.	obs. study	7,597 cryopreserved blastocysts were transferred in 4,597 autologous cryopreserved blastocyst transfer cycles during the study period. The mean age at oocyte retrieval and cryopreservation was 33.6 years (SD 3.8 years), and the mean age at transfer was 34.8 years (SD 3.9 years)	Cryopreserved blastocyst transfer patients from January 2003 to April 2012; 4,862 slow frozen blastocysts transferred in 2,842 cycles, SET (38%) DET (53%) TET (9%) and 2,735 vitrified blastocysts transferred in 1,755 cycles. SET (48%) DET (48%) TET (4%)	Birth per transfer LBR and children per embryo;	**LBR:** **Slow freezing:** SET vs DET: 19.4% vs 29.7%, p<0.0001 DET vs TET: 29.7% vs 41.4%, p=0.11 **After vitrification:** SET vs DET: 38.2% vs 51.9%, p<0.001 DET vs TET: 51.9% vs 54.7%, p=0.73 **Live born children per embryo transferred:** **Slow freezing**: **SET vs DET vs TET**: 22.5% vs 19.3% vs 18.2% **Vitrification: SET vs DET vs TET:** 39.2% vs 34.6% vs 30.1% **MPR:** **Slow freezing:** **SET vs DET vs TET:** 1.5% vs 21% vs 21%	Birth outcomes from cryopreserved blastocyst transfer are influenced by age, timing of expansion, cryopreservation protocol, visible cryodamage, and the number of embryos transferred. Vitrification substantially improves outcomes versus slow freezing.	

					Vitrification: **SET vs DET vs TET:** 0.6% vs 33% vs 46%		
Clayton et al 2007	Retrospective study	207 heterotopic 132660 intrauterine-only pregnancies	None From 1999 to 2002	**Pregnancies outcomes:** Spontaneous abortion, induced abortion, stillbirth and live birth **Perinatal outcomes**: preterm; low birth weight LBW; preterm LBW; term LBW	**Heterotopic vs intrauterine:** **Spontaneous abortion**: RR 2.05; 95%CI 1.67-2.51 **Induced abortion:** RR: 10.28, 95%CI6.76-15.65. **LBR**: RR 0.72; 95%CI 0.64-0.81 **No difference in perinatal outcomes**	Heterotopic pregnancies were more likely to result in spontaneous or induced abortions than were intrauterine-only pregnancies. There was no difference in perinatal outcomes between heterotopic and intrauterine-only pregnancies progressing to live birth.	
Anzhel et al 2022	Observational study	15006 clinical pregnancies SET: 9207; DET: 5799 Fresh ET: 8952 Frozen ET: 6054	SET vs DET Fresh vs frozen From 2000 to 2017	Ectopic pregnancy rate	**Ectopic pregnancy rate**: **Fresh vs frozen**: 2.2% vs 2.4%, p=0.3 **Top-quality vs non-top-quality:** 1.9% vs 2.7%, p<0.0001; OR: 0.72; 95%CI 0.56-0.92 **Tubal factor infertility:** 21.2% vs 11.0% in intrauterine, OR221; 95%CI1.68-2.91, p=0.2; **DET vs SET:** OR 1.35; 95%CI 1.05-1.70, p=0.02	Transfer of non- top-quality embryos is associated with a higher rate of ectopic pregnancy. This is particularly important to keep in mind in treatments with only non- top embryos available even in the absence of tubal factor infertility. To minimize the risk of ectopic pregnancy, the number of embryos transferred should be as low as possible	
Bu et al 2016	Retrospective study	18432 pregnancies	IVF/ICSI Autologous and donor cycles From June 2009 to August 2015	Ectopic pregnancy rate	CST vs blastocysts: 3.4% vs 2.47%; adjusted OR 0.715 (0.511-1.001) Fresh vs frozen: 3.22% vs 3.52%, p=0.304; adjusted OR1.111 (95%CI 0.922-1.338)	Irrespective of tubal infertility, for fresh IVF/ICSI cycles the rate of EP is positively associated with ovarian stimulation; for thawed IVF/ICSI cycles, blastocyst transfer or transfer	

					Tubal infertility: adjusted OR 1.716; (95%CI 1.444-2.039); Sperm donor cycles: 1.08% vs 3.54% for husbands; p=0.000 SET: 3.51% vs DET: 3.09% vs TET: 4.07%, p=0.660; OR 1044 (95%CI 0.871-1250)	with fewer embryos reduces the EP rate.	
Cirillo F, *Scientific reports* 2022;12: 20473.	Retrospective study	7352 pregnancies 132 ectopic pregnancies	IVF/ICSI fresh and frozen cycles From 2009 to 2018	Ectopic pregnancy (EP) rate	EP rate: 1.8% (95%CI 1.5-21) Fresh cycles: Prior pelvic adhesions: aOR 2.49 (95%CI1.53-4.07), p<0.001; Blastocyst transfer vs cCST: OR1.34 (95%CI 1.03-1.74) Fresh ET vs frozen ET: 0.73; 95%0.23-2.39 Fresh ET vs Frozen oocytes: OR0.75 (95%CI 0.23-2.39)	the incidence of EP observed was comparable to that reported after natural conception. On the other hand, pre-existing risk factors, traditionally more common in infertile population, appeared to influence the incidence of EP and should thus be modified if possible.	
Li et al 2015	Cohort study	44102 pregnancies	SET vs DET Between 2009 and 2011	Ectopic pregnancy rate	SET vs DET: 1.2% Vs 1.8%, p<0.01 CST vs BT: Fresh: 1.9% vs 1.3%, AOR 1.30; 95%CI 1.07-1.59 95% Frozen: 1.7% vs 0.8% Fresh BT vs Frozen BT: AOR 0.70; 95%CI 0.54-0.91	The lowest risk of ectopic pregnancy was associated with the transfer of a single frozen blastocyst.	
Perkins et al 2015	Cohort study	553577 pregnancies 9480 ectopic pregnancies, of which 483 were heterotopic.	Donor vs non donor cycles: SET vs DET vs TET vs ≥4 embryos Between 2001 and 2011	Ectopic pregnancy rate	Fresh nondonor cycles: 2.0% (n=7469; 95%CI 1.9-2.0) SET vs DET: 1.6% vs 1.7% (AOR: 1.11; 95%CI 0.94-0.30) SET vs TET: 1.6% vs 2.2% (AOR 1.33; 95%CI 1.12-1.56)	Ectopic pregnancy incidence after assisted reproductive technology has decreased over time, but factors such as multiple embryo transfer increase the	

					SET vs ≥4 embryos: vs 1.6% vs 2.5% (AOR 1.49; 95%CI 1.25-1.78) Fresh donor cycles: 1.0% (n=641; 95% 0.9-1.1)	risk of ectopic pregnancy.	
Pi et al 2020	Retrospective study	22 patients age of 29.0±3.4 years old (range, 21 years old to 36 years old), Diagnosis: gestation age of 56.0±11.5 days (range, 40 days to 79 days).	IVF From January 2015 to December 2018	Factors associated with Heterotopic pregnancy (HP) risk (compared to intrauterine pregnancies IUP) Abortion rate of treated HP and IUP	**Tubal factor**: HP risk: OR 4.184; 95%CI 1.080-16.217 **IVF with pelvic adhesion**: HP risk: OR 5.552; 95%CI 1.677-18.382 **IVF with >2 embryos:** HP risk: OR 23.253; 95%CI23.253; 5%CI 1.804-299.767. **Abortion rates HP vs IUP**: 27.8% vs 10.3%, p=0.42	These results demonstrate IVF with tubal infertility, pelvic adhesion or multi-embryos transfer are risk factors of HP. Furthermore, surgery could induce abortion	

Papers included as background information

(Min et al. 2004), (Min et al., 2010), (ASRM, 2021); (De Geyter et al., 2022); (Wyns et al., 2020); (Wyns et al., 2021); (Wyns et al., 2022)

PICO 21: In any patient undergoing ART, should the transfer of more than two embryos with embryo reduction after implantation be applied considering the risks of the procedure?

Evidence Table

Reference	**Study Type**	**Patients** **Include: No. of patients** **Patient characteristics + group comparability**	**Interventions (+comparison)** **Include: Study duration / follow-up**	**Outcome measures** **Include: Harms / adverse events**	**Effect size**	**Authors conclusion**	**Comments (if excluded, list exclusion criterion)**
Zipori Y, et al., *Reproductive*	Meta-analysis	Total number 3209 patients in 24 studies. Conception	Triplets reduced to twins vs no reduction of	Preterm delivery, gestational diabetes, hypertensive	Preterm delivery <36 OR 0.14 95% CI (0.06, 0.35)	MPR of triplet pregnancies to twins is associated with a better	Limitation is inclusion of

***biomedicine online* 2017;35: 296-304.**		not just using ART. Non substantial heterogeneity between the groups in most comparisons	triplets. Follow up to birth, mean 40 weeks.	disorders, small for gestational age, prenatal hospitalisation, rate of caesarean section, neonatal death	preterm delivery <34 0.16 (0.09, 0.28) Gestational diabetes 0.36 (0.19, 0.67) Hypertensive disorders 0.47 (0.31, 0.72) Small for gestational age 0.93 (0.63, 1.38) Rate of caesarean section 0.18 (0.10, 0.33) Neonatal death 0.32 (0.12, 0.84)	pregnancy outcome compared with that of non-reduced triplets. Single embryo transfer during ART, should remain the mainstay approach for triplet pregnancies. Should this fail, multifetal pregnancy reduction may be the appropriate alternative to reduce perinatal morbidity and mortality in trichorionic triplet pregnancies.	non-ART pregnancies
Dodd JM, et al., The Cochrane database of systematic reviews 2015: Cd003932.	Cochrane review	No RCTs to include					
Anthoulakis C, et al., Human reproduction (Oxford, England) 2017;32: 1351-1359.	Meta-analysis	Total number 1416 patients in 8 studies. Conception not just using ART. Some heterogeneity between studies.	Triplets reduced to twins vs no reduction of triplets. Follow up to birth, mean 40 weeks.	Miscarriage <24 and preterm birth <34	TCTA vs reduced: miscarriage 8.1 versus 7.4%, P = 0.661 and RR = 1.08, 95% 0.58–1.98; preterm birth 17.3 versus 50.2%, P <0.005 and RR = 0.36, 95% CI: 0.28–0.48. DCTA vs reduced: miscarriage 8.5 versus 13.3%, P = 0.628 and RR = 1.22, 95% CI: 0.38–3.95, respectively; preterm birth 51.9 versus 46.2%, P = 0.778 and RR = 0.5, 95% CI: 0.04–5.7, respectively	The principal finding of our study is that ER to twins in TCTA pregnancies reduces the risk of preterm birth (<34 weeks) without significantly increasing the risk of miscarriage (<24 weeks).	Limitation is inclusion of non-ART pregnancies
Groutz A, et al., Human reproduction (Oxford, England) 1996;11: 1334-1336.	Prospective cohort	10 quadruplets (group 1) and 30 triplets reduced to twins (group 2) and 30 spontaneous twins (group 3). Groups comparable in terms of maternal age and parity.	Reduction of multiple pregnancy to twins vs spontaneous twins.	Gestational age at delivery, caesarean section rate, birth weight and overall complications.	Insufficient data for effect size calculations. Group 1 vs. Group 2 vs. Group 3: Mean Gestational age at delivery: 33.2 w vs. 35.9 w vs.36.9 weeks Mean Birth weight: 1843g vs. 2209g vs. 2361g Premature contractions rate: 50% vs. 27% vs. 13%, Pregnancy induced hypertension rate 40% vs. 23% vs. 7%.	The initial number of foetuses before reduction was inversely correlated with gestational age at delivery and birthweight, and positively correlated with pregnancy complications. Contrary to previous studies, we found a higher incidence of pregnancy complications after MFPR compared with spontaneous twins, especially PMC and PIH.	
Jin B, et al., Medicine 2020;99: e20730.	Systematic review and Meta-analysis	Six retrospective cohort studies involving 7398 participants	Between 2011 and 2019 A total of 530 twin gestations that	The primary outcomes of interest were preterm birth rate, birth weight, and miscarriage	MPR of DCDA twin pregnancy to singleton vs. expectant management: A lower risk of preterm birth (5 studies with 7297 participants;	Compared to expectant management, MPR of DCDA twin pregnancy to singleton prevents preterm birth and low	

			underwent MPR and 6868 controls that underwent expectant management	rate. The secondary outcomes were the rates of intrauterine growth retardation (IUGR), cesarean section, and gestational diabetes mellitus (GDM). T	RR: 0.30,95%CI: 0.22–0.40; P<.001) Higher birth weight (4 studies with 5763 participants; mean differences: 548.10g, 95% CI: 424.04–672.15; P<.001) No difference in the occurrence of miscarriages (5 studies with 7355 participants; RR: 1.57, 95% CI: 0.90–2.75; P=.11).	birth weight, without increasing the risk of miscarriages. Regarding perinatal morbidity related to preterm birth, MPR can be reserved as a remediation measure to improve the perinatal outcomes of DCDA twin pregnancies.	
Liu Y, et al., *Taiwanese journal of obstetrics & gynecology* 2019;58: 133-138.	Retrospective cohort	57 triplets, 670 triplets reduced to twins. Groups comparable in terms of maternal age, BMI, duration of infertility, treatment used.	Triplets reduced to twins vs no reduction. Follow up to birth, mean 40 weeks.	Abortion, live birth, caesarean section, preterm birth, gestation at delivery, perinatal mortality, birth weight	**Triplets vs triplets reduced to twins:** abortion 15% vs 5% p=0.071; live birth 85% vs 95% p=0.099; caesarean section 88% vs 93% p=0.51; preterm delivery 85% vs 53% p<0.001; gestation at delivery 34.6w vs 36.1w p<0.001; perinatal mortality 1% vs 1% p=0.73; birth weight 2083g vs 2432g p<0.001	For DCT and TCT pregnancies, MFPR application could reduce the miscarriage rate, while improving live birth and take-home baby rates compared to the expectant groups. Especially, when reduced to a single fetus, MFPR could provide the better perinatal outcomes.	
Yimin Z, et al., Frontiers in endocrinology 2022;13: 851167.	Retrospective cohort study	502 women underwent MFPR to twins or singletons and 9641 non-reduced women.	2002 – 2016 331 women with twins reduced from triplets at 6-13 weeks 45 women with singletons reduced from triplets at 7-12 weeks 126 women with singletons reduced from twins at 7-16 weeks Primary singletons: 6853 Primary twins: 2788 women	GA at delivery, the rates of preterm delivery before <32 weeks, <34 weeks, and <37 weeks of gestation, pregnancy loss < 24 weeks, abortion of one fetus and caesarean section as well as neonatal outcomes such as neonatal birth weight, the rates of at least one fetus LBW, at least one fetus very low birth weight (VLBW) and SGA.	**Singletons reduced from triplets/twin**s vs primary singletons: higher rates of preterm delivery (15.8% vs. 7.3%, P<0.001), LBW (12.3% vs. 4.32%, P<0.001), VLBW (2.3% vs. 0.4%, P=0.002), and SGA (14.6%vs.6.6%, P<0.001) comparable pregnancy loss rate (5.3% vs. 5.4%, P=0.671).	the pregnancy loss rate is similar between reduction and non-reduction groups. MFPR improves pregnancy outcomes, including the risk of preterm delivery, LBW, and SGA, but still could not completely reverse the adverse pregnancy outcomes of multiple pregnancies.	
Kristensen SE, et al., *American journal of obstetrics and gynecology* 2022.	Retrospective cohort study	9735 dichorionic twin pregnancies	9563 dichorionic twin pregnancies 172 reduced twins. 16,465 primary singletons.	Primary outcome: adverse pregnancy outcome: miscar-riage before 24^{+0} weeks, stillbirth from 24^{+0} weeks, or	Adverse pregnancy outcome was observed in 4.1% (95%CI 1.7%-8.2%) of reduced twin pregnancies, and 2.4% (95%CI 0.7%-6.1%) were delivered before 28	all dichorionic twin pregnancies, transabdominal fetal reduction by needle guide for fetal or maternal indication was shown to be safe, with good outcomes for the	

			Fetal reductions were performed between 11 and 23 weeks between January 2008 and December 2018.	single intrauterine fetal death in the nonreduced twin pregnancies, preterm delivery before 28^{+0}, 32^{+0}, or 37^{+0} weeks, rate of live-born children, and gestational age at delivery. Secondary outcomes: pregnancy complications defined as preterm prelabour rupture of membranes (PPROM), preeclampsia, placenta previa, and placental abruption, and birthweight z-scores	weeks, and 4.2% (95% CI 1.7%-8.5%) before 32 weeks. When fetal reduction was performed before 14 weeks, adverse pregnancy outcomes occurred in only 1.4% (95% CI 0.0%-7.4%), and delivery before 28 and 32 weeks diminished to 0% (95% CI 0.0%-5.0%) and 2.8% (95% CI 0.3%-9.7%), respectively. In contrast, 3.0% (95%CI 2.7%-3.4%) of nonreduced dichorionic twins had an adverse pregnancy outcome, and 1.9% (95% CI 1.7%-2.1%) were delivered before 28 weeks, and 7.3% (95%CI 6.9%-7.7%) before 32 weeks. Adverse pregnancy outcomes occurred in 0.9% (95% CI 0.7%-1.0%) of primary singletons, and 0.2% (95% CI 0.1%-0.3%) were delivered before 28 weeks, and 0.7% (95%CI 0.6%-0.9%) before 32 weeks.	remaining co-twin. Results were best when the procedure was performed before 14 weeks.	
van de Mheen L, et al., ***Human reproduction (Oxford, England)*** **2015;30: 1807-1812.**	Retrospective cohort study	118 women with a twin pregnancy that was reduced to a singleton, 818 women with an ongoing dichorionic twin pregnancy and 611 women with a primary singleton pregnancy.	From 2000 to 2010. Fetal reduction was performed trans-abdominally by intracardiac or intrathoracic injection of potassium chloride using a 20 Gauge or 22 Gauge needle.	Gestational age at delivery Neonatal birthweight Number of perinatal deaths.	Loss of the entire pregnancy ,24 weeks and preterm delivery occurred significantly more in the reduction group compared with the ongoing twin group (11.9 versus 3.1%, 24 weeks, P,0.001 and 18.6 versus 11.5% ,32 weeks, respectively, P, 0.001). In the reduction group, the percentage of women without any surviving child was significantly higher compared with the ongoing twin and primary singleton group (14.4, 3.4 and 0.7%, respectively, P, 0.001). Median gestational age was 38.9weeks (interquartile range (IQR) 34.7–40.3) for	Only when a lethal abnormality is threatening the normal co-twin, for instance in case of development of severe polyhydramnion, should selective feticide be considered. Parents need to be counselled that undergoing fetal reduction always exposes the healthy remaining fetus to a risk of serious complications possibly resulting in preterm birth.	indications for reduction were heterogeneous.

					reduced pregnancies, 37.1 weeks (IQR 35.3–38.1) for ongoing twin pregnancies and 40.1 (IQR 39.1–40.9) for primary singletons (P, 0.001 for all comparisons).		
Wang C, et al., *Reproductive biology and endocrinology: RB&E* 2022;20: 71.	Retrospective study	5922 patients with embryo transfer	March 2011 to January 2021 DET Elective reduction to singletons SEFR group (n=390) and spontaneous reduction to singletons SPFR group (n= 865) SET group (n=4667)	Clinical outcomes, including pregnancy outcomes, pregnancy complications, and newborn outcomes,	SEFR increased the risk of miscarriage (OR 2.368, 95% CI 1.423–3.939) and preterm birth (OR 1.515, 95% CI 1.114–2.060), and reduced the gestational age (βeta -0.342, 95% CI -0.544– -0.140). SPFR increased the risk of gestational diabetes mellitus (GDM) (OR 1.657, 95% CI 1.215–2.261), preterm premature rupture of membranes (PPROM) (OR 1.649, 95% CI 1.057–2.574), and abnormal amniotic fluid volume (OR 1.687, 95% CI 1.075–2.648). Both SEFR and SPFR were associated with reduced live birth rate (OR 0.522, 95% CI 0.330–0.825; OR 0.671, 95% CI 0.459–0.981), newborn birth weight (βeta -177.412, 95% CI -235.115–-119.709; βeta -42.165, 95% CI -83.104–-1.226) as well as an increased risk of low-birth-weight newborns (OR 2.222, 95% CI 1.490–3.313; OR 1.510, 95% CI 1.092–2.087).	DET with subsequent fetal reduction was related to poor clinical outcomes.	

Papers included as background information

(Evans et al., 2003), (Evans et al., 2014), (Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies: ACOG Practice Bulletin, Number 231, 2021), (Beriwal et al., 2020), (Multiple gestation pregnancy, The ESHRE Capri Workshop Group, 2000)

PICO 22. Which issues are crucial for decision-making regarding the number of embryos to transfer and how should they be discussed with the patients? (NARRATIVE)

Evidence Table

Not applicable, narrative chapter