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Failed thaw cycles as a key performance indicator: Accounting for patient diagnosis and preimplantation genetic testing

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Disclosures

- KAW, FC, BH, KM and ABC are employees of EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA
- MCM received consulting fees from DxNow, Inc., and EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA
- GM, MB and MG have nothing to disclose

Introduction

Assisted reproductive technology (ART) laboratories

- Have a crucial role in fertility treatments
- Involve a growing number of procedures and increasing complexity
- Are under intense scrutiny with regard to performance and success rates

Introduction

Key performance indicators (KPIs)

- Intrinsic to quality management systems[1]
- Important measures in ART; used for the evaluation of a technique or process, benchmarking, and quality management and improvement[2]
- Recommendation: KPIs should be developed by each laboratory[3]

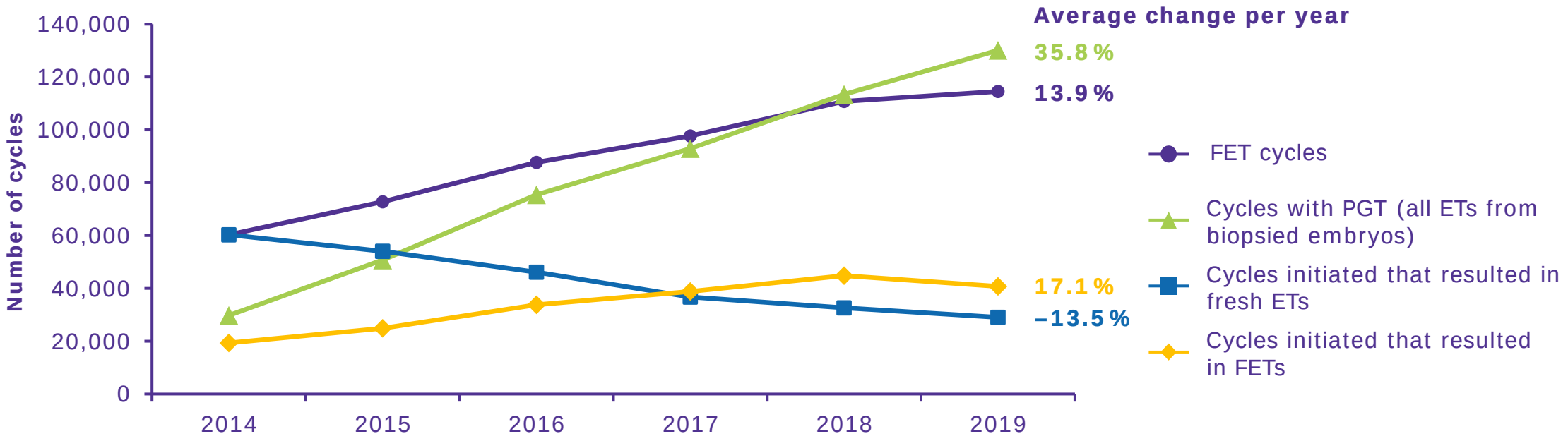
ART, assisted reproductive technology

1. Wirka KA et al. Panminerva Med 2022. Online ahead of print. doi: 10.23736/S0031-0808.22.04686-9; 2. Alpha Scientists in Reproductive Medicine. Reprod Biomed Online 2012;25:146–67;
3. ESHRE Special Interest Group of Embryology, Alpha Scientists in Reproductive Medicine. Hum Reprod Open 2017;2017:hox011.

Introduction

Shifts in ART clinical practice[1]

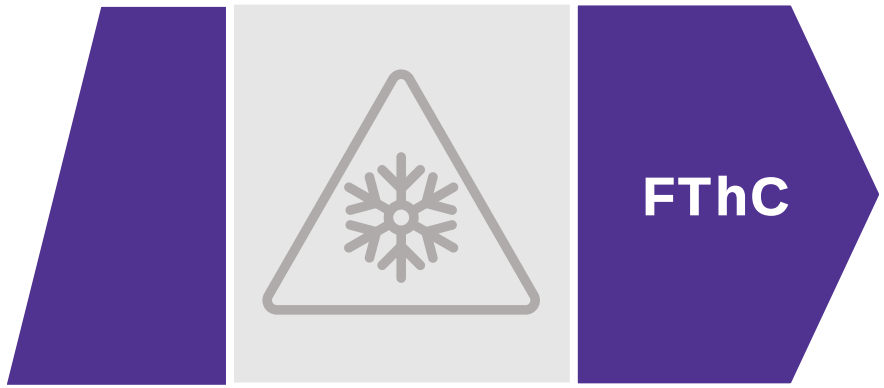
- FET cycles represented the majority of all ETs from 2017 to 2019
- Utilization of PGT[a] increased by an average of 35.8% per year (2014–2019), from 15,859 to 51,887 retrievals
- Similarly, FET cycle utilization increased at an average rate of 13.9% per year (2014–2019)



ART, assisted reproductive technology; ET, embryo transfer; FET, frozen embryo transfer; PGT, preimplantation genetic testing
[a]PGT includes testing for aneuploidy, monogenic/single gene defects and structural chromosome rearrangements
1. Wirka KA et al. PCRS 2021 [E11]

Introduction

Embryo cryosurvival



- Embryo cryosurvival rate is a recommended KPI used for benchmarking in embryo cryopreservation[1,2]
- FThC are thaw procedures that fail to produce any embryos suitable for transfer
- The proportion of FThC stratified by age and diagnosis has been suggested as a surrogate for laboratory competency in freezing and thawing procedures, thereby functioning as a potential KPI for IVF laboratories[3]

FThC, failed thaw cycles; IVF, *in vitro* fertilization; KPI, key performance indicator

1. Alpha Scientists in Reproductive Medicine. Reprod Biomed Online 2012;25:146–67; 2. Society for Assisted Reproductive Technology (SART). https://www.sart.org/ [Accessed January 27, 2022].

Introduction

Embryo cryosurvival

Change per year in percentage of failed thaw procedures, mean number of embryos transferred and LBR by infertility diagnosis (2014–2019)[1]

	FThC		Mean number of embryos transferred		LBR	
	Change per year, %	p-value	Change per year, n	p-value	Change per year, %	p-value
All diagnoses	−0.28	<0.0001	−0.09	<0.0001	2.17	<0.0001
Endometriosis	−0.38	0.0716	−0.09	<0.0001	2.72	0.0005
Diminished ovarian reserve	−0.07	0.4035	−0.05	<0.0001	1.14	0.0074
Multiple female factors	−0.20	0.113	−0.11	<0.0001	1.85	<0.0001
Ovulatory dysfunction	0.45	0.1928	−0.09	0.0002	3.53	0.0067
Tubal factor	−0.09	0.6299	−0.09	<0.0001	1.29	0.0027
Uterine factor	−0.05	0.7977	−0.11	<0.0001	0.99	0.1552
Female and male factors	−0.37	<0.0001	−0.09	<0.0001	2.09	<0.0001
Male factor	−0.35	0.0003	−0.10	<0.0001	2.35	<0.0001
Unknown	−0.33	0.0001	−0.12	<0.0001	2.11	<0.0001
Other	−0.30	0.0637	−0.11	<0.0001	2.44	<0.0001

Parameter estimates and p-values for year of thaw procedures are from linear regression models adjusted for year, number of embryos transferred and SART age group (overall infertility diagnoses and for each diagnosis)

FThC, failed thaw cycles; LBR, live birth rate; SART, Society for Assisted Reproductive Technology

1. Wirka KA et al. ASRM 2021 [P329].

Objective

To assess whether the presence of a specific infertility diagnosis, in addition to PGT, impacts the proportion of FThC and LBRs

FThC, failed thaw cycles; LBR, live birth rate; PGT, preimplantation genetic testing

Methods

Society for Assisted Reproductive Technology (SART) database

- The SART database captures real-world data related to ART clinical practice (including patient care) in the USA[1]
- There were 359 clinics reporting to SART in 2020
- Public access to data: https://www.sart.org/

✓ All clinics are required to advertise truthfully

✓ All clinics are required to report outcomes accurately

✓ Involves nationally accredited laboratories

ART, assisted reproductive technology

1. Society for Assisted Reproductive Technology (SART). https://www.sart.org/ [Accessed January 27, 2022]

Methods

- SART data from thaw cycles from 2014 to 2020 were analysed by diagnoses
  - A total of 268,284 thaw cycles were analysed, including first transfer ≥12 months after retrieval, second or later FETs, given the database output limitation (fresh and frozen embryo transfers taking place <12 months combined)
- Five diagnoses were chosen based on the high prevalence of thaw cycles and/or historical difficulty to treat:
  - Diminished ovarian reserve, endometriosis, ovulatory dysfunction, male factor and unknown factor (n=161,507 thaw cycles)
- Outcomes included:
  - Differences between PGT status over time
  - FThC and LBR stratified by diagnoses and by PGT status
- Fisher's exact tests were used to identify differences in PGT use over time; Chi-square tests were used to examine the impact of PGT on the proportion of FThC and LBRs by diagnosis
- Linear regression was used to determine test of trend over time for LBRs

FET, frozen embryo transfer; FThC, failed thaw cycles; LBR, live birth rate; PGT, preimplantation genetic testing; SART, Society for Assisted Reproductive Technology

Results

Rate of PGT use by diagnosis from 2014 to 2020

	PGT use, n/N (%)							
	2014	2015	2016	2017	2018	2019	2020	p-value
DOR	229/2201 (10.4)	497/2586 (19.2)	714/2980 (24.0)	999/2995 (33.4)	1222/3466 (35.3)	1505/4627 (32.5)	1553/3741 (41.5)	<0.0001
E	38/1137 (3.3)	118/1287 (9.2)	197/1544 (12.8)	314/1666 (18.8)	357/1767 (20.2)	499/1929 (25.9)	562/1857 (30.3)	<0.0001
OD	224/3418 (6.6)	439/4008 (11.0)	465/2557 (18.2)	125/814 (15.4)	106/467 (22.7)	55/325 (16.9)	32/227 (14.1)	<0.0001
MF	314/6709 (4.7)	703/7473 (9.4)	1218/9033 (13.5)	2019/10,273 (19.7)	2537/10,907 (23.3)	3215/11,383 (28.2)	3752/11,476 (32.7)	<0.0001
UF	340/4875 (7.0)	744/5896 (12.6)	1177/6554 (18.0)	1662/6834 (24.3)	2415/7967 (30.3)	3045/8393 (36.3)	3168/8135 (38.9)	<0.0001

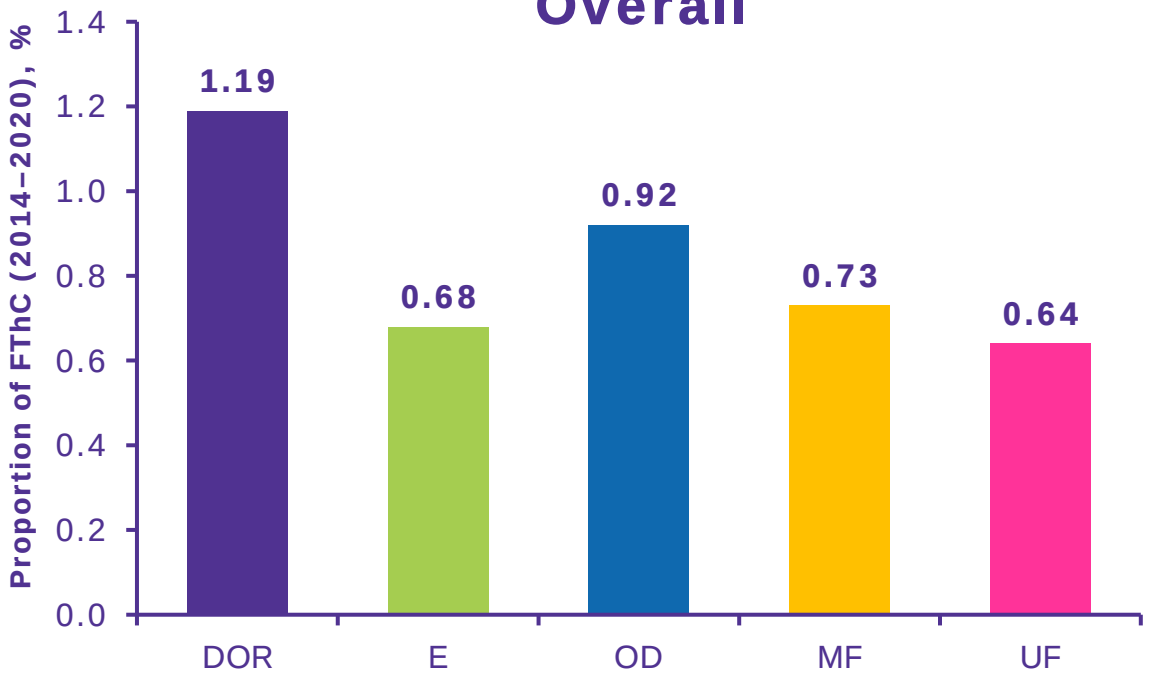
PGT use increased for all diagnoses from 2014 to 2020 (p<0.0001)
The greatest increase in PGT use was observed in patients with DOR, MF and UF

p-values were obtained using Fisher's exact test of significance for the differences observed over time from 2014 to 2020
DOR, diminished ovarian reserve; E, endometriosis; MF, male factor; OD, ovarian dysfunction; PGT, preimplantation genetic testing; UF, unknown factor

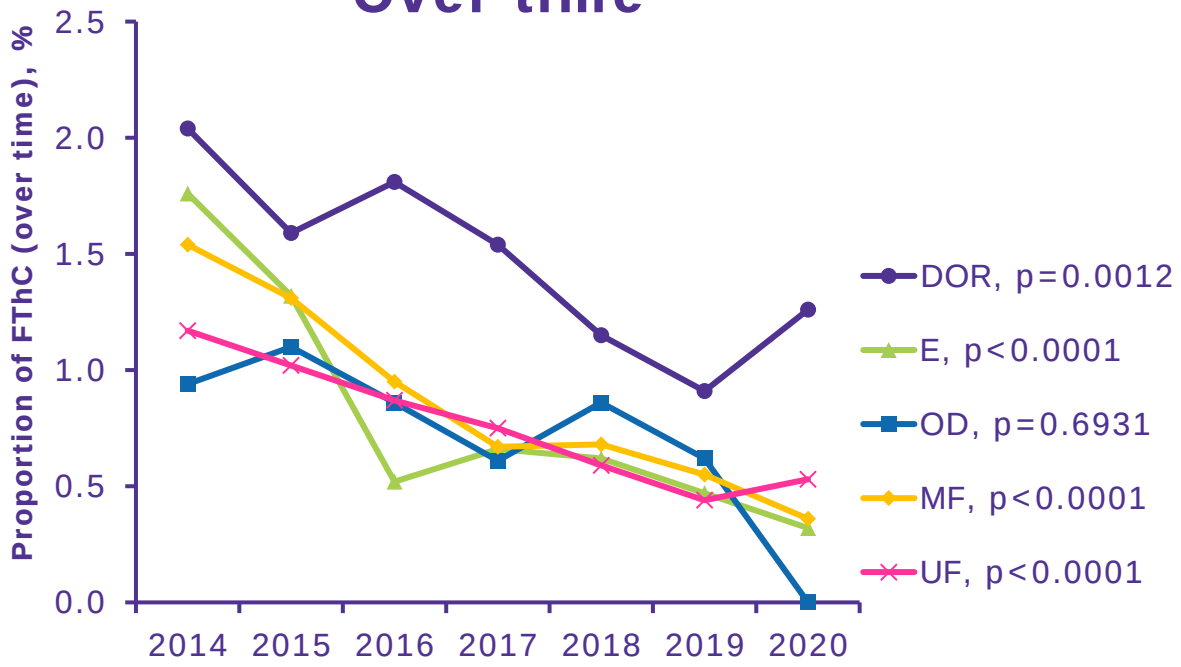
Results

Proportion of FThC by diagnosis

Overall



Over time



The proportion of FThC was highest for patients with DOR

The proportion of FThC differed over time except for patients with OD

p-values were obtained using Fisher's exact test of significance for the differences observed over time from 2014 to 2020
DOR, diminished ovarian reserve; E, endometriosis; FThC, failed thaw cycles; MF, male factor; OD, ovarian dysfunction; UF, unknown factor

Results

Proportion of FThC over time and by diagnosis

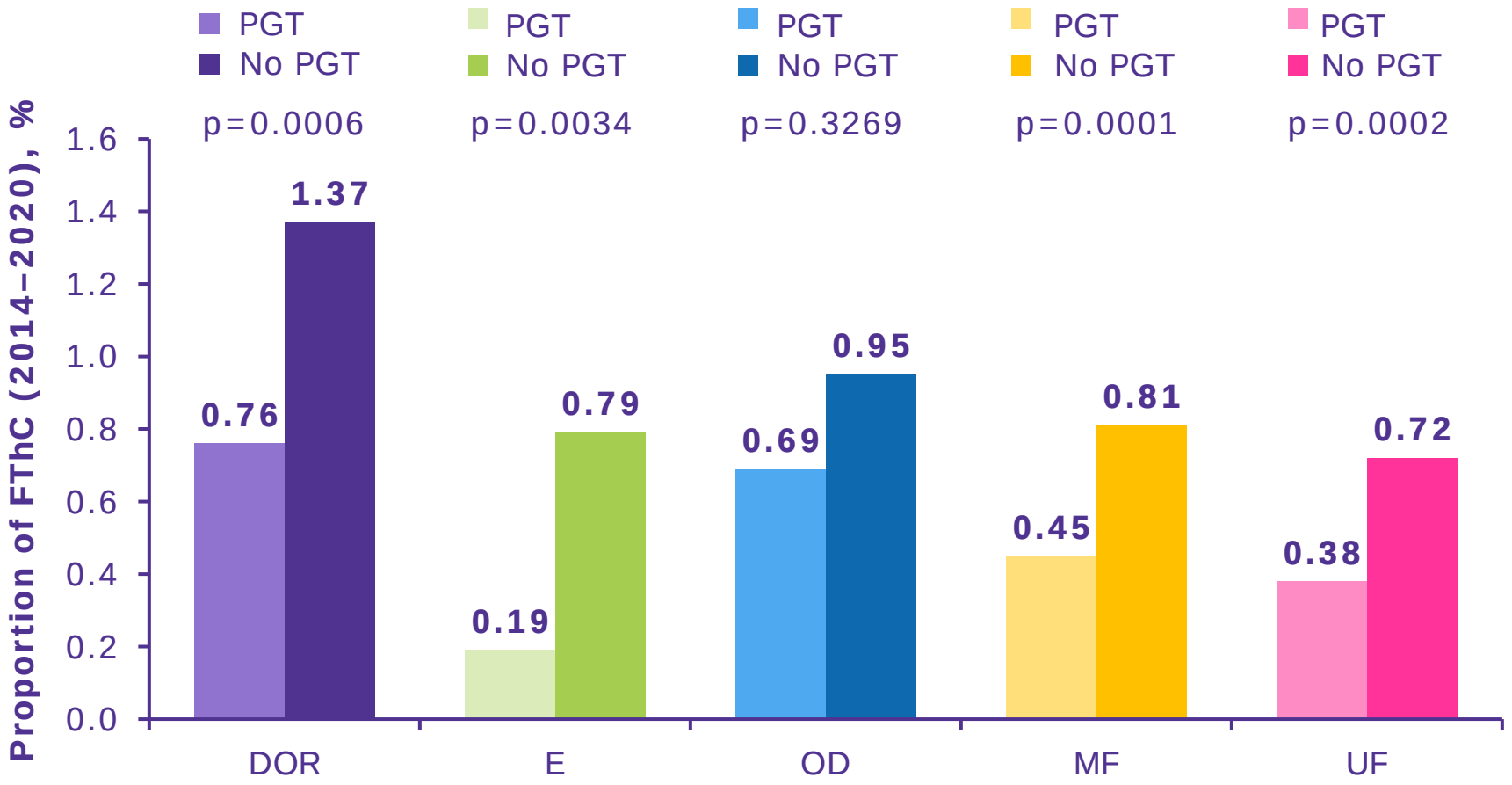
	Proportion of failed thaw cycles, n/N (%)							
	2014	2015	2016	2017	2018	2019	2020	p-value
DOR	45/2201 (2.04)	41/2586 (1.59)	54/2980 (1.81)	46/2995 (1.54)	40/3466 (1.15)	42/4627 (0.91)	47/3741 (1.26)	0.0012
E	20/1137 (1.76)	17/1287 (1.32)	8/1544 (0.52)	11/1666 (0.66)	11/1767 (0.62)	9/1929 (0.47)	6/1857 (0.32)	<0.0001
OD	32/3418 (0.94)	44/4008 (1.1)	22/2557 (0.86)	5/814 (0.61)	4/467 (0.86)	2/325 (0.62)	0/227 (0)	0.6931
MF	103/6709 (1.54)	98/7473 (1.31)	86/9033 (0.95)	69/10,273 (0.67)	74/10,907 (0.68)	63/11,383 (0.55)	41/11,476 (0.36)	<0.0001
UF	57/4875 (1.17)	60/5896 (1.02)	57/6554 (0.87)	51/6834 (0.75)	47/7967 (0.59)	37/8393 (0.44)	43/8135 (0.53)	<0.0001

The proportion of FThC decreased for all diagnoses from 2014 to 2020 except OD; patients with DOR had the highest proportion of FThC

Proportion of FThC: **green** = <0.75%, **yellow** = 0.75–1.5%, **orange** = 1.5–2%, **red** = >2%
p-values were obtained using Fisher's exact test of significance for the differences observed over time from 2014 to 2020
DOR, diminished ovarian reserve; E, endometriosis; FThC, failed thaw cycles; MF, male factor; OD, ovarian dysfunction; UF, unknown factor

Results

Proportion of FThC by diagnosis and by PGT status



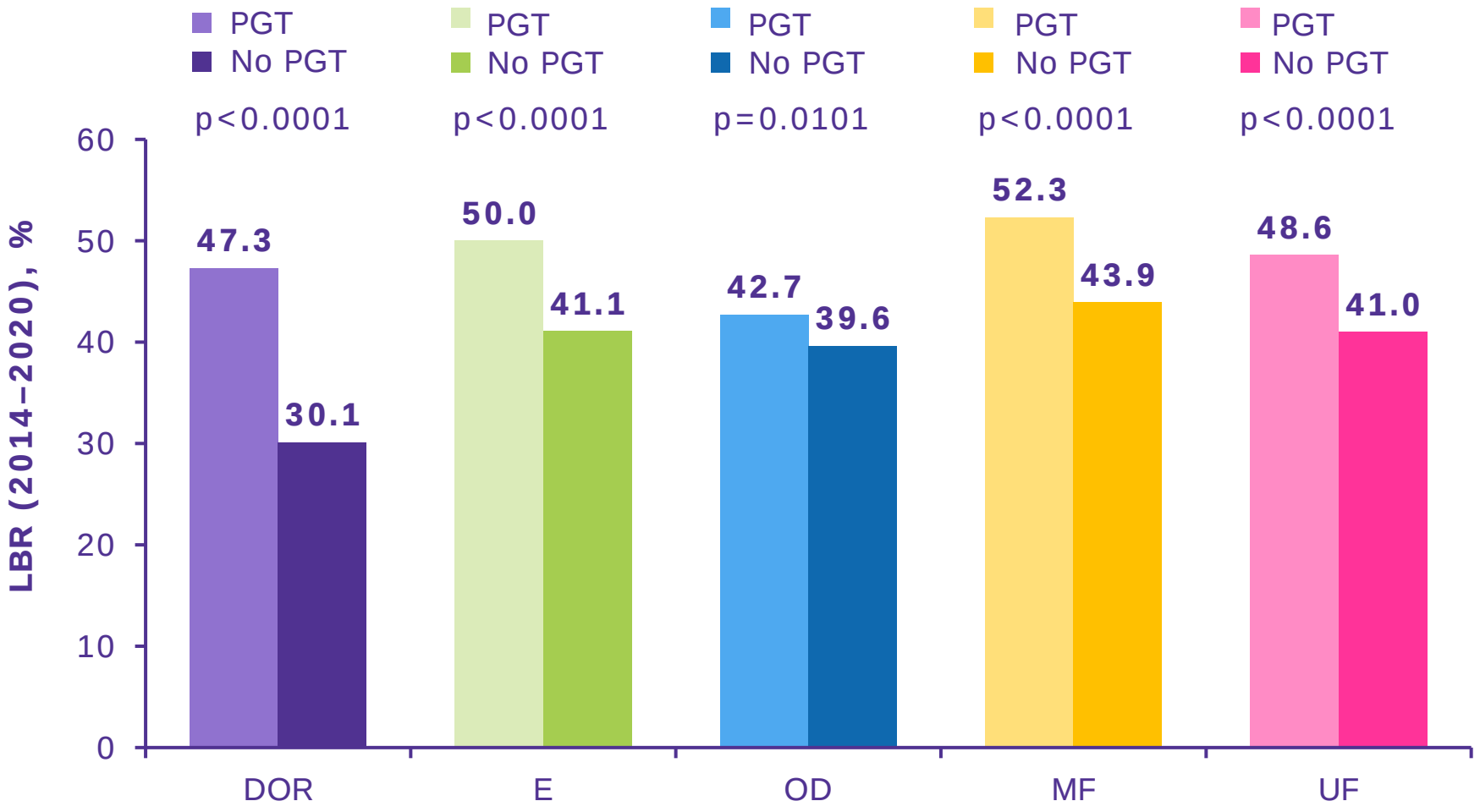
Compared with patients without PGT, those with PGT had a lower proportion of FThC for all diagnoses except OD

Patients with DOR had the highest proportion of FThC (independent of PGT)

p-values were obtained using two-sided Chi-square tests
DOR, diminished ovarian reserve; E, endometriosis; FThC, failed thaw cycles; MF, male factor; OD, ovarian dysfunction; PGT, preimplantation genetic testing; UF, unknown factor

Results

LBRs by diagnosis and PGT status



LBRs were higher for patients with versus without PGT

LBRs for all diagnoses improved over time; the smallest improvement was observed in patients with OD

The changes in LBR were small over time but clinically meaningful

DOR, diminished ovarian reserve; E, endometriosis; LBR, live birth rate; MF, male factor; OD, ovarian dysfunction; PGT, preimplantation genetic testing; UF, unknown factor

Limitations

- Lower numbers of FThC with PGT may limit data interpretability
- Breakdown of data by SART age group was not possible
- The presence of specific diagnoses in this dataset did not exclude other diagnoses
- PGT included all types of PGT
- Analysis assumed the report of FThC as one cycle for one embryo
- Freezing technique was not specified
- Practices in 2014 may not be reflective of practices in 2020
- Due to the COVID-19 pandemic, IVF clinics were closed for a period of time in 2020
- Clinics should review internal data to develop KPI values for FThC
  - In the absence of internal data, registry data could be used as a reference, considering patient/cycle factors and confounders

COVID-19, coronavirus disease 2019; FThC, failed thaw cycles; IVD, *in vitro* fertilization; KPI, key performance indicator; PGT, preimplantation genetic testing; SART, Society for Assisted Reproductive Technology

Conclusions

- This is the first study evaluating the impact of specific diagnoses and PGT on the proportion of FThC
- PGT increased significantly from 2014 to 2020 for all diagnoses
  - The highest proportions of PGT use were for patients with DOR
- The proportion of FThC decreased from 2014 to 2020
  - The highest proportions of FThC were observed in patients with DOR
- LBRs were higher with than without PGT for all diagnoses
  - OD showed the smallest improvement in LBR
- FThC as a KPI can guide embryo thawing performance goals and help set clinician and patient expectations regarding the proportion of FThC along with specific diagnoses and PGT status
- Laboratories should determine their own KPIs for embryo freezing and thawing procedures,[1] and KPIs should be adjusted frequently for benchmarking[2]

DOR, diminished ovarian reserve; FThC, failed thaw cycles; KPI, key performance indicators; LBR, live birth rate; OD, ovarian dysfunction; PGT, preimplantation genetic testing

1. ESHRE Special Interest Group of Embryology, Alpha Scientists in Reproductive Medicine. Hum Reprod Open 2017;2017:hox011; 2. Wirka KA et al. Panminerva Med 2022. Online ahead of print. doi: 10.23736/S0031-0808.22.04686-9

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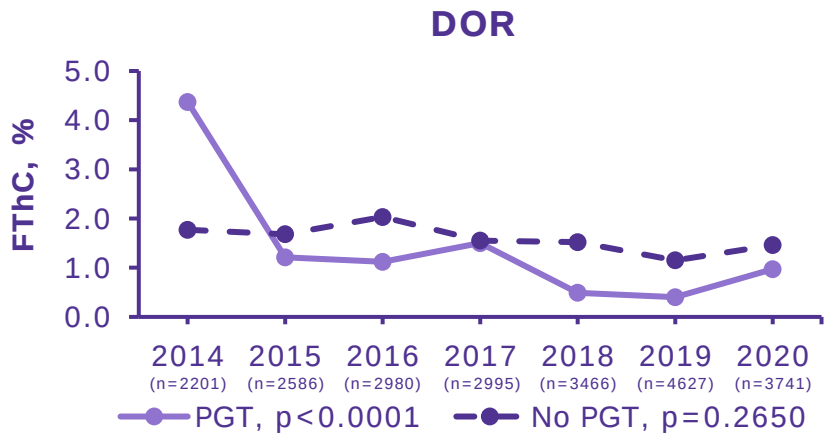
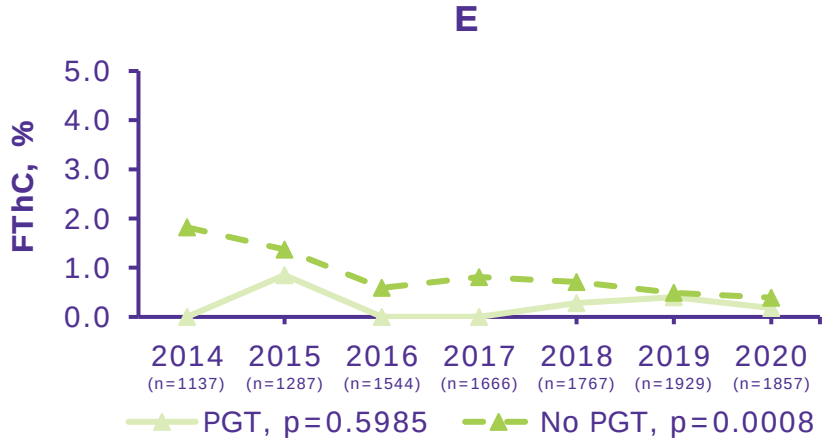
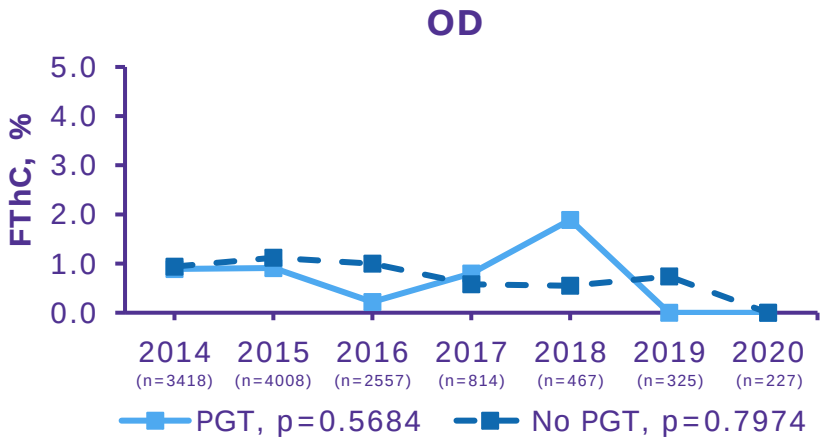
- This study was sponsored by EMD Serono, Inc., Rockland, MA, USA, an affiliate of Merck KGaA

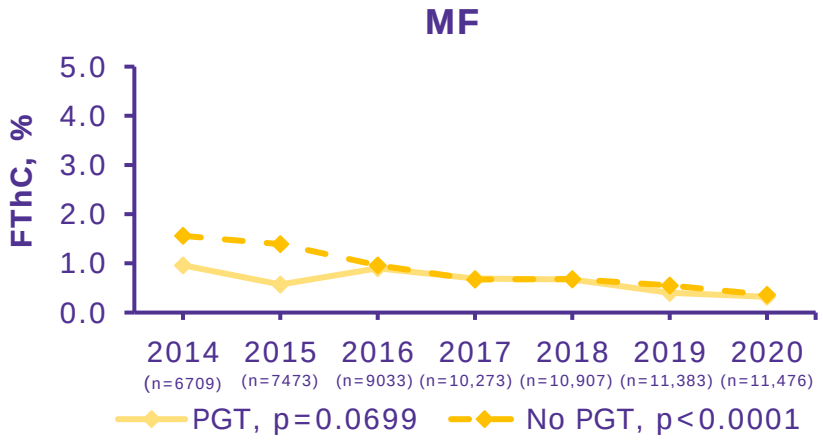
Results

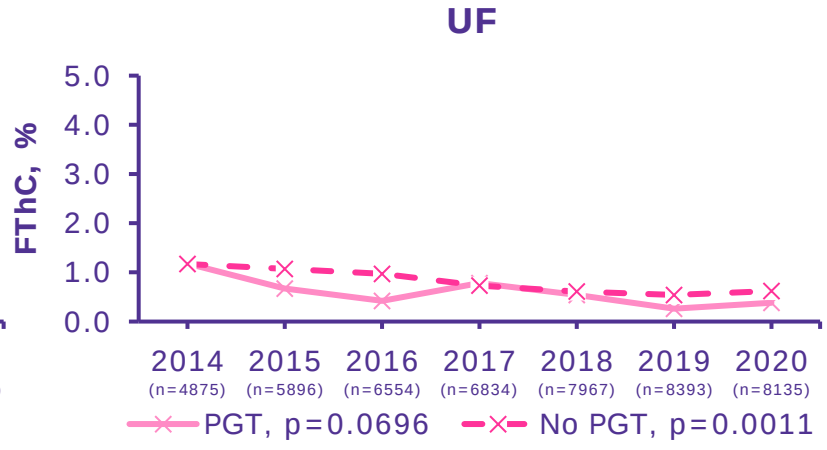
Proportion of FThC over time, stratified by PGT status and diagnosis







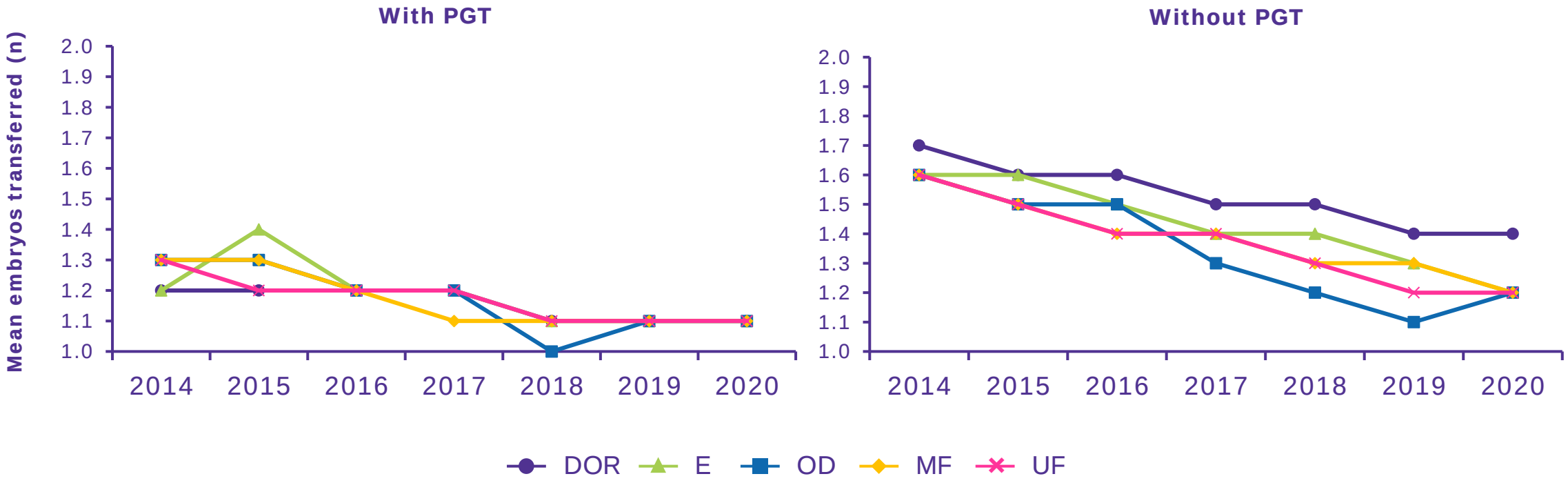




p-values were obtained using Fisher's exact test of significance for the differences observed over time from 2014 to 2020
DOR, diminished ovarian reserve; E, endometriosis; FThC, failed thaw rate; MF, male factor; OD, ovarian dysfunction; PGT, preimplantation genetic testing; UF, unknown factor

Results

Mean number of embryos transferred



DOR, diminished ovarian reserve; E, endometriosis; MF, male factor; OD, ovarian dysfunction; PGT, preimplantation genetic testing; UF, unknown factor