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ARTICLE

Cumulative live birth rate after ovarian stimulation with freeze-all in women with polycystic ovaries: does the polycystic ovary syndrome phenotype have an impact?

BIOGRAPHY

Shari Mackens, MD, PhD, is a gynaecologist at the Centre for Reproductive Medicine at the University Hospital Brussels and an associate professor at the Vrije Universiteit Brussel, with a specific interest in reproductive endocrinology and translational research focusing on the role of the endometrium in assisted reproductive technology.

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KEY MESSAGE

When patients with polycystic ovary syndrome achieve hyper-response after ovarian stimulation, they have excellent success rates following the freeze-all approach, irrespective of their phenotype. It is still, however, unclear how to stimulate these women to obtain optimal reproductive outcomes without compromising safety.

ABSTRACT

Research question: Do cumulative live birth rates (CLBR) differ between polycystic ovary syndrome (PCOS) phenotypes when a freeze-all strategy is used to prevent OHSS after ovarian stimulation?

Design: A single-centre, retrospective cohort study of 422 women with PCOS or polycystic ovarian morphology (PCOM), in whom a freeze-all strategy was applied after GnRH agonist triggering because of hyper-response in their first or second IVF/ICSI. Primary outcome was CLBR; multivariate logistic regression analysis was used.

Results: Phenotype A (hyperandrogenism + ovulation disorder + PCOM [HOP]) (n = 91/422 [21.6%]); phenotype C (hyperandrogenism + PCOM [HP]) (33/422 [7.8%]; phenotype D (ovulation disorder + PCOM [OP]) (n = 161/422 [38.2%]); and PCOM (n = 137/422 [32.5%]. Unadjusted CLBR was similar among the groups (69.2%, 69.7%, 79.5% and 67.9%, respectively; P = 0.11). According to multivariate logistic regression analysis, the phenotype did not affect CLBR (OR 0.72, CI 0.24 to 2.14 [phenotype C]; OR 1.55, CI 0.71 to 3.36 [phenotype D]; OR 0.84, CI 0.39 to 1.83 [PCOM]; P = 0.2, with phenotype A as reference).

Conclusions: In women with PCOS, hyper-response after ovarian stimulation confers CLBR of around 70%, irrespective of phenotype, when a freeze-all strategy is used. This contrasts with unfavourable clinical outcomes in women with hyperandrogenism and women with PCOS who underwent mild ovarian stimulation targeting normal ovarian response and fresh embryo transfer. The results should be interpreted with caution because the study is retrospective and cannot be generalized to all cycles as they pertain to those in which hyper-response is observed.

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KEYWORDS
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INTRODUCTION

Ovarian response after ovarian stimulation can be predicted based on markers of functional ovarian reserve, including anti-Mullerian hormone (AMH), follicle number per ovary (Dewailly *et al*., 2011) and can be modulated by daily gonadotrophin dose. In a subset of women who undergo assisted reproductive technology (ART), the dose-response correlation may be less gradual, and targeted ovarian response may be challenging. As a corollary of this, women with polycystic ovaries, who generally have elevated AMH levels, typically have a narrow dose-response curve. When standard doses of gonadotrophins are administered in these women, hyper-response is commonly observed. Ovarian hyper-response to gonadotrophins used to be an undesirable outcome in ART cycles, because of the risk of ovarian hyperstimulation syndrome (OHSS), and ovarian stimulation using low doses of gonadotrophins has been advocated as a safe and efficacious strategy in predicted hyper-responders (*Oudshoorn et al., 2017*). The introduction of gonadotrophin releasing hormone (GnRH) agonist triggering and the freeze-all approach has reduced the overall incidence of OHSS dramatically (*Devroey et al., 2011*; *Blockeel et al., 2016*) and eliminated the occurrence of severe OHSS (*Ioannidou et al., 2020*). Moreover, the observation that a higher oocyte yield after ovarian stimulation resulted in more embryos available for cryopreservation and higher cumulative live birth rates (CLBR) (*Drakopoulos et al., 2016*; *Polyzos et al., 2018*) has resulted in a gradual shift from a cautious approach to ovarian stimulation in predicted hyper-responders to a more liberal dosing of gonadotrophins in this patient population.

We, and others, have previously reported the effect of PCOS phenotypes on the outcome of an ART cycle: women with a hyperandrogenic PCOS phenotype had less favourable reproductive outcomes after ovarian stimulation compared with their normo-androgenic counterparts in two independent observational studies (*Ramezanali et al., 2016*; *De Vos et al., 2018*). Although a negative influence of biochemical hyperandrogenism on oocyte quality, endometrium quality, or both (*Palomba et al., 2010*; Qiao *et al*., 2011; *Schulte et al., 2015*) could be invoked as a potential explanation, both studies were conducted in a setting in which fresh embryo transfer was pursued while avoiding hyper-response. In view of this, the aim of the present study was to investigate the effect of the PCOS phenotype on CLBR when hyper-response was observed after ovarian stimulation, and a strategy of GnRH agonist trigger and freeze-all was used.

MATERIALS AND METHODS

Ethical approval

The study was approved by the local Ethics Committee on 29 April 2020 (BUN 1432020000058) and was carried out in accordance with the endorsed guidelines.

Study design and participants

This is a single-centre, retrospective cohort study encompassing data from unique, consecutive patients with polycystic ovaries and undergoing a first or second IVF and intracytoplasmic sperm injection (ICSI) cycle in which a freeze-all strategy was selected because of ovarian hyper-response (defined as the observation of 18 or more follicles measuring 11 mm or wider at the moment of ovulation trigger) (*Papanikolaou et al., 2006*; *Griesinger et al., 2016*). Data pertaining to all cycles between January 2015 and December 2019 were ascertained.

Polycystic ovary morphology (PCOM) was defined as an antral follicle count of 20 or more, ovarian volume of 10 ml or more on either ovary, or both (*Teede et al., 2018*), or an AMH of 4.9 ng/ml or more (35 pmol/l) (*Lauritsen et al., 2014*).

Polycystic ovary syndrome was diagnosed according to the Rotterdam criteria (*Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004*). Patients were categorized as phenotype A (hyperandrogenism + ovulatory dysfunction + polycystic ovaries [HOP], B (hyperandrogenism + ovulatory dysfunction [HO], C (hyperandrogenism + polycystic ovaries [HP]) and D (ovulatory dysfunction + polycystic ovaries [OP]) (*Lizneva et al., 2016*). None of the patients in this study had PCOS phenotype B (HO). Clinical hyperandrogenism was defined as the presence of hirsutism (Ferriman–Gallwey score >8), severe acne or alopecia, or both hirsutism and acne or alopecia; biochemical hyperandrogenism was defined as total serum testosterone over 52 ng/dl and calculated free testosterone over 0.64 ng/dl, based on the distribution (mean ± 2 SD) of these parameters in our population. Analysis of serum testosterone was conducted using validated automated immunoassay methods (Elecsys electrochemiluminescence immunoassays on Cobas 6000, Roche Diagnostics, Basel, Switzerland). Serum AMH was analysed using the automated Elecsys® AMH assay (Roche Diagnostics, Basel, Switzerland).

Patients were excluded from the analysis when preimplantation genetic testing had been carried out, when ovarian stimulation was conducted in the context of fertility preservation and in case of oocyte donation. Additional exclusion criteria were the use of surgically retrieved spermatozoa, the presence of congenital adrenal hyperplasia, androgen secreting tumours or Cushing syndrome. Freeze-all cycles with indications other than hyper-response, e.g. elevated serum progesterone on the day of ovulation trigger or suboptimal endometrial thickness, were not included in the present study. Ovulation trigger methods other than GnRH agonist only were also excluded.

Ovarian stimulation

After confirmation of basal serum levels of oestradiol (<80 pg/ml) and progesterone (<1.5 ng/ml), ovarian stimulation started on cycle day 2. The dose of gonadotrophins was selected according to the patient's endocrine profile and body mass index, and at the physician's discretion. Either recombinant FSH or highly purified urinary human menopausal gonadotrophins were administered. All patients had ovarian stimulation in a fixed antagonist protocol in which GnRH antagonist suppression started from day 6 of stimulation onwards. Cycle monitoring was carried out using serial hormonal analyses and pelvic ultrasound scans. Final oocyte maturation was triggered with 0.2 mg triptorelin as soon as at least three follicles with a diameter wider than 17 mm was observed. Oocytes were retrieved about 36 h after GnRH agonist administration.

IVF and intracytoplasmic sperm injection treatment

Oocytes were inseminated using IVF, ICSI or a combination of both. Fertilization was assessed 16–18 h after insemination by

the presence of two pronuclei. Embryos were cultured in individual droplets of 25 µl medium with oil overlay until day 3 or until day 5 (or day 6), depending on the number of embryos available on day 3; in cycles with at least four embryos on day 3 that were classified as transferable or good-quality embryos according to the criteria described by *Van Landuyt et al. (2013)*, embryos were cultured until day 5 or day 6. Embryos were vitrified electively, as previously described (*Van Landuyt et al., 2011*).

Embryo transfer

Vitrified–warmed embryo transfer (frozen embryo transfer [FET]) was carried out in a natural or hormone replacement therapy cycle. In the case of a natural cycle FET, serial hormone analyses and ultrasound scans were carried out to monitor the cycle. Spontaneous ovulation was awaited, or ovulation was triggered with HCG and additional luteal phase support was given according to the preferences of the patient and the physician. In the case of hormone replacement therapy and FET, the endometrium was primed with transdermal or oral oestradiol valerate at a dose of 2 mg three times daily, again based on the preferences of the patient and physician. When an endometrial thickness of 6.5 mm or more was reached, luteal support was started using exogenous progesterone supplementation. The transfer of one or two embryos was scheduled as previously described depending on the stage of the embryo (*Mackens et al., 2017*). Serum HCG levels were measured 12 days after the FET. If the women achieved a positive pregnancy, they were followed according to the centre's routine practice of monitoring.

Outcome parameters

The primary outcome parameter was CLBR, defined as the number of deliveries with at least one live birth resulting from one IVF/ICSI cycle, including all subsequent FET cycles, until a live birth occurred or until all embryos were used (*Zegers-Hochschild et al., 2017*). The secondary outcome parameter was LBR after the first FET.

Statistical analysis

Continuous data were presented as mean ± SD and categorical data were described by number of cases and corresponding percentages. Categorical data and continuous data that did not show normal distribution were analysed by Pearson's chi-squared test, Fisher's exact test or Kruskal–Wallis test as appropriate. The following variables potentially predictive of CLBR were investigated by univariate regression analyses: age, body mass index, parity, duration of stimulation, consumption of gonadotrophins, number of oocytes retrieved, fertilization method, fertilization rate, number of embryos obtained and the embryo stage at vitrification. Variables showing $P < 0.25$ in the univariate analyses were included in the multivariate logistic regression model with CLBR per IVF/ICSI cycle as the dependent variable and the PCOS phenotype as the main independent variable. All variables were simultaneously entered into the logistic regression model. The likelihood of CLBR is presented as an odds ratio with SE and 95% confidence interval. Stata 13.0 (Stata Statistical Software: Release 13; StataCorp., College Station, TX, USA) was used for all statistical analyses.

RESULTS

In total, 422 unique PCOS and PCOM patients were included. Of these, 91 out of 422 (21.6%) patients had PCOS phenotype A (HOP), 33 out of 422 (7.8%) had phenotype C (HP), 161 out of 422 (38.2%) had phenotype D (OP) and 137 out of 422 (32.5%) had PCOM. The relevant baseline characteristics underscoring the different phenotypes are presented in TABLE 1. Of note,

TABLE 1 BASELINE CHARACTERISTICS

	Phenotype groups (*n* = 422)				*P*-value
	PCOS A HOP	PCOS C HP	PCOS D OP	PCOM	
	(*n* = 91)	(*n* = 33)	(*n* = 161)	(*n* = 137)	
Age, years, mean (SD)	30.3 (4.1)	30.7 (4.1)	30.9 (3.4)	31.2 (4.4)	0.4[a,c]
BMI, kg/m^2, mean (SD)	27.3 (5.0)	26.0 (5.5)	24.0 (5.1)	23.4 (4.2)	<0.001[a,c]
AMH, µg/l, mean (SD)	8.8 (4.8)	6.6 (3.4)	6.9 (3.4)	6.2 (2.8)	<0.001[a,c]
AFC, *n*, mean (SD)	41.0 (18.1)	36.0 (15.8)	39.0 (13.1)	32.1 (9.3)	<0.001[a,c]
Testosterone, ng/dl, mean (SD)	61.0 (20.4)	57.2 (13.8)	29.0 (11.2)	30.1 (11.1)	<0.001[a,c]
Calculated free testosterone ng/dl, mean (SD)	0.86 (0.43)	0.79 (0.36)	0.36 (0.78)	0.33 (0.50)	<0.001[a,c]
SHBG, nmol/l, mean (SD)	64.4 (57.5)	62.2 (40.5)	103.4 (66.9)	98.7 (47.3)	<0.001[a,c]
Main cause infertility, *n* (%)					
Male	3 (3.3)	12 (36.4)	16 (9.9)	69 (50.4)	<0.001[b,c]
Endometriosis	0 (0.0)	0 (0.0)	4 (2.5)	10 (7.3)	
Unexplained	0 (0.0)	17 (51.5)	0 (0.0)	44 (32.1)	
PCOS	87 (95.6)	0 (0.0)	138 (85.7)	0 (0.0)	
Tubal	1 (1.1)	4 (12.1)	3 (1.9)	14 (10.2)	

AFC, antral follicle count; AMH, anti-Mullerian hormone; BMI, body mass index; HP, hyperandrogenism + PCOM; HOP, hyperandrogenism + ovulation disorder + PCOM; OP, ovulation disorder + PCOM; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome; SHBG, sex-hormone binding globulin.

[a] Kruskal–Wallis test.

[b] Fisher's exact test.

[c] Statistically significant.

TABLE 2 STIMULATION CYCLE CHARACTERISTICS

	PCOM phenotype groups (*n* = 422)				*P*-value
	PCOS A HOP	PCOS C HP	PCOS D OP	PCOM	
	(*n* = 91)	(*n* = 33)	(*n* = 161)	(*n* = 137)	
Daily gonadotrophin dose, IU, mean (SD)	149.9 (33.8)	161.5 (37.1)	149.2 (35.6)	146.7 (32.7)	0.3[a]
Total gonadotrophin consumption (IU), mean (SD)	1594.5 (568.4)	1498.1 (511.4)	1518.7 (577.1)	1403.9 (402.8)	0.07[a]
Duration of stimulation, days, mean (SD)	11.2 (2.3)	10.2 (1.5)	11.0 (2.5)	10.3 (1.6)	0.02[a]
Follicles ≥11 mm at trigger mean, *n* (SD)	24.0 (8.7)	24.9 (7.9)	23.3 (6.7)	22.8 (6.7)	0.5[a]
Total oocytes retrieved, mean, *n* (SD)[d]	22.4 (10.8)	21.4 (7.1)	20.5 (7.8)	22.2 (9.7)	0.5[a]
Fertilization method, *n* (%)					<0.001[b,c]
ICSI	72 (79.1)	26 (78.8)	101 (62.7)	114 (83.2)	
IVF	9 (9.9)	4 (12.1)	14 (8.7)	8 (5.8)	
ICSI + IVF	10 (11.0)	3 (9.1)	46 (28.6)	15 (10.9)	
Fertilization rate, %	59.2	60.1	61.9	54.1	0.002[a,c]
Total vitrified embryos, mean, *n* (SD)[d]	4.4 (3.7)	5.7 (3.4)	5.7 (3.4)	5.2 (3.7)	0.005[a,c]

ICSI, intracytoplasmic sperm injection; PCOM, polycystic ovarian morphology; PCOS, polycystic ovary syndrome.

[a] Kruskal–Wallis test.

[b] Fisher's exact test

[c] Statistically significant.

[d] For all 422 patients, oocytes were retrieved, and no fertilization was observed in only one patient. Of the 422 included patients, 25 (5.9%) had no good-quality embryos available for vitrification.

body mass index (BMI), anti-Müllerian hormone and antral follicle count were significantly different between phenotype groups ($P < 0.001$) and highest in PCOS phenotype A.

The ovarian stimulation cycle characteristics are presented in TABLE 2. The mean daily and total stimulation dose were comparable in all groups. The mean number of cumulus oocyte complexes (COC) was comparable among groups (22.4 ± 10.8 for phenotype A, 21.4 ± 7.1 for phenotype C, 20.5 ± 7.8 for phenotype D and 22.2 ± 9.7 for PCOM; $P = 0.46$), whereas the mean number of embryos available for vitrification differed significantly (4.4 ± 3.7, 5.7 ± 3.4, 5.7 ± 3.4 and 5.2 ± 3.6, respectively; $P = 0.005$), as well as the fertilization method and fertilization rate (TABLE 2). The fertilization rate was calculated as the number of fertilized oocytes divided by the total number of COC given that different fertilization methods were applied, and the exact number of mature oocytes was not known for all patients.

The unadjusted CLBR was similar among all phenotype groups (69.2%, 69.7%, 79.5% and 67.9%, respectively; $P = 0.11$) and no difference was found in the total number of FET cycles or total number of embryos transferred before a live birth was achieved, or before all embryos had been warmed and used for transfer (TABLE 3). The Supplementary Table presents the crude live birth rates after the first FET; no difference in LBR was observed after the first FET (41.5%, 43.3%, 49.3% and 38.5%, respectively; $P = 0.31$).

The multivariate logistic regression model shown in TABLE 4 adjusting for age, BMI, number of oocytes retrieved, fertilization rate and embryo stage at vitrification, i.e. the confounders identified as significant using univariate regression analyses, confirmed that the PCOS and PCOM phenotype did not affect CLBR (OR 0.72, CI 0.24 to 2.14 [phenotype C); OR 1.55, CI 0.71 to 3.36 [phenotype D]; OR 0.84, CI 0.39 to 1.83 [PCOM]; $P = 0.2$, with phenotype A as reference). The number of retrieved oocytes and the fertilization rate, however, were shown

TABLE 3 CUMULATIVE LIVE BIRTH RATE

	Phenotype groups (*n* = 422)				*P*-value
	PCOS A HOP	PCOS C HP	PCOS D OP	PCOM	
	(*n* = 91)	(*n* = 33)	(*n* = 161)	(*n* = 137)	
Unadjusted CLBR, *n* (%)	63 (69.2)	23 (69.7)	128 (79.5)	93 (67.9)	0.1[c]
FET cycles, Mean, *n* (SD)	1.7 (0.9)	2.0 (1.2)	1.8 (1.3)	2.0 (1.2)	0.2[a]
Transferred embryos, mean, *n* (SD)	1.9 (1.1)	2.2 (1.3)	2.0 (1.7)	2.1 (1.4)	0.09[a]

CLBR, cumulative live birth rate; FET, frozen embryo transfer; HOP, hyperandrogenism + ovulation disorder + PCOM; OP, ovulation disorder + PCOM; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

[a] Kruskal–Wallis.

[c] Pearson's chi square test.

TABLE 4 MULTIVARIATE LOGISTIC REGRESSION MODEL

CLBR	Odds ratio	SE	95% CI	*P*- value
Phenotype				0.2
A (HOP)	Reference	–	–	
C (HP)	0.72	0.40	0.24 to 2.14	
D (OP)	1.55	0.61	0.71 to 3.36	
PCOM	0.84	0.33	0.39 to 1.83	
Age	0.97	0.03	0.90 – 1.03	0.3
BMI	0.98	0.03	0.93 – 1.04	0.6
Number of oocytes retrieved	1.11	0.02	1.06 – 1.15	<0.001[a]
Fertilization rate	1.04	0.01	1.02 – 1.05	<0.001[a]
Embryo stage at vitrification				0.05
Cleavage	Reference	–	–	
Blastocyst	1.37	0.22	1.00 to 1.86	

BMI, body mass index; CLBR, cumulative live birth rate; HOP, hyperandrogenism + ovulation disorder + PCOM; HP, hyperandrogenism + PCOM; OP, ovulation disorder + PCOM; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome.

[a] Statistically significant.

to be predictors of CLBR in this specific dataset (OR 1.11, CI 1.06 to 1.15, $P < 0.001$ and OR 1.04, CI 1.02 to 1.05, $P < 0.001$, respectively).

DISCUSSION

In the present study, the reproductive outcome of one complete ART cycle with freeze-all strategy in patients with different PCOS and PCOM phenotypes in whom ovarian stimulation resulted in hyper-response was investigated. According to our data, patients with polycystic ovaries who hyper-responded after ovarian stimulation had excellent CLBR irrespective of their phenotype. The number of retrieved oocytes and the fertilization rate were the only determinants identified to be significantly correlated with CLBR in this specific dataset. This observation contrasts with reports from previous studies that have explored clinical outcomes after ART in women with PCOS; in those studies, patients with hyperandrogenic PCOS phenotypes (A/HOP and C/HP) had significantly lower CLBR compared with their normo-androgenic counterparts (*Ramezanali et al., 2016*; *De Vos et al., 2018*). Previous studies have suggested that increased androgen levels in women with PCOS may have a deleterious effect on oocyte (*Lebbe and Woodruff, 2013*) and endometrial quality (*Gonzalez et al., 2012*; *Rosas et al., 2016*). On a similar note, serum AMH levels have been found to correlate with the severity of PCOS (*Teede et al., 2019*), and patients with the highest AMH levels seem to have the least favorable reproductive outcomes after ART according to several observational studies (*Xi et al., 2012*; *Tal et al., 2020*). Hence, according to these data, it would seem plausible that, when women with a more severe PCOS phenotype embark on ART treatment, those PCOS patients with the highest levels of circulating AMH and androgens should be warned against undue optimism despite elevated markers of functional ovarian reserve. Nevertheless, when comparing the results of the present study with previous results, caution is warranted. First, when CLBR was reported in previous studies investigating outcome of ART in women with different PCOS phenotypes, cumulative outcomes were calculated after consecutive transfer of all embryos derived from one egg retrieval, including fresh embryo transfer. In contrast, all CLBR data in the present study were derived from cycles with observed hyper-response resulting in a freeze-all strategy and deferred embryo transfer. Of note, a relatively low incidence of freeze-all cycles was observed in our previous study in patients with PCOS undergoing ART (*De Vos et al., 2018*). Second, although most women with PCOS are predicted hyper-responders because of their elevated antral follicle count, serum AMH levels, or both, not all women with PCOS will hyper-respond. Indeed, ovarian response correlates with serum AMH, but is also modulated by daily gonadotrophin dose, BMI, and FSH and LH action (*Bosch et al., 2021*). Patients included in the present retrospective study with its inherent potential of bias owing to unmeasured confounders may represent a subset of patients with PCOS who have favourable prognoses but apparently developed ovarian hyper-response. This could have led to the selection of a subpopulation with a better prognosis compared with the predicted hyper-responders in our previous study (*De Vos et al., 2018*). Although the mean daily gonadotrophin dose in patients included in the present study was higher than in patients from the previous study (*De Vos et al., 2018*), the observation from the present study provides no guidance on how to achieve hyper-response in an individual woman with PCOS and holds no evidence that all patients with PCOS should be administered high doses of gonadotrophins to achieve hyper-response.

In general, ovarian stimulation in women with PCOS can be challenging because of the narrow window of gonadotrophin dosage to obtain a targeted normal ovarian response. One could argue that in the current era of GnRH antagonist protocols with the possibility of GnRH agonist trigger followed by a freeze-all strategy in the case of observed hyper-response, avoidance of poor response has become more prominent than avoidance of OHSS, because severe OHSS can be eliminated when no HCG is administered and a freeze-all strategy is adopted. Moreover, the freeze-all strategy in observed hyper-responders confers highly successful reproductive

outcomes and has been shown to be safe at the same time (*Santos-Ribeiro et al., 2020*). Nevertheless, even though severe OHSS can be avoided, the possible burden of hyper-response for the patient, e.g. abdominal discomfort and the risk of ovarian torsion, should not be neglected (*Vesztergom et al., 2021*). A considerable proportion of women would consider a less efficient fertility treatment if the perceived burden of the treatment would be lower (*Braam et al, 2020*). Therefore, the selection of a specific ovarian stimulation approach in a predicted hyper-responder should be tailored to the patient's preference, after appropriate counselling on the pros and cons of a cautious approach with targeted normal response versus the 'one-and-done' approach targeting hyper-response (*Vaughan et al., 2017*). The most suitable gonadotrophin dose for ovarian stimulation in patients with different PCOS phenotypes, considering the possibility of a non-elective freeze-all strategy in case of observed hyper-response, should be investigated in a prospective study, using a design in which participants are randomized between mild versus standard ovarian stimulation and taking into account the patient's BMI.

Although the present data show excellent and comparable CLBR across all PCOS and PCOM phenotypes after hyper-response when using a freeze-all approach and subsequent FET cycles, hyperandrogenic PCOS phenotypes may have increased metabolic, cardiovascular and obstetric risks, and increased health risks, in their offspring. We would like to seize the opportunity of this discussion to draw attention to the progressive insights on PCOS being a transgenerational problem (the Developmental Origins of Health and Disease hypothesis) (Moen *et al*., 2021). Patients should be counselled and given guidance to reach an optimal pre-conceptional health status before fertility treatment, because health of the offspring starts before conception. Also, in the context of the freeze-all strategy, the optimal endometrial preparation method for FET in PCOS and PCOM patients deserves further research. Pregnancies achieved after artificial cycle FET may carry a higher risk of miscarriage compared with natural cycle FET (*Veleva et al., 2008*; *Tomàs et al., 2012*; *Liu et al., 2020*) potentially caused by inadequate luteal phase support (*Alvarez et al., 2021*; *Labarta et al., 2021*). Furthermore, a higher incidence of hypertensive disorders of pregnancy, including preeclampsia, has been reported owing to the absence of vasoactive molecules otherwise produced by the corpus luteum (*von Versen-Höynck et al., 2019*; *Conrad et al., 2019*). It has been suggested that ovulation induction with letrozole for FET cycles in patients with oligomenorrhoea or amenorrhoea may lead to better reproductive outcomes compared with artificial cycles (*Zhang et al., 2019*; *2021*).

In conclusion, the data suggest that patients with polycystic ovaries who achieve hyper-response after ovarian stimulation may expect excellent CLBR per cycle irrespective of their phenotype. Predicted and observed hyper-response, however, are not the same, and the preferred approach of ovarian stimulation in patients with a specific PCOS phenotype, to achieve optimal reproductive outcomes without compromising safety, is still unclear. At best, the selected approach should depend on what is prioritized as the most valuable outcome parameter: this can be time-to-pregnancy, the highest possible chance of one child, the highest chance of several children with one complete ART cycle, or the lowest risk of side-effects or complications after ovarian stimulation or during the subsequent pregnancy. Most importantly, patient preference should be respected after appropriate counselling of the pros and cons of the various potential ovarian stimulation strategies in patients with polycystic ovaries.

UNCITED REFERENCES

Moen et al., 2020, *Qiao and Feng, 2011*, *Dewailly et al., 2014*

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.rbmo.2021.11.009.

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