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Original Article

Infertility

Protocol change improves live birth and recurrent cycle cancellation rates after a previous IVF cycle cancellation: an analysis of 13 000 autologous cycles reported to SART CORS

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ABSTRACT

STUDY QUESTION: After an IVF cycle cancellation, does changing the stimulation protocol affect the odds of live birth and recurrent cancellation in the subsequent cycle?

SUMMARY ANSWER: After IVF cycle cancellation, compared to those who repeated the same stimulation protocol, those who changed their protocol had higher odds of live birth and lower odds of recurrent cycle cancellation.

WHAT IS KNOWN ALREADY: There is limited data addressing the effect of changing the stimulation protocol after an IVF cycle is cancelled during initial stimulation. The odds of live birth outcomes are not known so far in studies addressing the effect of changing the protocol.

STUDY DESIGN, SIZE, DURATION: Retrospective Cohort Study using the 2014–2017 Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database

PARTICIPANTS/MATERIALS, SETTING, METHODS: The data included 13 135 patients with a first autologous IVF cycle that resulted in a cycle cancellation and was followed by a second autologous cycle within the study period. We excluded fertility preservation cycles, supernumerary cycle attempts after the second IVF cycle attempt, and cycles with more than one stimulation protocol documented per cycle start. Patients who received the same protocol for both cycles (n = 6434) were compared to those who changed their protocol in the second cycle (n = 6701). Multivariable logistic regression analyses were performed to estimate the adjusted odds of live birth and recurrent cancellation.

MAIN RESULTS AND THE ROLE OF CHANCE: Changing the protocol in the second cycle resulted 14% lower odds of recurrent cycle cancellation ($P = 0.01$) and 17% higher odds of live birth after fresh transfers ($P = 0.04$). When stratifying the data by specific combinations of protocol change (agonist flare, agonist suppression, antagonist), there was an increase in live birth when switching from antagonist to agonist suppression (odds ratio (OR) = 1.36, $P = 0.03$) and from agonist suppression to antagonist (OR = 1.73, $P = 0.01$) compared to those who repeated their same stimulation protocol. Specifically in poor responders, outcomes were worse when using the agonist flare protocol and significantly improved with the agonist suppression protocol.

LIMITATIONS, REASONS FOR CAUTION: Comparison of response to stimulation between first and second cycles cannot be made in this study because the index IVF cycle was cancelled during ovarian stimulation, and thus there is no reportable outcome data for that cycle. Additionally, SART only tracks the three stimulation protocols addressed in this study and does not have data on more contemporary protocols that are used in poor responders thus limiting the generalizability of our findings

WIDER IMPLICATIONS OF THE FINDINGS: Using the SART CORS database, which includes >90% of all reported IVF cycles in the USA, provides generalizability to the demographically diverse IVF populations found here. In agreement with prior studies assessing change in IVF protocols, the agonist flare protocol seems to result in worse IVF outcomes, and based on our results, we believe that there is no role for the agonist flare protocol in patients with a prior poor response to stimulation.

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Introduction

Since the first live birth from IVF in 1978, advancements in laboratory and clinical techniques have significantly improved success rates and greatly increased its utilization, with nearly 1 million live births resulting from ART over the last decade in the USA alone (Newton *et al.*, 1990; Centers for Disease Control and Prevention, 2021). Despite these advancements, there are still a substantial number of cycles that are cancelled leading to significant wasted resources, financial expense, as well as added emotional and psychological stress to patients (Newton *et al.*, 1990; de Klerk *et al.*, 2007; Yu Jen Huang and Rosenwaks, 2012).

In 2019, a total of 13 319 autologous IVF cycles with intended retrievals (about 10%) were cancelled before the egg retrieval step (Centers for Disease Control and Prevention, 2021). Reasons for cycle cancellation are varied and include poor follicle production, over-response to ovarian stimulation, concurrent illness, and withdrawal from treatment for personal, financial, or other reasons (Society for Assisted Reproductive Technology (SART) National Summary Report 2019, 2022). Low response to ovarian stimulation is by far the most common reason for cancelled cycles, but little is known about live birth rates (LBR) or patient characteristics that may predict success in subsequent cycles. Prior studies looking at subsequent cycles after IVF cycle cancellation are small and do not examine demographic variables that might contribute to future live births or repeated failures (Kailasam *et al.*, 2004; Nicopoullos and Abdalla, 2011). Specifically considering modifiable variables that may contribute to future cycle success, prior studies looking at the effect of changing the stimulation protocol after IVF cycle cancellations use varying definitions of cycle cancellation and often do not look at the outcome of live birth (Sunkara *et al.*, 2014; Xu *et al.*, 2018; Wald *et al.*, 2021).

In this current study, using data from a self-reported national registry of IVF programs in the USA (SART Clinic Outcome Reporting System (SART CORS) database), we sought to (i) understand which patients are most likely to have a live birth from a second cycle after a cancellation and determine possible predictive variables for cycle success, and (ii) determine which patients are at risk for recurrent cancellation and (iii) assess if changing the stimulation protocol in the next IVF cycle affects the odds of recurrent cancellation or live birth.

Materials and methods

Study design and population

The data used for this study were obtained from the SART CORS database. Data were collected through voluntary submission, verified by SART, and reported to the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). SART maintains the Heath Insurance Portability and Accountability Act (HIPAA)-compliant business associate agreements with reporting clinics. In 2004, following a contract change with the CDC, SART gained access to the SART CORS data system for the purposes of conducting research. Over 90% of all ART cycles in the USA are performed at SART-member clinics.

SART annually selects up to 10 clinics, approximately 2.5% of SART clinics, for an onsite validation visit utilizing metrics and a blinded selection process to identify outlier clinics. Medical records are reviewed during the validation visit to verify the designation, outcome, and reporting of cycles. Clinics with significant systematic reporting errors undergo data correction. Six primary metrics and 26 secondary metrics are used for clinic selection. The metrics include low prospective reporting for both egg retrieval cycles and total cycles, high LBRs in the various age groups, low cancellation rate, high percentage of total fertility preservation cycles, high percentage of embryo banking and oocyte banking cycles, high percentage of fertility preservation cycles where oocytes were thawed or embryos were transferred within a year, high percentage of deleted cycles, high percentage of cycles converted from IUI, and low percentage of cycles in which no embryos were suitable for transfer with and without preimplantation genetic testing (PGT). SART does not validate the accuracy of data entry fields such as gonadotropin dosage, number of oocytes retrieved, number of fertilized oocytes, number of embryos cryopreserved, PGT results, or demographic fields such as age and diagnosis.

In the current study, we analyzed the SART CORS database from 2014 to 2017. The data included 17 459 patients with a first (index) autologous IVF cycle that resulted in a cycle cancellation and was followed by a second autologous cycle within the study period. We defined a cycle cancellation as an IVF cycle started with the intention of either fresh transfer or 'freeze-all' with subsequent frozen embryo transfer (FET) that was terminated during ovarian stimulation, prior to oocyte retrieval. Patients were excluded if they either received an ovulation trigger shot or had an egg retrieval in their index cycle. If a patient underwent multiple IVF cycles and had multiple cycle cancellations, only the first cycle cancellation and the result of the next cycle were included in the analysis. Additional exclusion criteria included cycles conducted for the purpose of fertility preservation. Subjects with missing data were not excluded from the database.

A total of 13 340 index cycles were included and analyzed for demographic and clinical predictors of their linked second IVF cycle outcomes. Primary outcomes were odds of a live birth from the first embryo transfer (ET) and odds of recurrent cycle cancellation. Live birth was defined according to SART CORS criteria as a cycle that resulted in the birth of at least one live-born infant, with the delivery of multiple infants counted as one live birth. The live births included were only those which resulted from the first ET (either fresh or FET) of the second IVF cycle.

Both intended fresh and 'freeze-all' second cycles were included in the analysis as patients may start a cycle with the intent to freeze all embryos, however, may actually end in another cancellation, which was an end-point we wanted to capture. Approximately 5% of our population started their cycle with the intention of having a FET, however, <1% ultimately had a FET. Pre-implantation Genetic Testing for Aneuploidy (PGT-A) was not excluded given the small number of cycles and aim to make our findings as generalizable as possible.

To assess the effect of change in stimulation protocol on second cycles, we additionally excluded all patients with multiple stimulation protocols documented per given cycle, giving a total of 13 135 cycles to be analyzed. Change in protocol was defined as the exclusive use of either agonist flare, agonist suppression, or antagonist in the index cycle and the use of a different protocol in the second cycle. All initiated cycles were used for the outcome of recurrent cancellation and only intended fresh cycles were used for the outcome of live birth. Results were stratified by those with prior cancellation for 'low response' (which we refer to as poor responders), 'high response', and 'withdrawal from treatment'.

Demographic data including maternal age, BMI, race, smoking status, gravidity, parity, and infertility diagnosis were collected from the index IVF cycle. A 'mixed' race variable was created for those who had more than one race documented. Cycle

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characteristics of both the first and second cycles including baseline ovarian reserve testing (FSH and Antimullerian Hormone (AMH)), total IU gonadotropins (FSH) used, stimulation protocol (agonist flare, agonist suppression, or antagonist), day of stimulation in which the index cycle was cancelled (defined as a total number of days of stimulation), and indication for index cycle cancellation were extracted. We used an AMH cutoff of ≤1.0 ng/ml and FSH >10 mIU/ml to define Diminished Ovarian Reserve, which was based on previously published definitions (Cohen et al., 2015).

Statistical methods

Multivariable logistic regression analyses were performed. Demographic variables, infertility diagnoses, and clinical variables were modeled as independent variables and livebirth and recurrent cycle cancellation were modeled as outcomes. For demographic characteristics, including age, BMI, history of smoking, gravidity, parity, and race, all variables were fitted in one model and mutually adjusted. For models of infertility diagnoses and clinical variables such as maximum historical FSH, last known AMH, and change in stimulation protocol, models were adjusted for age, BMI, race, and smoking status. For cancellation indication, we additionally adjusted for AMH. Models for change in the protocol were adjusted for age, race, BMI, smoking status, AMH, and infertility diagnosis. For secondary outcomes such as the number of eggs retrieved and a number of 2 pronuclei (2PN) embryos, we used linear regression models.

Multiple sub-analyses were performed based on the initial findings; which included (i) sub-analysis of poor responders, defined as patients with an index cycle cancellation indication of 'low response'; (ii) sub-analysis of patients in which an ET was performed in the second cycle to determine how our predictor variables specifically affect odds of live birth per ET, rather than per cycle start and (iii) sub-analysis of specific types of protocol change in both the total population and in poor responders. This analysis could not be performed for the high responders due to the low sample size in this subgroup.

Results

Between 2014 and 2017, there were 13 340 patients identified that met the inclusion and exclusion criteria. More than 80% of second cycles were performed within the same reporting year as the index cycle. In the second cycle, there were 10 228 (76.7%) egg retrievals and 3112 (23.3%) recurrent cycle cancellations. Forty-five percent (4582/10228) of patients who had a retrieval did not have an ET. Of the 5646 patients (55%) that did have an ET, 5130 (91%) were fresh transfers. There were 2355 (41.7%) clinical pregnancies leading to 1860 live births (32.9% of all transfers) after the first ET. The unadjusted probabilities of recurrent cycle cancellation, embryo transfer, and live birth in the second cycle stratified by age are shown in Supplementary Table S1.

Demographic characteristics and infertility diagnoses of our population are summarized in Supplementary Table S2. The average patient age was 36.6 ± 4.68 years. The most common infertility diagnosis was Diminished Ovarian Reserve (DOR) (45.6%). Cycle characteristics of both the index and second IVF cycles are summarized in Table 1. In the index IVF cycle, the mean baseline FSH was 10.36 ± 8.35 mIU/ml, and the mean AMH was 1.19 ng/ml. The primary cancellation indication was due to a low response to stimulation (78.1%). Higher mean baseline FSH levels (12.97 vs 9.99 mIU/ml) and lower mean AMH (0.61 vs 1.4 ng/ml) were noted in the cancellation group compared to those that had an egg retrieval.

Sub-analysis of the poor responders did not demonstrate any statistically or clinically significant differences in demographic or cycle characteristics compared to the total population (Supplementary Table S3).

Predictors of live birth

Diagnosis of male factor infertility, index cycle cancellation indications of withdrawal from treatment for any reason, and inadequate endometrial response were associated with higher odds of live birth (all $P \leq 0.01$, Table 2). Lower odds of live birth were associated with age ≥35, current cigarette smoking, Asian and Black races, diagnosis of DOR, FSH >10 mIU/ml (all $P < 0.001$, Table 2), and AMH ≤1.0 ng/ml ($P < 0.03$, Table 2). Sub-analysis of those

Table 1. Characteristics of the first cancelled cycle and subsequent (second) cycle from 13 340 participants.

		Second cycle*	
	Cancelled index cycle (n = 13 340)	**Cancelled (n = 3112)**	**Not cancelled (n = 10 228)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Day of cancellation	8.75 (5.27)	9.37 (5.49)	N/A
Maximum baseline FSH (mIU/ml)	10.37 (8.35)	12.97 (11.86)	9.99 (7.83)
FSH dosage	2989.24 (1698.16)	3436.20 (1961.75)	4067.34 (2027.44)
AMH	1.19 (2.76)	0.61 (2.21)	1.41 (2.88)
Days of stimulation	N/A	N/A	12.30 (2.89)
Stimulation protocol	**N (%)**	**N (%)**	**N (%)**
Antagonist suppression	7189 (53.9)	1488 (47.8)	5612 (54.9)
Agonist flare	1674 (12.5)	652 (21.0)	2141 (20.9)
Agonist suppression	1813 (13.6)	283 (9.1)	1378 (13.5)
Cancellation indication			
Low response	10 417 (78.1)	2561 (82.3)	N/A
High response	726 (5.4)	103 (3.3)	N/A
Inadequate endometrial response	465 (3.5)	125 (4.0)	N/A
Concurrent illness	172 (1.3)	33 (1.1)	N/A
Withdrawal from treatment (psychological)	40 (0.3)	9 (0.3)	N/A
Withdrawal from treatment (financial)	67 (0.5)	13 (0.4)	N/A
Withdrawal from treatment (family emergency)	70 (0.5)	19 (0.6)	N/A
Withdrawal from treatment (other)	1383 (10.4)	249 (8.0)	N/A

* 3112 patients who had a cancelled first cycle also had a cancelled second cycle.
N/A, not applicable; AMH, antimullerian hormone.

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Table 2. Estimated associations of demographic factors and cycle characteristics with odds of live birth and recurrent cycle cancellation.

	Live birth			Recurrent cycle cancellation		
Demographic factors 1	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Age						
<35		Ref			Ref	
35–37	0.55	0.46, 0.66	<0.001	1.68	1.41, 1.99	<0.001
38–40	0.32	0.26, 0.39	<0.001	2.31	1.95, 2.73	<0.001
41–42	0.11	0.07, 0.17	<0.001	2.61	2.14, 3.18	<0.001
43+	0.09	0.05, 0.14	<0.001	3.94	3.19, 4.87	<0.001
BMI						
<25		Ref			Ref	
25–30	1.07	0.89, 1.28	0.45	1.02	0.88, 1.18	0.77
30–35	1.19	0.95, 1.48	0.13	1.34	1.12, 1.6	<0.001
35+	1.16	0.91, 1.48	0.21	1.25	1.02, 1.52	0.03
Ever smoking	0.76	0.63, 0.9	<0.001	0.91	0.79, 1.04	0.17
Gravidity						
0		Ref			Ref	
1+	1.02	0.85, 1.22	0.86	1.12	0.97, 1.29	0.13
Previous full term births						
0		Ref			Ref	
1	1.00	0.79, 1.26	0.98	1.08	0.91, 1.29	0.38
2+	1.05	0.76, 1.45	0.75	0.97	0.76, 1.22	0.78
Race						
White		Ref			Ref	
Indigenous	1.03	0.41, 2.26	0.95	0.84	0.36, 1.75	0.66
Asian	0.58	0.45, 0.74	<0.001	0.94	0.79, 1.12	0.49
Black or African American	0.54	0.39, 0.74	<0.001	1.13	0.93, 1.38	0.21
Latino	1.15	0.88, 1.5	0.29	0.95	0.76, 1.18	0.65
Mixed	0.84	0.49, 1.37	0.50	0.84	0.55, 1.25	0.40
Infertility diagnosis[1]	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Male infertility	1.26	1.08, 1.46	<0.001	0.88	0.77, 1.01	0.07
Endometriosis	1.09	0.86, 1.38	0.46	0.99	0.8, 1.23	0.95
Polycystic ovaries	1.00	0.8, 1.24	0.99	0.73	0.58, 0.91	0.01
Diminished ovarian reserve	0.56	0.47, 0.66	<0.001	1.89	1.66, 2.14	<0.001
Tubal factor	1.19	0.97, 1.46	0.10	0.89	0.74, 1.05	0.18
Uterine	1.21	0.88, 1.64	0.23	0.86	0.67, 1.1	0.24
Recurrent pregnancy loss	0.57	0.17, 1.43	0.28	0.91	0.46, 1.67	0.77
Unexplained	1.22	0.97, 1.54	0.09	0.77	0.61, 0.95	0.02
Cancelled cycle characteristics	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Max historical FSH 1						
≤10		Ref			Ref	
>10	0.59	0.47, 0.74	<0.001	1.90	1.64, 2.19	<0.001
Last known AMH 1						
>1		Ref			Ref	
≤1	0.84	0.72, 0.98	0.03	2.83	2.42, 3.31	<0.001
Change in stimulation (COH) protocol[2]	1.07	0.92, 1.23	0.38	0.88	0.79, 0.99	0.03
Cancellation indication[3]						
Low response	0.72	0.61, 0.86	<0.001	1.36	1.16, 1.59	<0.001
High response	0.90	0.66, 1.21	0.50	1.01	0.76, 1.33	0.94
Concurrent illness	1.52	0.87, 2.55	0.13	0.49	0.24, 0.89	0.03
Inadequate endometrial response	1.87	1.3, 2.63	<0.001	0.99	0.71, 1.36	0.94
Withdrawal from treatment	1.39	1.1, 1.76	0.01	0.63	0.51, 0.78	<0.001

[1] Adjusted for age, BMI, smoking status, and race.
[2] Defined as either having no transfer or having a canceled cycle (RCC + no transfer).
[3] Adjusted for age, BMI, smoking status, race, AMH.
OR, odds ratio; Ref, reference value.

who underwent ET in the second cycle demonstrated that live birth was persistently negatively associated with increasing age ≥35, Black and Asian races, and patients with DOR (all $P < 0.05$).

Predictors of recurrent cycle cancellation

Odds of recurrent cycle cancellation were positively associated with age, obesity (BMI > 30), diagnosis of DOR, FSH >10 mIU/ml, AMH ≤1.0 ng/ml, and index cycle cancellation of low response to stimulation, (all $P < 0.001$, Table 2). Those with PCOS, unexplained infertility, or index cycle cancellation indication of withdrawal from treatment or concurrent illness had lower odds of cancellation (all $P \leq 0.03$, Table 2).

Change in protocol

Patients who received the same protocol for both cycles (n = 6434) were compared to those who changed their protocol in the second cycle (n = 6701). No differences in demographic characteristics, infertility diagnoses, or index cycle cancellation

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indication were noted (Supplementary Tables S4 and S5). However, the two groups differed in some cycle characteristic variables. The same protocol group had a mean AMH of 1.49 ng/ml vs 0.98 ng/ml in the changed protocol group. Second cycles in both groups had higher gonadotropin doses, however, the changed protocol group used an average of FSH 410 International Units (IU) more per cycle ($P < 0.001$). Specifically, in the first, cancelled cycles, an average of 2980 IU FSH (SD 1695) was used. In second cycle, in the changed protocol group, an average of 4105 IU FSH (SD 2028 IU) was administered compared to an average of 3695 (SD 2011 IU) administered in the same protocol group. (Supplementary Table S5).

After adjusting for confounders, changing the protocol in the second cycle resulted in 0.36 fewer oocytes retrieved and 0.29 fewer 2PN embryos ($P = 0.02$, 95% CI [−0.68, −0.05] and [−0.52, −0.06], respectively). While there appears to be minimal clinical relevance in these findings, the pertinent outcomes indicated a 14% lower odds of recurrent cycle cancellation ($P = 0.01$, 95% CI [−0.76, −0.97]) and 17% higher odds of live birth from fresh transfers ($P = 0.04$, 95% CI [1.0, 1.37]). When stratified by reason for prior cancellation, the low responders demonstrated similar results; a change in stimulation protocol was associated with a 20% lower odds of recurrent cancellation ($P < 0.001$, 95% CI [0.7, 0.92]) and an 18% higher odds of live birth ($P = 0.06$, 95% CI [0.99,1.41]). The high responders who changed their protocol showed a 76% lower odds of cancellation ($P = 0003$, 95% CI [0.15, 0.67]) and had twice the odds of live birth compared to those who stayed on the same protocol in the second cycle ($P = 0.02$, 95% CI [1.1, 3.83]). As expected, among those who withdrew from treatment for any reason in their first cycle, changing the protocol did not worsen or improve their outcomes (Table 3).

We then stratified the data by index cycle protocol type (agonist flare, agonist suppression, or antagonist) to further qualify our results (Table 4). Results for all cycles were similar to those for poor responders (Table 4). Specifically in the poor responders (Table 4), compared with those who repeated an agonist flare, a switch to agonist suppression led to 3.16 more eggs retrieved and 75% lower odds of cycle cancellation ($P < 0.001$, 95% CI [1.53, 4.78] and $P = 0.03$, 95% CI [0.05, 0.78], respectively). Changing to an antagonist protocol did not statistically improve or worsen

Table 3. Associations of stimulation protocol change with IVF outcomes in subsequent cycles.

	All cycles			Restricted to low response[1]			Restricted to high response[1]			Restricted to withdrawal[1]		
	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
Total retrieved	−0.36	−0.68, −0.05	0.02	0.04	−0.27, 0.35	0.80	2.81	0.73, 4.88	0.01	−0.07	−1.26, 1.12	0.91
Total 2PN[2]	−0.29	−0.52, −0.06	0.02	−0.28	−0.51, −0.05	0.02	1.49	0.04, 2.95	0.04	−0.39	−1.24, 0.45	0.36
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Cancellation	0.86	0.76, 0.97	0.01	0.80	0.7, 0.92	0.001	0.33	0.15, 0.67	0.003	0.97	0.61, 1.53	0.91
Clinical pregnancy	1.02	0.89, 1.17	0.77	1.17	1, 1.37	0.05	1.74	0.99, 3.08	0.06	0.79	0.5, 1.23	0.30
Live birth[3]	1.17	1, 1.37	0.04	1.18	0.99, 1.41	0.06	2.05	1.1, 3.83	0.02	0.96	0.58, 1.56	0.86

[1] Restrictions based on the reason for cancellation in the index cycle. Outcomes taken from subsequent cycle.
[2] Restricted to those who had successful retrievals.
[3] Fresh cycles only.
All models adjusted for age, BMI, smoking status, race, AMH, and reasons for seeking fertility (male factor, unexplained, diminished ovarian reserve, endometriosis, polycystic ovaries, ovulations disorders).
2PN, 2 pronuclei; OR, odds ratio.

Table 4. Association of protocol change with IVF outcomes in second cycles.

First cycle	Second cycle		Oocytes retrieved			Total 2PN			Cancellation			Live birth*		
		N	β	95% CI	P-value	β	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Total population														
AF	**AF**	476	Reference											
AF	**AS**	80	3.25	1.63, 4.87	<0.001	0.99	−0.25, 2.23	0.117	0.33	0.09, 0.89	0.047	0.77	0.21, 2.29	0.663
AF	**A**	898	−0.21	−0.87, 0.46	0.542	−0.06	−0.62, 0.5	0.828	1.08	0.77, 1.52	0.674	0.95	0.57, 1.61	0.848
AS	**AS**	474	Reference											
AS	**AF**	337	−3.11	−4.62, −1.6	<0.001	−1.93	−2.92, −0.93	<0.001	1.02	0.62, 1.64	0.951	1.54	0.92, 2.6	0.103
AS	**A**	848	−2.14	−3.29, −0.98	<0.001	−1.59	−2.45, −0.74	<0.001	0.68	0.45, 1.02	0.059	1.73	1.13, 2.69	0.013
A	**A**	4199	Reference											
A	**AF**	1605	−2.43	−3.01, −1.86	<0.001	−1.87	−2.29, −1.45	<0.001	1.16	0.94, 1.41	0.159	0.89	0.68, 1.15	0.379
A	**AS**	857	0.08	−0.67, 0.83	0.833	−0.25	−0.79, 0.29	0.360	0.83	0.63, 1.07	0.160	1.36	1.02, 1.79	0.033
Patients with prior cycle cancellation for 'low response'														
AF	**AF**	396	Reference											
AF	**AS**	59	3.16	1.53, 4.78	<0.001	0.66	−0.51, 1.83	0.268	0.25	0.05, 0.78	0.033	0.81	0.18, 2.77	0.764
AF	**A**	830	0.05	−0.62, 0.73	0.875	0.28	−0.29, 0.86	0.338	1.00	0.7, 1.43	1.000	0.88	0.51, 1.55	0.648
AS	**AS**	274	Reference											
AS	**AF**	311	−1.07	−2.53, 0.39	0.152	−0.86	−1.93, 0.20	0.112	0.88	0.51, 1.53	0.657	1.49	0.84, 2.69	0.174
AS	**A**	701	−1.27	−2.4, −0.15	0.027	−1.67	−2.46, −0.89	<0.001	0.59	0.37, 0.96	0.034	1.65	1, 2.76	0.053
A	**A**	3305	Reference											
A	**AF**	1475	−1.68	−2.24, −1.13	<0.001	−1.42	−1.83, −1.00	<0.001	1.05	0.85, 1.29	0.639	0.90	0.68, 1.19	0.474
A	**AS**	740	0.32	−0.42, 1.06	0.400	−0.18	−0.73, 0.36	0.512	0.83	0.62, 1.08	0.175	1.36	1, 1.84	0.048

All models adjusted for age, BMI, smoking status, race, AMH and infertility diagnosis.
* Live birth analysis was restricted to fresh cycles.
AF, agonist flare; AS, agonist suppression; A, antagonist; OR, odds ratio.

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outcomes ($P = 0.85$). Compared with those who repeated an agonist suppression protocol, a switch to either agonist flare or antagonist had significantly fewer eggs retrieved and 2PN embryos. However, those who changed to an antagonist protocol, trended towards less cancellation and had a 65% higher odds of live birth ($P = 0.05$, 95% CI [1.0, 2.76]). Compared with those who repeated an antagonist protocol, a switch to agonist flare had significantly fewer eggs retrieved and 2PN embryos. Cancellation and live birth were not affected. Switching to an agonist suppression protocol was associated with higher odds of live birth by 36% ($P = 0.05$, 95% CI [1.0, 1.84]). In a separate model, we additionally adjusted for gonadotropin (FSH) dosing and did not see differences in our model estimates (Supplementary Table S6). Ultimately, the FSH dosing covariate was left out of the final model due to a significant amount of missing data in this category.

Discussion

This study aimed to identify predictors of live birth and recurrent IVF cycle cancellation in patients with a prior cycle cancellation. Our results demonstrated that increasing age and Black and Asian races are independent predictors of reduced LBRs. Additionally, biomarkers for and diagnosis of DOR were also independent predictors of reduced live birth and recurrent cycle cancellation. We also found that changing the stimulation protocol in the second cycle improves the odds of live birth.

To our knowledge, this was the first epidemiologic study evaluating predictors of IVF outcomes after a cycle cancellation that occurred before the oocyte retrieval. Unsurprisingly, age was the most significant predictor of live birth in IVF patients. According to the CDC, the LBRs per intended retrieval for women ages <35, 35–37, 38–40, and >40 years are approximately 52.7, 38, 24.4, and 7.9%, respectively (Centers for Disease Control and Prevention, 2021). In our study, the age-stratified LBRs (Supplementary Table S1) are half that reported by the CDC. In fact, they are most similar to LBRs reported for poor responders by Bologna criteria, highlighting the impact of a prior cycle cancellation for poor response on the outcomes of future cycles regardless of meeting other poor responder criteria (Xu *et al.*, 2018). Current prediction models for IVF use completed cycles, and do not include cycles that did not make it to an egg retrieval (Sunkara *et al.*, 2014), though future comprehensive IVF prediction models should consider doing so. Women of Black and Asian races were less likely to have a live birth in the cycle following a cycle cancellation. While these findings are congruent with the existing literature, the amount of missing data in the race category within the SART CORS database makes its interpretation limited (Purcell *et al.*, 2007; Fujimoto *et al.*, 2010; Vu *et al.*, 2021).

When cycle cancellation occurs, alternative stimulation protocols are considered. There are a handful of studies that evaluated response to second stimulation after a completed cycle, but fail to look at live birth outcomes (Sunkara *et al.*, 2014; Wald *et al.*, 2021). To our knowledge, this was the largest study addressing the effect of protocol change after cycle cancellation on live birth outcomes in the next fresh cycle attempt. In our study, there were fewer recurrent cancellations and more live births in patients who had a protocol change, which was consistent across both poor and high responders. In clinical practice, a consequence to a poor response in a cycle is to add more gonadotropin units in the next cycle. This study confirmed this behavior as we noted the total gonadotropin dosing was significantly higher in the changed protocol group. Ultimately, gonadotropin dosing was excluded from the final model because nearly 20% of patients had missing values.

When stratified by type of protocol change, the decrease in odds of recurrent cancellation was driven entirely by the change from agonist flare to agonist suppression group. When we controlled for FSH dosing, the results were unchanged. We did see more oocytes retrieved in this group, so it is possible that lower rates of cancellation among patients who switched from agonist flare to agonist suppression were due to improved response to stimulation.

Management of poor responders is one of the biggest challenges facing the field of ART (Xu *et al.*, 2018). Selection of the ideal stimulation protocol in poor responders has been a popular subject of debate. Congruent with our findings, both the agonist suppression and antagonist protocols have proven to show acceptable outcomes in this population (Ovarian Stimulation Guideline Development Group, 2019). More controversial is the use of GnRH-agonist flare protocol in poor responders. A number of older studies have suggested some benefits with an agonist flare protocol. However, more recent studies that use more standardized definitions of poor responders, including one randomized control trial, have similarly demonstrated the superiority of agonist suppression and antagonist cycles compared to the less effective agonist flare protocol based on fewer eggs retrieved (Surrey *et al.*, 1998; Tarlatzis *et al.*, 2003; Sunkara *et al.*, 2014; Xu *et al.*, 2018; Wald *et al.*, 2021). One hypothesis to explain the finding of lower follicular recruitment in agonist flare protocols is that the GnRH agonist can re-establish an incompletely involuted corpus luteum from the prior cycle, resulting in an early follicular progesterone rise, which has been shown to impair follicle recruitment (Sims *et al.*, 1994).

Based on these and other studies, ESHRE guidelines recommend an agonist suppression or antagonist protocol as first line IVF stimulation protocols rather than an GnRH agonist flare in both normal and poor responder patients (Ovarian Stimulation Guideline Development Group, 2019). In our population, we demonstrated that when an index cycle using agonist flare ends in cancellation, changing to a non-flare protocol improves the odds of live birth. Additionally, we demonstrated that when either an agonist suppression or antagonist protocol ends in a cancellation, switching to a flare protocol in the following cycle worsens outcomes. Thus, we argue that there is no utility of an agonist flare stimulation protocol in patients with a prior cycle cancellation. In poor responders, either changing to or continuing agonist suppression protocols show an advantage, especially in terms of numbers of eggs retrieved. Further, in this population, agonist suppression protocols appear potentially to out-perform antagonist protocols.

There are multiple limitations of our study including those inherent to a retrospective study design. A limitation is that our definition of a 'poor responder' was a prior cancellation indication of low response to stimulation, rather than the more specific definitions outlined by the 'Bologna' and 'POSEIDON' (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) criteria (Ferraretti *et al.*, 2011; Younis *et al.*, 2015; Drakopoulos *et al.*, 2020). Further, there is no way for us to know if the improved outcomes with protocol change truly represent an improvement in response to stimulation, or rather, regardless of response, represents cycles that providers regarded as giving the patient their 'best shot' and thus warranting proceeding to retrieval despite a discouraging ovarian response. Unfortunately, a direct comparison of stimulation outcomes between the index and second cycles cannot be made because the index IVF cycle

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was cancelled during ovarian stimulation and therefore no reportable outcome exists for that cycle within SART CORS. For our analysis, we had to assume that in a patient with a prior cancellation for poor response, if their cycle was not cancelled during stimulation, it was because at least one oocyte grew and there was at least a chance for cycle success. Another limitation is that SART only tracks the three stimulation protocols addressed in this study and does not have data on more contemporary protocols that are used in poor responders including but not limited to Estrogen Priming, DuoStim, Mini-stim, use of growth hormone and other adjuvants, thus limiting the generalizability of our findings. Lastly, there may be limitations to modern extrapolation, as the COVID-19 pandemic has led to a higher rate of cancellation for illness in recent years, even as the pandemic is shifting in severity. Future prospective studies that assess more contemporary stimulation protocols specifically in patients with a prior cancellation indication of 'low response', or better yet, in those within each type of poor responder defined by POSEIDON criteria are needed.

Our study was strengthened by the use of recent data obtained from a large national database which includes >90% of all reported IVF cycles in the United States, providing statistical power and generalizability to our results and minimizes selection bias that can occur in analyses from single centers.

Conclusion

Cycle cancellation is a challenging and unfortunate outcome of IVF cycles for both patients and their physicians. Age, race, and markers of DOR are characteristics that predict recurrent poor outcomes in IVF cycles. Overall, there seems to be some benefit in changing the protocol in the second cycle after a cancellation, except with the use of an agonist flare protocol which shows poorer outcomes in patients with a prior cancellation. Poor responders may benefit from agonist suppression cycles. However, future prospective studies that assess more contemporary stimulation protocols, specifically in poor responders by accepted definitions, are needed. In addition, future ART prediction models should incorporate prior cancelled cycles into their algorithms, as this history alone has a clear negative impact on the chance of live birth from subsequent IVF cycles.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Authors' roles

J.L.K.: study design, analysis interpretation, manuscript drafting, critical discussion. H.W.: study design, data analysis, manuscript drafting, critical discussion. R.G.: study design, manuscript drafting. T.S.: study design, manuscript drafting. H.L.: study design, analysis interpretation, manuscript drafting, critical discussion. S.E.P.: study design, analysis interpretation, manuscript drafting, critical discussion. M.S.: study design, manuscript drafting, critical discussion. S.J.: study design, analysis interpretation, manuscript drafting, critical discussion.

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Conflict of interest

None to declared.

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