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Authors

Quinn, Molly M
Rosen, Mitchell P
Allen, Isabel Elaine
et al.

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ORIGINAL ARTICLE *Reproductive epidemiology*

Decreased clinical pregnancy and live birth rates after short interval from delivery to subsequent assisted reproductive treatment cycle

Molly M. Quinn[1,*], Mitchell P. Rosen[1], Isabel Elaine Allen[2], Heather G. Huddleston[1], Marcelle I. Cedars[1], and Victor Y. Fujimoto[1]

[1]Department of Obstetrics, Gynecology and Reproductive Sciences, University of California San Francisco School of Medicine, 550 16th Street, 7th Floor, San Francisco, CA 94158-2519, USA [2]Department of Epidemiology and Biostatistics, University of California San Francisco School of Medicine, 550 16th Street, 7th Floor, San Francisco, CA 94158-2519, USA

*Correspondence address. Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Reproductive Endocrinology and Infertility, University of California San Francisco School of Medicine, 550 16th Street, 7th Floor, San Francisco, CA 94158-2519, USA. Tel: +1-415-353-7475; Fax: +1-415-353-7744; E-mail: molly.quinn@ucsf.edu

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STUDY QUESTION: Does the interval from delivery to initiation of a subsequent ART treatment cycle impact clinical pregnancy or live birth rates?

SUMMARY ANSWER: An interval from delivery to treatment start of <6 months or ≥24 months is associated with decreased likelihood of clinical pregnancy and live birth.

WHAT IS KNOWN ALREADY: Short interpregnancy intervals are associated with poor obstetric outcomes in the naturally conceiving population prompting birth spacing recommendations of 18–24 months from international organizations. Deferring a subsequent pregnancy attempt means a woman will age in the interval with an attendant decline in her fertility.

STUDY DESIGN, SIZE, DURATION: Retrospective analysis of the Society for Assisted Reproductive Technology Clinical Outcome Reporting System (SARTCORS) cohort containing 61 686 ART cycles from 2004 to 2013.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The delivery-to-cycle interval (DCI) was calculated for patients from SARTCORS with a history of live birth from ART who returned to the same clinic for a first subsequent treatment cycle. Generalized linear models were fit to determine the risk of clinical pregnancy and live birth by DCI with subsequent adjustment for factors associated with outcomes of interest. Predicted probabilities of clinical pregnancy and live birth were generated from each model.

MAIN RESULTS AND THE ROLE OF CHANCE: A DCI of <6 months was associated with a 5.6% reduction in probability of clinical pregnancy (40.1 ± 1.9 versus 45.7 ± 0.6%, $P = 0.009$) and 6.8% reduction in live birth (31.6 ± 1.7 versus 38.4 ± 0.6%, $P = 0.001$) per cycle start compared to a DCI of 12 to <18 months. A DCI of ≥24 months was associated with a 5.1% reduction in probability of clinical pregnancy (40.6 ± 0.5 versus 45.7 ± 0.6%, $P < 0.001$) and 5.7% reduction in live birth (32.7 ± 0.5 versus 38.4 ± 0.6%, $P < 0.001$) compared to 12 to <18 months.

LIMITATIONS, REASONS FOR CAUTION: The SART database is reliant upon self-report of many variables of interest including live birth. It remains unclear whether poorer outcomes are a result of residual confounding from factors inherent to the population with a very short or long DCI or the interval itself.

WIDER IMPLICATIONS OF THE FINDINGS: Birth spacing recommendations for naturally conceiving populations may not be generally applicable to patients with a history of infertility. Patients planning ART treatment should wait a minimum of 6 months, but not more than 24 months, from a live birth for optimization of clinical pregnancy and live birth rates.

STUDY FUNDING/COMPETING INTEREST(S): National Center for Advancing Translational Sciences, National Institutes of Health, UCSF-CTSI Grant number UL1TR001872. The authors have no competing interests.

Key words: interpregnancy interval / live birth / ART / clinical pregnancy / SART / birth spacing / IVF outcomes / maternal aging

Introduction

In the naturally conceiving population, a short interval between delivery and subsequent conception, or interpregnancy interval (IPI), has been associated with an increased risk of poor maternal and neonatal outcomes, including low birth weight, small size for gestational age, preterm delivery, and increased maternal, infant, neonatal and perinatal mortality (Khoshnood *et al.*, 1998; Zhu *et al.*, 1999; Conde-Agudelo *et al.*, 2006; de Weger *et al.* 2011). These findings have prompted Healthy People 2020 to campaign for a 10% reduction of pregnancies occurring within 18 months of delivery as an objective (Centers for Disease Control and Prevention, 2014) while the World Health Organization (WHO) recommends an IPI of 24 months (WHO, 2005).

Among women undergoing ART, the implications of IPI may differ in important ways from women conceiving naturally. Women who utilize ART are older and have increased baseline risk of adverse pregnancy outcomes compared to the naturally conceiving population (Luke, 2017). Furthermore, patients with a prior live birth from ART may want to initiate treatment sooner given their history of infertility, particularly in the setting of advanced maternal age. Waiting 18–24 months from live birth to attempt conception for an older ART patient may result in a subsequent failure to conceive a genetically-related offspring due to the impact of maternal aging. In a preconception cohort of women with a history of spontaneous pregnancy loss (<20 weeks), women who waited greater than 12 months had reduced fecundability compared with women who had shorter interval from spontaneous pregnancy loss to attempting conception (Schliep *et al.*, 2016).

There are minimal data available for counseling patients planning ART regarding the impact of the time elapsed from delivery to subsequent attempt at conception on the likelihood of achieving pregnancy and live birth. We evaluated whether the interval from delivery to initiation of a subsequent treatment cycle (delivery-to-cycle interval, DCI) is associated with rate of clinical pregnancy or live birth. The objective of this analysis is to provide insight into the impact of a short DCI on likelihood of conception and live birth with ART.

Methods

Study design and population

This is a retrospective analysis of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SARTCORS) cohort which contains comprehensive data from more than 91% of all IVF cycles in the United States (Toner *et al.*, 2016). Data were collected and 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). The data in the SART CORS are validated annually with some clinics having on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. Ten out of 11 data fields selected for validation were found to have discrepancy rates of ≤5% (CDC, ASRM and SART, 2014).

The study population included patients from SARTCORS with a history of live birth from ART who returned to the same clinic for a subsequent autologous IVF or frozen embryo transfer (FET) cycle from 2004 to 2013. Only the first treatment cycle following an index live birth was included for each subject. The research was determined not to involve human subjects and was, therefore, exempted from further review by the University of California San Francisco Institutional Review Board. The study was approved by the SART Research Committee.

Primary predictor

DCI was defined as the interval from live birth to subsequent start of an IVF or FET cycle. This was divided into six month intervals for consistency with prior literature. Female age at time of initial live birth, ethnicity, body mass index (BMI), parity, number of prior cycles and infertility diagnosis were collected as independent variables.

Outcome measures

Primary outcomes of interest were clinical pregnancy per cycle start, defined as the presence of an intrauterine gestational sac on ultrasound, and live birth per cycle start. Secondary outcomes included biochemical pregnancy and pregnancy loss, defined as a clinical pregnancy that did not result in a delivery.

Statistical methods

Analysis was restricted to the initial autologous (non-donor) IVF and FET cycle following a live birth from ART. Demographic and clinical characteristics of women were stratified by DCI. Continuous variables were analyzed with ANOVA and categorical variables via chi-square test. When the one-way *P*-value was <0.05, pairwise comparisons were performed with Bonferroni correction for multiple comparisons.

Generalized linear models were built to investigate the impact of DCI (with reference the most common DCI of 12 to <18 months) on clinical pregnancy, live birth, biochemical pregnancy, and pregnancy loss. An adjusted linear model accounted for patient age at time of initial live birth, mode of embryo transfer (fresh versus frozen), parity, Caucasian ethnicity and BMI. Results were considered significant with *P* values <0.05 and when the 95% confidence intervals did not include 1. Predicted probabilities for each dichotomous outcome were generated from the adjusted linear model with pairwise comparisons performed with Benjamini-Hochberg correction for multiple comparisons. Stratified analyses were performed to address the impact of age category and mode of embryo transfer (fresh versus frozen) on the relationship between DCI and live birth. All models were checked for misspecification and appropriateness of model fit. Analyses were performed using STATA, version 14 (STATA, College Station, TX, USA).

Results

Of 61 686 initial cycles following a live birth, 26 452 clinical intrauterine gestations and 21 788 live births resulted. Slightly more than half

(31 045) of all cycles following a live birth occurred within a DCI of 18 months. Baseline characteristics including female age at the time of initial live birth, ethnicity, body mass index (BMI), parity, number of prior cycles, and infertility diagnosis were stratified by DCI (Table I). Statistical differences without substantial clinical meaning were seen in age, ethnicity, parity and infertility diagnosis between groups. Patients with a DCI of <6 months had a higher BMI than all other groups (BMI 26.4 ± 6.2 for <6 months, 25.1 ± 5.5 for 6 to <12 months, 24.6 ± 5.2 for 12 to <18 months, 24.6 ± 5.2 for 18 to <24 months, and 25.1 ± 5.4 for ≥24 months).

In univariate analyses, a DCI of <6 months was associated with a reduction in clinical pregnancy (RR 0.88; 95% CI 0.83–0.93) and live birth (RR 0.84; 95% CI 0.78–0.90) compared to the reference DCI 12 to <18 months. A long DCI of ≥24 months was also associated with a reduction in clinical pregnancy (RR 0.94; 95% CI 0.92–0.96) and live birth (RR 0.91; 95% CI 0.89, 0.94) when compared to a DCI of 12 to <18 months. There was no consistent relationship between DCI and biochemical pregnancy or pregnancy loss (Table II).

In a multivariate analysis, the impact of DCI on clinical pregnancy and live birth was adjusted for maternal age at the time of initial live birth, BMI, fresh versus frozen embryo transfer, parity and ethnicity. The adjusted risk ratio for clinical pregnancy remained significantly reduced for a DCI of <6 months (RR 0.88; 95% CI 0.80–0.97) and ≥24 months (0.89; 95% CI 0.86–0.92) when compared with 12 to <18 months. Additionally, adjusted risk ratios for live birth were lower for DCI <6 months (RR 0.82; 95% CI 0.74–0.92), 18 to <24 months (RR 0.93; 95% CI 0.89–0.97) and ≥24 months (RR 0.85; 95% CI 0.82–0.89) when compared to the reference interval (Table II).

Predicted probabilities of clinical pregnancy and live birth were derived from the adjusted generalized linear model. DCI was associated with clinical pregnancy and live birth. A DCI of <6 months was associated with a 5.6% reduction in clinical pregnancy (40.1 ± 1.9 versus 45.7 ± 0.6%, $P = 0.009$) and 6.8% reduction in live birth (31.6 ± 1.7 versus 38.4 ± 0.6%, $P = 0.001$) per cycle start compared to a DCI of 12 to <18 months (Fig. 1). A DCI of ≥24 months was associated with a 5.1% reduction in clinical pregnancy (40.6 ± 0.5 versus 45.7 ± 0.6%, $P < 0.001$) and 5.7% reduction in live birth (32.7 ± 0.5 versus 38.4 ± 0.6%, $P < 0.001$) compared to 12 to <18 months.

An analysis of fresh versus frozen embryo transfers demonstrated similar reductions in live birth rates for DCI < 6 months and ≥24 months compared with 12 to <18 months regardless of mode of transfer (Supplementary Table SI). When stratifying by age category,

Table I Demographic and clinical characteristics of women undergoing autologous IVF stratified by delivery-to-cycle interval ($n = 61\,686$).

	Delivery-to-cycle interval (DCI) months					
	<6 $n = 1926$	**6 to <12 $n = 11\,139$**	**12 to <18 $n = 17\,980$**	**18 to <24 $n = 12\,122$**	**≥24 $n = 18\,519$**	***P*-value**
Age (years) at initial live birth	34.9 ± 4.8[a]	34.9 ± 4.4[a]	34.0 ± 4.1[b]	33.5 ± 4.0[c]	32.8 ± 3.9	<0.001
Ethnicity White (*n*, %)	920 (48%)[de]	5740 (52%)	9520 (53%)[f]	6451 (53%)[g]	9529 (51%)	<0.001
BMI (kg/m^2)	26.4 ± 6.2[h]	25.1 ± 5.5[e]	24.6 ± 5.2[c]	24.6 ± 5.2[c]	25.1 ± 5.4	<0.001
Parity	1.2 ± 0.9[ie]	1.1 ± 0.6[c]	1.1 ± 0.6[c]	1.1 ± 0.6[c]	1.2 ± 0.6	<0.001
Prior Fresh + Frozen Cycles	1.9 ± 1.6[j]	1.8 ± 1.5[k]	1.7 ± 1.4	1.7 ± 1.5	1.8 ± 2.3	0.001
Infertility diagnosis *N* (%)						
Male factor	754 (39.2)	4,47 (40.2)	7716 (42.9)	5357 (44.2)	8465 (45.7)	<0.001
Unexplained	211 (11.0)	1459 (13.1)	2,54 (14.2)	1564 (12.9)	2198 (11.9)	
Endometriosis	214 (11.1)	1298 (11.7)	2269 (12.6)	1578 (13.0)	2563 (13.8)	
PCOS	404 (21.0)	1987 (17.8)	3420 (19.0)	2436 (20.1)	3770 (20.4)	
DOR	326 (16.9)	2036 (18.3)	2553 (14.2)	1599 (13.2)	2185 (11.8)	
Tubal	334 (17.30)	1685 (15.1)	2594 (14.4)	1795 (14.8)	3055 (16.5)	
Uterine	78 (4.1)	494 (4.4)	746 (4.2)	522 (4.3)	680 (3.7)	

Data are mean ± SD unless stated otherwise.
ANOVA or Chi-squared, for continuous versus categorical variables.
PCOS, Polycystic ovary syndrome; DOR: diminished ovarian reserve.
For infertility diagnoses, more than one diagnosis possible per subject.
Pairwise comparisons with Bonferroni correction for multiple comparisons.
[a]$P < 0.001$ for comparison with 12 to <18 months, 18 to <24 months, and ≥24 months.
[b]$P < 0.001$ for comparison with 18 to <24 months and ≥24 months.
[c]$P < 0.001$ for comparison with ≥24 months.
[d]$P = 0.020$ for comparison with 6 to <12 months and ≥24 months.
[e]$P < 0.001$ for comparison with 12 to <18 months and 18 to <24 months.
[f]$P = 0.043$ for comparison with ≥24 months.
[g]$P = 0.025$ for comparison with ≥24 months.
[h]$P < 0.001$ for comparison with all others.
[i]$P = 0.005$ for comparison with 6 to <12 months.
[j]$P = 0.034$ for comparison with 12 to <18 months.
[k]$P = 0.024$ for comparison with 12 to <18 months.

Table II Pregnancy outcome by delivery-to-cycle-Interval: univariate and adjusted analyses.

Outcome	Delivery-to-cycle interval (DCI) months				
	<6	6 to <12 s	12 to <18	18 to <24	≥24
Clinical pregnancy					
n (%)	747 (38.8)	4865 (43.7)	7925 (44.1)	5252 (43.3)	7663 (41.4)
RR (95% CI)	**0.88 (0.83,0.93)**	0.99 (0.96,1.02)	Ref	0.98 (0.96,1.01)	**0.94 (0.92,0.96)**
aRR (95%CI)	**0.88 (0.80,0.97)**	1.02 (0.97,1.06)	Ref	**0.95 (0.91,0.99)**	**0.89 (0.86,0.92)**
Live birth					
n (%)	596 (30.9)	3997 (35.9)	6633 (36.9)	4322 (35.7)	6240 (33.7)
RR (95% CI)	**0.84 (0.78,0.90)**	0.97 (0.94,1.00)	Ref	**0.97 (0.94,1.00)**	**0.91 (0.89,0.94)**
aRR (95% CI)	**0.82 (0.74,0.92)**	1.00 (0.96,1.05)	Ref	**0.93 (0.89,0.97)**	**0.85 (0.82,0.89)**
Biochemical pregnancy					
n (%)	173 (9.0)	927 (8.3)	1641 (9.1)	1111 (9.2)	1733 (9.4)
RR (95% CI)	0.98 (0.85,1.14)	**0.91 (0.84,0.98)**	Ref	1.00 (0.93,1.08)	1.03 (0.96,1.09)
aRR (95% CI)	0.94 (0.76,1.16)	0.93 (0.84,1.03)	Ref	0.98 (0.89,1.07)	1.00 (0.92,1.09)
Pregnancy loss[a]					
n (%)	143 (7.4)	825 (7.4)	1234 (6.9)	890 (7.3)	1357 (7.3)
RR (95% CI)	1.08 (0.92,1.28)	1.08 (0.99,1.17)	Ref	1.07 (0.98,1.16)	1.07 (0.99,1.15)
aRR (95% CI)	1.12 (0.91,1.40)	1.06 (0.95,1.18)	Ref	1.09 (0.99,1.21)	1.10 (1.00,1.20)

RR: Risk Ratio (95 CI) derived from generalized linear model (GLM).
aRR: adjusted risk ratio, GLM adjusted for maternal age at initial live birth, BMI, fresh versus frozen embryo transfer, parity, ethnicity.
[a]Pregnancy loss defined as clinical pregnancy that did not result in live birth.
Bold indicates statistically significant RR and aRR at $P < 0.05$.

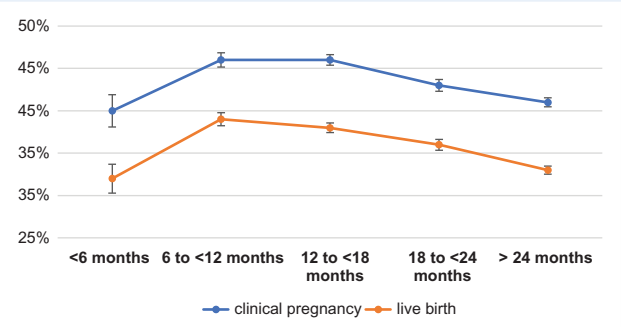

Figure 1 Predicted probabilities of clinical pregnancy and live birth by delivery to cycle interval derived from a fully-adjusted generalized linear model with adjustment for maternal age, BMI, fresh versus frozen embryo transfer, parity and ethnicity.

the reduction in probability of live birth associated with a short DCI was no longer seen in the 35 to <40 and ≥40 years age groups, which each contained fewer individuals than the <35 year group (Table III).

Discussion

While literature demonstrating a relationship between short interpregnancy intervals and adverse birth outcomes in naturally conceiving populations has led to birth spacing recommendations, it is unknown how a delay in subsequent attempts at childbearing may impact likelihood of conception among patients with a history of infertility. As far as we know, this is the first exploration of the impact of the interval from delivery to initiation of a subsequent treatment cycle on pregnancy and live birth rates in an ART population. Using a large, national database, we demonstrate that an interval from delivery to treatment start of <6 months or ≥24 months is associated with decreased likelihood of clinical pregnancy and live birth despite adjusting for potentially confounding maternal factors.

The decline in fecundity with advancing maternal age has been well-documented in populations attempting natural and assisted reproduction (CDC, 2017; Wesselink *et al.*, 2017). Traditional reports of non-contracepting populations have suggested that the decline becomes more rapid in a woman's mid-30s (Menken *et al.*, 1986; Larsen and Yan, 2000), while more recent reports suggest the significant reduction in fecundity and probability of infertility may occur in the late-30s (Steiner and Jukic, 2016). In 2015, 62% of all ART cycles in the United States were performed on women 35 years of age or older (CDC, 2017); a percentage that is likely to be higher in women who have a history of a prior live birth from ART. As such, we controlled for maternal age at the time of initial live birth in our multivariate analysis and performed a separate age-stratified analysis. Nevertheless, a long DCI was associated with a reduced clinical pregnancy and live birth rate when compared to the reference interval of 12–18 months.

In the naturally conceiving population, short (variably defined as <12–18 months) and long (≥24 months) interpregnancy intervals have been associated with poorer pregnancy outcomes (Khoshnood *et al.*, 1998; Zhu *et al.*, 1999; Conde-Agudelo *et al.*, 2006; de Weger *et al.* 2011). The 'physiological regression hypothesis' is the leading hypothesis proposed to explain the relationship between long intervals and adverse perinatal outcomes. This hypothesis posits that after delivery,

Table III Adjusted[a] risk ratio (95% CI) for live birth by delivery-to-cycle interval and age category compared with reference interval of 12 to <18 months.

Age category (years)	Delivery-to-cycle interval (DCI) months				
	<6	6 to <12	12 to <18	18 to <24	≥24
<35 (*n* = 37,931)	**0.81 (0.70,0.93)**	0.99 (0.93,1.06)	Ref	**0.92 (0.87,0.97)**	**0.86 (0.82,0.90)**
35 to <40 (*n* = 19,270)	0.96 (0.79,1.16)	1.06 (0.98,1.16)	Ref	0.94 (0.86,1.03)	**0.80 (0.73,0.87)**
≥40 (*n* = 4485)	0.88 (0.58,1.33)	1.06 (0.85,1.30)	Ref	**0.74 (0.56,0.98)**	**0.65 (0.48,0.88)**

[a]Generalized linear model (GLM) adjusting for BMI, fresh versus frozen embryo transfer, parity, ethnicity and age at the time of initial live birth.

women's reproductive capacities slowly decline over time, becoming similar to primigravid women at very long intervals. Evidence for this hypothesis arises from the observation that infants born to women following a long IPI have similar outcomes to those born to primigravid women (Zhu *et al.*, 1999). It is possible that a long DCI may, therefore, also be associated with reduced probability of conception or live birth as a result of the body's 'unlearning' a previously held reproductive capacity. Alternatively, despite adjusting for age, residual confounding related to more significant infertility may explain the association between a long DCI and reduced likelihood of conception and live birth. An example is the occurrence of a pregnancy complication such as intrauterine adhesions from a postpartum dilation and curettage requiring interval surgery for correction, thereby delaying the start of treatment and simultaneously rendering the patient poorer prognosis for subsequent IVF.

We also demonstrate a reduction in predicted probability of clinical pregnancy and live birth among women undergoing ART with a very short DCI of <6 months. The association between a short interval between pregnancies and adverse perinatal outcomes in the naturally conceiving population is often attributed to maternal nutritional depletion wherein pregnancy and nutrition worsen a mother's nutritional status and inadequate time is allowed for her to recover from the stress of the preceding pregnancy prior to a subsequent conception (Miller, 1991; Winkvist *et al.* 1992). This depletion of nutritional stores, and, specifically, reduction in folate availability is thought to increase the risk of adverse perinatal outcomes such as intrauterine growth restriction (IUGR) and preterm birth (Smits and Essed, 2001; van Eijsden *et al.*, 2008). However, short interpregnancy intervals in the naturally conceiving population are associated with low folic acid levels thought to result from a low prevalence of prenatal vitamin or folic acid supplementation in a population with unintended subsequent pregnancies. This is unlikely to occur in our cohort undergoing treatment with goal to achieve a highly-planned pregnancy.

Nevertheless, while we do not investigate birth weight or gestational age at delivery in this report, one can imagine that the impact of general nutritional depletion may run on a continuum from failure to conceive to IUGR. We would, however, expect to find an increased risk of miscarriage if the nutritional depletion is causative of poor implantation. Our data did not demonstrate this association. However, it remains plausible that the maternal environment may be compromised after a short DCI. Given that advancing age and the associated decline in fertility treatment success due to increasing rates of embryonic aneuploidy is likely to drive a desire for shorter DCI, it may be reasonable to have patients undergo ART within a short interval from delivery with subsequent embryo cryopreservation for use at a longer interval. Conversely, given the apparent effect modification wherein the association between reduction in live birth rates is attenuated in women of advanced age, it may be reasonable to consider proceeding with treatment at a short interval in an older population. Unfortunately, we are unable to address the prudence of this strategy within this dataset. Finally, women who return for ART within 6 months of a delivery may inherently differ from those who wait a longer interval in ways that impact their prognosis. Embryo cryopreservation after a short DCI would not ameliorate outcomes if residual unrecognized confounding explained the relationship between a short and a long DCI and likelihood of conception or live birth.

This study is limited by the use of a national database with incomplete collection of variables of interest. For example, concurrent breastfeeding at the time of a repeat attempt at conception is not collected by SART. Patients with a short DCI may be more likely to be breastfeeding at the time of a subsequent treatment cycle. Prolactin and its receptor have been demonstrated in human endometrium from the late luteal phase of the menstrual cycle through pregnancy (Tseng and Mazella, 1999). It is uncertain precisely the role of prolactin in implantation or whether increased levels due to breastfeeding might impact conception or live birth rates. Nevertheless, we are unable to explore this relationship further within this database. Additionally, several of the variables in the SART registry, including live birth and parity, are self-reported by patients. While validation in the medical record of outcomes and co-variates of interest would be ideal, this is not possible in a database of this magnitude. Finally, while recommendations regarding the timeline for initiation of ART for an individual may ultimately be based upon a more comprehensive set of outcomes (including a history of uterine rupture or preterm delivery), we are unable to create all-inclusive guidelines from this observational data.

Despite these limitations, this analysis offers novel data for use in patient counseling surrounding birth spacing after ART. In summary, we demonstrate, from a national population with a history of live birth from ART, that delaying the start of IVF treatment a minimum of 6 months, but not more than 24 months, from a live birth is associated with optimal clinical pregnancy and live birth outcomes.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/

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Authors' roles

MMQ was involved in the acquisition, analysis and interpretation of data in addition to drafting and revising the manuscript. MPR, HGH, MIC, VF provided contributions to conception and design of the manuscript and its revision. IEA assisted with interpretation of data in addition to revision of manuscript. All authors have given final approval of the version of the manuscript to be submitted for consideration for publication.

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Conflict of interest

None declared.

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