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U.S. national utilization patterns and live birth rates for various ovarian stimulation protocols for in vitro fertilization

Running Title: Ovarian stimulation protocols for IVF

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Word Count: 2026

Abstract

Objective: Alternative ovarian stimulation protocols for in vitro fertilization (IVF) have grown in popularity. Yet, patient populations best suited for these protocols have not been defined. Our objective was, therefore, to determine national IVF utilization patterns and live birth rates of various ovarian stimulation protocols.

Design, Setting, Participants: Aggregate data published by Society for Assisted Reproductive Technologies (SART) for autologous IVF cycles performed in the U.S. during 2014 and 2015 were analyzed in this retrospective cohort study based on ovarian stimulation protocols. IVF cycles were stratified based on ovarian stimulation protocol: 205,705 conventional stimulations, 4,397 minimal stimulations, 2,785 natural cycles and 514 *in vitro* maturation (IVM) cycles**.** Repeat cycles could not be determined in this analysis.

Intervention(s): None

Outcome measures: Utilization patterns and age-specific live birth rates for various ovarian stimulation protocols.

Results: With advancing female age, utilization of conventional stimulation protocols decreased, while minimal stimulation and natural cycle IVF increased. Diminished ovarian reserve diagnoses were in all age groups less prevalent in patients undergoing conventional stimulation than with all other protocols. Live birth rates were highest with conventional stimulation at 42.4%, 33.1%, 22.1%, 11.7% and 3.9% for <35, 35-37, 38-40, 41-42 and >42 female age groups, respectively. The difference in live birth rates between conventional stimulation and other protocols widened with advancing age from 1.6-3.9-fold among women <35 years of age, reaching 4.4-6.6-fold among women > 42 years of age.

Conclusions: In comparison to conventional stimulation IVF - minimal stimulation, natural cycle IVF and IVM protocols offer lower but still acceptable live birth rates among young women. These alternative protocols are frequently used in older women and those with diminished ovarian reserve, despite their lower live birth rates. The reasons for this apparent incongruity warrant further careful exploration.

Key words: Ovarian stimulation protocols, live birth rates, in vitro fertilization (IVF)

List of abbreviations: in vitro fertilization (IVF); Society for Assisted Reproductive Technologies (SART); in vitro maturation (IVM); ovarian hyperstimulation syndrome (OHSS), diminished ovarian reserve (DOR)

Article Summary

Strengths and limitations of this study

- Retrospective cohort study of aggregate U.S. national data on autologous IVF cycles performed during 2014 and 2015
- Data were analyzed to determine utilization patterns and age-specific live birth rates for various ovarian stimulation protocols
- Limitiations stem from lack of standardized definitions and confounding patient characteristics which could not be fully adjusted for

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Competing interests: V.A.K. previously served as a consultant to the CDC. The Center for Human Reproduction (CHR) annually routinely reports IVF outcome data to CDC and SART. N.G., D.H.B., and

V.A.K. are listed as co-owners of several already awarded and still pending U.S. patents, none related to the topic of this manuscript. N.G. is a shareholder in Fertility Nutraceuticals, LLC and owner of the CHR. N.G. and D.H.B. receive patent royalties from Fertility Nutraceuticals, LLC. N.G., and D.H.B have received research support, travel funding and lecture fees from various Pharma and medical device companies, none, in any way related to this manuscript.

Authors' contributions: V.A.K., D.H.B., and N.G. developed the concept of the study; All authors contributed to data accumulation; S.K.D. and V.A.K. contributed to data analysis; All authors contributed to data interpretation. V.A.K. wrote the manuscript. All authors contributed to revisions of the manuscript, and approved of the final submission. V.A.K. takes responsibility for the accuracy of the data analysis.

Reporting Statement: see STROBE checklist

Ethics approval and consent to participate: Because this study investigated only publicly available anonymized data, it received expedited IRB approval.

Consent for publication: Not applicable

Data sharing: Source data are available from the Society for Assisted Reproductive Technology: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2015

or by contacting the corresponding author.

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Introduction

Selection of ovarian stimulation protocols for in vitro fertilization (IVF) greatly affects chances of live birth. Multiple studies have demonstrated that live birth rates increase in parallel with oocyte yields and number of available embryos for transfer. [1–6] Yet, ovarian stimulation protocols that, a priori, produce lower oocyte and embryo yields in IVF cycles, have become increasingly popular, [7] including natural cycle IVF, [8] minimal stimulation IVF [9] and *in vitro* maturation (IVM). [10,11]

Utilization of these protocols has increased with different motivations. For example, minimal stimulation IVF has been promoted as being more physiologic, gentle, patient-friendly and cost-effective, causing controversy. [12–14] Though cumulative live birth rates with minimal stimulation IVF in a recent randomized controlled trial report were lower than with conventional stimulation, [15] the same authors, nevertheless, concluded that minimal stimulation IVF for many patients represents an overall superior approach. [16]

Controversy regarding the efficacy of minimal stimulation protocols is further highlighted by two recent review articles which reached quite different conclusions. The first review concluded that in routine practice conventional stimulation is superior to minimal stimulation IVF based of four fundamental issues: prevalence of severe ovarian hyperstimulation syndrome (OHSS), oocyte/embryo quality, pregnancy/live birth rates, and cost. [17] On the other hand, another review article summarizing a heterogeneous group of clinical studies reached more favorable conclusions of minimal stimulation IVF suggesting that its use should be increased worldwide. [18]

Since utilization patterns and live birth rates for various ovarian stimulation protocols have never been compared on a large scale, we here analyze published U.S. national IVF live birth rates based on type of ovarian stimulation. The purpose of this study was not to confirm or reject claims made in the literature in support of any one of these stimulation protocols. For that purpose, readers are referred to recent publications. [17,19] To facilitate patient counseling, we here instead, simply, wish to report how in the U.S.

utilization patterns and live birth rates differ at varying ages with various ovarian stimulation protocols with reference point cycle start.

As this study will demonstrate, national U.S. outcome data for IVF largely are contradictory to current utilization patterns of alternative ovarian stimulation protocols.

Methods

Patient and Public Involvement – not applicable

As reported in the 2014-2015 publicly available data set of the Society for Assisted Reproductive Technology (SART), [20] we compared female age-stratified IVF live birth for various ovarian stimulation protocols, including conventional and minimal stimulations, natural cycles and IVM cycles. IVF cycles were stratified based on ovarian stimulation protocols: 205,705 conventional stimulations, 4,397 minimal stimulations, 2,785 natural cycle, and 514 IVM cycles**.** Since ovarian reserve is a major predictor of response to ovarian stimulation and ultimately chance of live birth with IVF, we also performed above analyses specifically for patients with diminished ovarian reserve (DOR) diagnosis for each age group and treatment protocol.

SART reports are based on anonymized aggregate data of U.S. fertility centers, which collectively perform over 90% of all U.S. IVF cycles. As previously described, these source data undergo annual validation. [21] Because this study investigated only publicly available anonymized aggregate data, it received expedited IRB approval.

SART allows each reporting fertility center to assign to each IVF cycle the stimulation protocol that is most fitting to the following common definitions: (i) Conventional stimulation, "*administration of injectable gonadotropins for approximately 8 to 10 days to recruit multiple mature eggs*"; (ii) Minimal stimulation, "*uses lower doses of injectable gonadotropins than those used for conventional ovarian*

stimulation. The lower doses of medication may lead to recruitment of fewer eggs than conventional stimulation, the definition …may vary among clinic as there is no universal standard for minimal stimulation"; (iii) Natural cycle, "*requires no fertility medication*"; and (iv) IVM, "*collection of immature eggs that are then incubated in the laboratory prior to IVF*". [20]

Live birth rates are now assessed by SART with reference point cycle start, with first embryo transfers considered, whether fresh or the first frozen-thawed transfer in all-freeze cycles. [22]

Outcome comparisons between stimulation protocols were made using the two-tailed Fisher's exact test, and the Wilson confidence interval for binomial proportions. Conventional Stimulation IVF served as the reference for all statistical comparisons. P-values of < 0.05 were considered statistically significant. All statistical analyses were performed by the center's principal statistician (SKD), using SAS version 9.4 statistical software.

Results

Table 1 summarizes number of IVF cycles for each ovarian stimulation protocol and the mean number of transferred embryos stratified by female age. Mean numbers of transferred embryos with advancing female age increased more rapidly among women undergoing conventional stimulation IVF than among those undergoing all other stimulation protocols. With advancing age, the number and proportion of conventional stimulation cycles, however, decreased, while minimal stimulation and natural IVF cycles increased. As expected, the proportion of patients with DOR in all groups increased with advancing age but was somewhat lower among women undergoing conventional stimulation IVF than among those undergoing all other stimulation protocols. Interestingly, 57.9% of all minimal stimulation and natural IVF cycles were performed by only two U.S. IVF centers, suggesting that these two protocols have received only limited acceptance.

Figure 1 demonstrates the primary live birth rates for the various ovarian stimulation methods, stratified by female age. As the figure demonstrates, starting with youngest patients under age 35 years up to oldest patients above age 42, conventional ovarian stimulations uniformly resulted in the highest live birth rates, followed by minimal stimulations, natural cycles and IVM. While this order was most pronounced in youngest women under age 35, differences between minimal stimulation, natural cycles and IVM, disappeared above age 35 years, though dominance of conventional stimulations over all other stimulation protocols increased with advancing age.

The difference in live birth rates between conventional stimulation and other protocols, thus, widened with advancing female age from 1.6-3.9-fold among women under 35 years to 4.4-6.6-fold among women above age 42. Excluding data from the above mentioned two centers which performed 57.9% of all minimal stimulation and natural IVF cycles showed slightly higher live birth rates (between 0.7% and 6.1%) for these protocols in the remaining centers for all age groups, however, the live birth rates remained significantly lower than those achieved with conventional stimulation.

To assess the impact of DOR as a confounder, we separately assessed only patients with DOR (Figure 2). As expected, DOR patients across all age groups demonstrated lower live birth rates than the entire study population (Figure 1). However, even DOR patients, separately, again demonstrated the widening difference in live birth rates between conventional stimulation and other protocols with advancing female age from 2.8-fold among women under 35 years old to 5.2-fold among women above age 42.

Discussion

As expected, here presented data confirm universally declining live birth rates with advancing female age. However, somewhat unexpected, the data also reveal contradictory findings to current practice patterns. For example, as Table 1 demonstrates, alternative stimulations to conventional stimulations are increasingly used with advancing female age; yet, as Figure 1 demonstrates, especially minimal

stimulation and natural cycle IVF, while still producing lower live birth rates than conventional stimulation, are clearly more effective in younger women under age 35 than at older ages.

Especially minimal ovarian stimulation with a 26.1% live birth rate and natural cycle IVF with a 15.7% live birth rate in young women, should be considered potential alternatives to conventional stimulation, even though conventional IVF at 42.4% clearly produces higher live birth rates. Here observed live birth rates for minimal stimulation and natural cycles in women under age 35 are, indeed, surprisingly robust.

Though the DOR diagnosis was somewhat more common among patients undergoing alternative than conventional stimulations, this difference in DOR prevalence, at most, only partially explains the large difference in live birth rates (Figure 1) since restricting the analysis to only patients with DOR did not substantially alter the findings (Figure 2).

Our study is particularly timely since it shows that national outcome data from routine clinical practice, contradicts observations from small clinical trials, which have recently been used to promote increased worldwide utilization of minimal stimulation IVF. [18] Because live birth rates are significantly lower with minimal stimulation IVF than conventional IVF in national data cautious use in carefully selected patients appears to be appropriate. Current practice of increasing utilization of alternative stimulation protocols in older women and patients with DOR should, therefore, be reconsidered. Indeed, use of alternative stimulation protocols should likely be restricted to young women with normal ovarian reserve.

We previously noted that, after female age, number of oocytes retrieved and embryos available for transfer are the most important predictors of live births in IVF cycles [5,23–25]. Since implantation rates decline and aneuploidy rates increase with advancing female age, the importance of oocyte and embryo numbers increases because more embryos can be safely transferred into the uterus to compensate for lower implantation rates. Younger women with high implantation rates, in contrast, will often, even with only few embryos, still conceive.

Here presented findings, therefore, make clinical sense but are not reflected in how these alternative stimulations are currently clinically utilized in the U.S. Cumulative live birth rates (per embryo cohort in a single cycle) would, likely, favor conventional stimulation even more profoundly, since these protocols are more likely to result in surplus transferable embryos than any of the alternative protocols.

This analysis is limited by lack of a standardized definition of minimal stimulation IVF; SART permits individual clinics to designate the most fitting stimulation type for each cycle. Additionally, because this analysis is based on aggregate data we were, except for age and diagnosis of DOR, not able to assess confounding patient characteristics, including number of prior IVF attempts and repeat cycles. We, therefore, cannot rule out undiscovered patient selection biases for individual stimulation protocols. It is possible that some patients undergoing stimulation with alternative protocols had prior conventional stimulation with very low oocyte and embryo yields. Despite these limitations it is unlikely that adjustments for such biases would substantially change the principal findings given the large sample size and that live birth rates were 1.6 to 6.6-fold higher with conventional stimulation than all other protocols. We also note that most minimal stimulation and natural IVF cycles were performed by only two fertility centers, where selection of these protocols is likely more a reflection of practice patterns than biased patient selection of poor prognosis patients. Indeed, while these two centers reported marginally lower live birth rates than other centers, excluding their data from the analysis did not substantially alter the principal findings.

Here presented data are, in addition, also consistent with other reports: Silber et al, for example, recently reported in a large number of natural cycles that the chance of live birth per oocyte was 26% under age 35 but only 1% above age 42 years. [8] González-Foruria et al also concluded that natural cycle IVF should be restricted to younger women under age 35, [26] while Check et al reported similar outcomes

for conventional and minimal stimulation cycles under age 35 years but clearly superior outcomes for conventional stimulation at older ages. [27]

The literature also supports our observation that conventional ovarian stimulation at all ages, including in women under age 36, produces higher live birth rates than here investigated alternative stimulations. A recent randomized controlled trial over a 6-months period demonstrated clearly lower cumulative live birth rates with minimal stimulation IVF than conventional stimulation. [15] When paired with strict single embryo transfer policy, a recent European analysis of cost effectiveness found that three to six minimal stimulation cycles were comparable in cost to one conventional stimulation cycle. [28] This observation is relevant regarding the recently reported observation that the wide acceptance by Japanese IVF centers of minimal ovarian stimulation (with blastocyst-stage elective single embryo transfer) has resulted in a loss of two-thirds of the national fresh IVF cycle live birth rate over the last decade, while concomitantly tripling the number of IVF cycle starts. [19]

Conclusions

These data suggest that conventional stimulation IVF should be the preferred treatment strategy for most infertile women because it produces the highest live birth rates. Increasingly widely practiced alternative stimulation protocols including minimal stimulation, natural cycle IVF and in vitro maturation (IVM) may, under selective circumstances, have a place in treatment of young women but appear relatively ineffective in women above age 40 and younger women with DOR. Such protocols maybe useful in patients with severe DOR who previously did not respond to conventional stimulation.

Table 1. Number of IVF cycles and mean number of transferred embryos for each female age group.

Female Age Group		<35	35-37	38-40	41-42	>42
Conventional Stimulation IVF	Cycles	83,637 (98.5%)	43,661 (97.7%)	41,661 (96.0%)	21,809 (93.7%)	14,937 (87.1%)
	DOR	5%	12%	21%	34%	44%
	ET	1.6	1.8	2	2.4	2.7
Minimal Stimulation IVF	Cycles	678 (0.8%)	627 (1.4%)	1,050 (2.4%)	922 (4.0%)	1,120 (6.5%)
	DOR	14%	30%	46%	64%	67%
	ET	1.5	1.5	1.5	1.6	1.7
Natural Cycle IVF	Cycles	451 (0.5%)	314 (0.7%)	574 (1.3%)	443 (1.9%)	1,003 (5.8%)
	DOR	15%	17%	29%	41%	49%
	ET	1.2	1.2	1.2	1.2	1.2
In Vitro Maturation (IVM)	Cycles	120 (0.1%)	82 (0.2%)	130 (0.3%)	93 (0.4%)	89 (0.5%)
	DOR	12%	26%	42%	47%	52%
	ET	1.8	1.9	2	1.8	1.7

Cycle number is based on combined final 2014 and preliminary 2015 U.S. national data reported by Society for Assisted Reproductive Technology,

(DOR) proportion of patients with diminished ovarian reserve diagnosis are significantly different between ovarian stimulation protocols in all age groups ($P < 0.0001$).

Mean number of (ET) embryos transferred is based on final 2014 data

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Figure 1. Primary live birth rate per oocyte retrieval cycle for the whole study population stratified by ovarian stimulation protocol.

-Based on combined final 2014 and preliminary 2015 U.S. national data reported by Society for Assisted Reproductive Technology. Conventional Stimulation IVF served as the reference for all statistical comparisons. * P-value of < 0.05

Figure 2. Primary live birth rates per oocyte retrieval cycle for patients with diminished ovarian reserve (DOR) diagnosis stratified by ovarian stimulation protocol.

-Based on combined final 2014 and preliminary 2015 U.S. national data reported by Society for Assisted Reproductive Technology. Conventional Stimulation IVF served as the reference for all statistical comparisons. * P-value of < 0.05

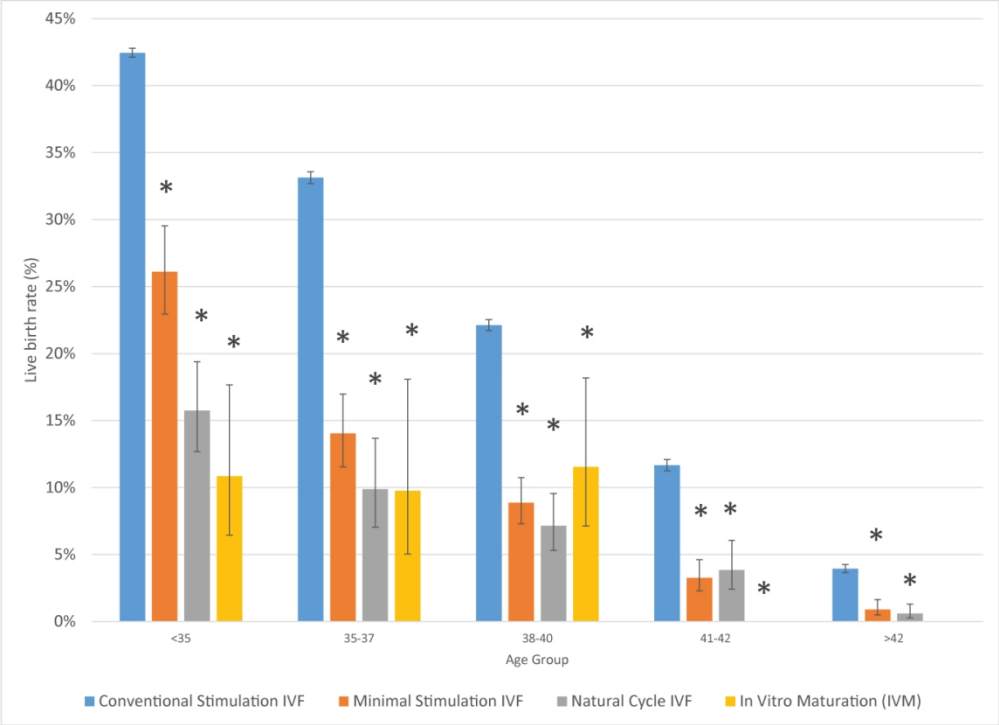

Figure 1: Primary live birth rate per oocyte retrieval cycle for the whole study population stratified by ovarian stimulation protocol.

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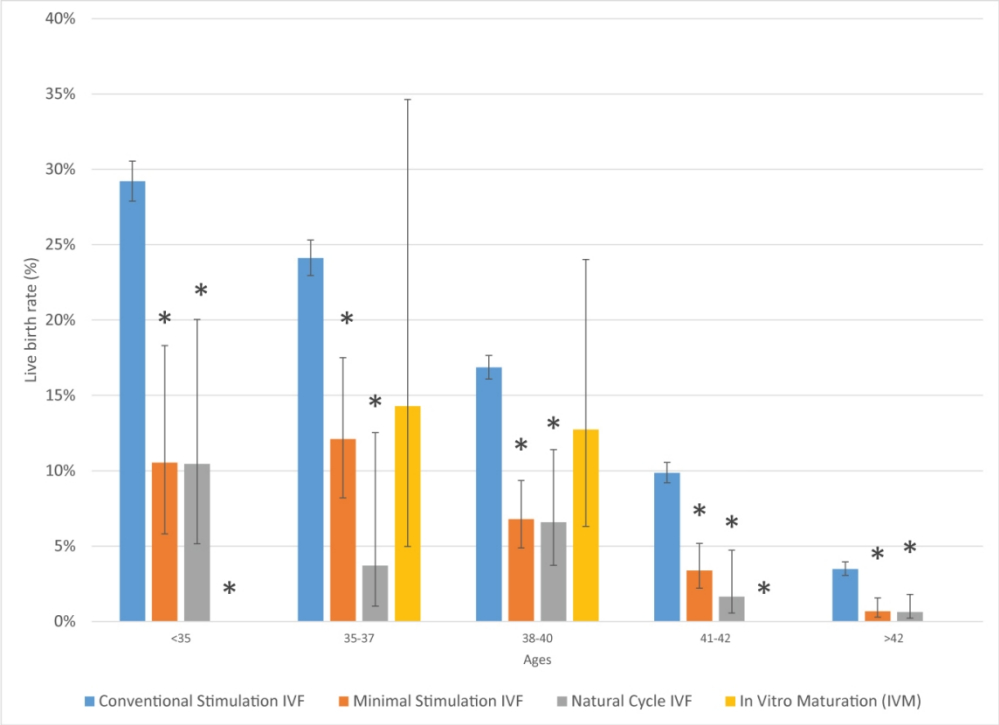

Figure 2: Primary live birth rates per oocyte retrieval cycle for patients with diminished ovarian reserve (DOR) diagnosis stratified by ovarian stimulation protocol.

115x84mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, table, figures
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table, figures
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6,7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table, figures
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Observational retrospective study of U.S. national utilization patterns and live birth rates for various ovarian stimulation protocols for in vitro fertilization

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Observational retrospective study of U.S. national utilization patterns and live birth rates for various ovarian stimulation protocols for in vitro fertilization

Running Title: Ovarian stimulation protocols for IVF

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Abstract

Objective: Alternative ovarian stimulation protocols for in vitro fertilization (IVF) have grown in popularity. Yet, patient populations best suited for these protocols have not been defined. Our objective was, therefore, to determine national IVF utilization patterns and live birth rates of various ovarian stimulation protocols.

Design: Retrospective cohort study

Setting: academic-affiliated private fertility center

Participants: Aggregate data published by Society for Assisted Reproductive Technologies (SART) for autologous IVF cycles performed in the U.S. during 2014 and 2015 were analyzed. IVF cycles were stratified based on ovarian stimulation protocol: 205,705 conventional stimulations, 4,397 minimal stimulations, 2,785 natural cycles and 514 *in vitro* maturation (IVM) cycles**.** Repeat cycles could not be determined in this analysis.

Intervention(s): None

Outcome measures: Utilization patterns and age-specific live birth rates for various ovarian stimulation protocols.

Results: With advancing female age, utilization of conventional stimulation protocols decreased, while minimal stimulation and natural cycle IVF increased. Diminished ovarian reserve diagnoses were in all age groups less prevalent in patients undergoing conventional stimulation than with all other protocols. Live birth rates were highest with conventional stimulation at 42.4%, 33.1%, 22.1%, 11.7% and 3.9% for <35, 35-37, 38-40, 41-42 and >42 female age groups, respectively. The difference in live birth rates between conventional stimulation and other protocols widened with advancing age from 1.6-3.9-fold among women <35 years of age, reaching 4.4-6.6-fold among women > 42 years of age.

Conclusions: In comparison to conventional stimulation IVF - minimal stimulation, natural cycle IVF and IVM protocols offer lower but still acceptable live birth rates among young women. These alternative protocols are frequently used in older women and those with diminished ovarian reserve, despite their lower live birth rates. The reasons for this apparent incongruity warrant further careful exploration.

Key words: Ovarian stimulation protocols, live birth rates, in vitro fertilization (IVF)

List of abbreviations: in vitro fertilization (IVF); Society for Assisted Reproductive Technologies (SART); in vitro maturation (IVM); ovarian hyperstimulation syndrome (OHSS), diminished ovarian reserve (DOR)

Article Summary

Strengths and limitations of this study

- Retrospective cohort study of aggregate U.S. national data on autologous IVF cycles performed during 2014 and 2015
- Data were analyzed to determine utilization patterns and age-specific live birth rates for various ovarian stimulation protocols
- Limitations stem from lack of standardized definitions and confounding patient characteristics which could not be fully adjusted for

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Competing interests: V.A.K. previously served as a consultant to the CDC. The Center for Human Reproduction (CHR) annually routinely reports IVF outcome data to CDC and SART. N.G., D.H.B., and V.A.K. are listed as co-owners of several already awarded and still pending U.S. patents, none related to

the topic of this manuscript. N.G. is a shareholder in Fertility Nutraceuticals, LLC and owner of the CHR. N.G. and D.H.B. receive patent royalties from Fertility Nutraceuticals, LLC. N.G., and D.H.B have received research support, travel funding and lecture fees from various Pharma and medical device companies, none, in any way related to this manuscript.

Authors' contributions: V.A.K., D.H.B., and N.G. developed the concept of the study; All authors contributed to data accumulation; S.K.D. and V.A.K. contributed to data analysis; All authors contributed to data interpretation. V.A.K. wrote the manuscript. All authors contributed to revisions of the manuscript and approved of the final submission. V.A.K. takes responsibility for the accuracy of the data analysis.

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Ethics approval and consent to participate: Because this study investigated only publicly available anonymized data, it received expedited IRB approval.

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Data sharing: Source data are available from the Society for Assisted Reproductive Technology: https://www.sartcorsonline.com/rptCSR_PublicMultYear.aspx?reportingYear=2015

or by contacting the corresponding author.

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Introduction

Selection of ovarian stimulation protocols for in vitro fertilization (IVF) greatly affects chances of live birth. Multiple studies have demonstrated that live birth rates increase in parallel with oocyte yields and number of available embryos for transfer. [1–6] Yet, ovarian stimulation protocols that, a priori, produce lower oocyte and embryo yields in IVF cycles, have become increasingly popular, [7] including natural cycle IVF, [8] minimal stimulation IVF [9] and *in vitro* maturation (IVM). [10,11]

Utilization of these protocols has increased with different motivations. For example, minimal stimulation IVF has been promoted as being more physiologic, gentle, patient-friendly and cost-effective, causing controversy. [12–14] Though cumulative live birth rates with minimal stimulation IVF in a recent randomized controlled trial report were lower than with conventional stimulation, [15] the same authors, nevertheless, concluded that minimal stimulation IVF for many patients represents an overall superior approach. [16]

Controversy regarding the efficacy of minimal stimulation protocols is further highlighted by two recent review articles which reached quite different conclusions. The first review concluded that in routine practice conventional stimulation is superior to minimal stimulation IVF based of four fundamental issues: prevalence of severe ovarian hyperstimulation syndrome (OHSS), oocyte/embryo quality, pregnancy/live birth rates, and cost. [17] On the other hand, another review article summarizing a heterogeneous group of clinical studies reached more favorable conclusions of minimal stimulation IVF suggesting that its use should be increased worldwide. [18]

Since utilization patterns and live birth rates for various ovarian stimulation protocols have never been compared on a large scale, we here analyze published U.S. national IVF live birth rates based on type of ovarian stimulation. The purpose of this study was not to confirm or reject claims made in the literature in support of any one of these stimulation protocols. For that purpose, readers are referred to recent publications. [17, 18,19] To facilitate patient counseling, we here instead, simply, wish to report how in the

U.S. utilization patterns and live birth rates differ at varying ages with various ovarian stimulation protocols with reference point cycle start.

As this study will demonstrate, national U.S. outcome data for IVF largely are contradictory to current utilization patterns of alternative ovarian stimulation protocols.

Methods

As reported in the 2014-2015 publicly available data set of the Society for Assisted Reproductive Technology (SART), [20] we compared female age-stratified IVF live birth for various ovarian stimulation protocols, including conventional and minimal stimulations, natural cycles and IVM cycles. IVF cycles were stratified based on ovarian stimulation protocols: 205,705 conventional stimulations, 4,397 minimal stimulations, 2,785 natural cycle, and 514 IVM cycles**.** Since ovarian reserve is a major predictor of response to ovarian stimulation and ultimately chance of live birth with IVF, we also performed above analyses specifically for patients with diminished ovarian reserve (DOR) diagnosis for each age group and treatment protocol.

SART reports are based on anonymized aggregate data of U.S. fertility centers, which collectively perform over 90% of all U.S. IVF cycles. As previously described, these source data undergo annual validation. [21] Because this study investigated only publicly available anonymized aggregate data, it received expedited IRB approval.

SART allows each reporting fertility center to assign to each IVF cycle the stimulation protocol that is most fitting to the following common definitions: (i) Conventional stimulation, "*administration of injectable gonadotropins for approximately 8 to 10 days to recruit multiple mature eggs*"; (ii) Minimal stimulation, "*uses lower doses of injectable gonadotropins than those used for conventional ovarian stimulation. The lower doses of medication may lead to recruitment of fewer eggs than conventional*

stimulation, the definition …may vary among clinic as there is no universal standard for minimal stimulation"; (iii) Natural cycle, "*requires no fertility medication*"; and (iv) IVM, "*collection of immature eggs that are then incubated in the laboratory prior to IVF*". [20]

Live birth rates are now assessed by SART with reference point cycle start, with first embryo transfers considered, whether fresh or the first frozen-thawed transfer in all-freeze cycles. [22]

Outcome comparisons between stimulation protocols were made using the two-tailed Fisher's exact test, and the Wilson confidence interval for binomial proportions. Conventional Stimulation IVF served as the reference for all statistical comparisons. P-values of < 0.05 were considered statistically significant. All statistical analyses were performed by the center's principal statistician (SKD), using SAS version 9.4 statistical software.

Patient and Public Involvement

Patients were not involved in the design of the study

Results

Table 1 summarizes the characteristics of IVF cycles for each ovarian stimulation protocol, it is stratified by female age group. . Mean numbers of transferred embryos with advancing female age increased more rapidly among women undergoing conventional stimulation IVF than among those undergoing all other stimulation protocols. With advancing age, the number and proportion of conventional stimulation cycles, however, decreased, while minimal stimulation and natural IVF cycles increased. As expected, the proportion of patients with DOR in all groups increased with advancing age but was somewhat lower among women undergoing conventional stimulation IVF than among those undergoing all other stimulation protocols. Interestingly, 57.9% of all minimal stimulation and natural IVF cycles

were performed by only two U.S. IVF centers, suggesting that these two protocols have received only limited acceptance.

Table 2 summarizes the pregnancy outcomes for each ovarian stimulation protocol used during the IVF cycle, the data is stratified by female age group. In addition, Figure 1 demonstrates in more detail the primary live birth rates for the various ovarian stimulation protocols, stratified by female age. As the figure demonstrates, starting with youngest patients under age 35 years up to oldest patients above age 42, conventional ovarian stimulations uniformly resulted in the highest live birth rates, followed by minimal stimulations, natural cycles and IVM. While this order was most pronounced in youngest women under age 35, differences between minimal stimulation, natural cycles and IVM, disappeared above age 35 years, though dominance of conventional stimulations over all other stimulation protocols increased with advancing age.

The difference in live birth rates between conventional stimulation and other protocols, thus, widened with advancing female age from 1.6-3.9-fold among women under 35 years to 4.4-6.6-fold among women above age 42. Excluding data from the above mentioned two centers which performed 57.9% of all minimal stimulation and natural IVF cycles showed slightly higher live birth rates (between 0.7% and 6.1%) for these protocols in the remaining centers for all age groups, however, the live birth rates remained significantly lower than those achieved with conventional stimulation.

To assess the impact of DOR as a confounder, we separately assessed only patients with DOR (Figure 2). As expected, DOR patients across all age groups demonstrated lower live birth rates than the entire study population (Figure 1). However, even DOR patients, separately, again demonstrated the widening difference in live birth rates between conventional stimulation and other protocols with advancing female age from 2.8-fold among women under 35 years old to 5.2-fold among women above age 42.

Discussion

As expected, here presented data confirm universally declining live birth rates with advancing female age. However, somewhat unexpected, the data also reveal contradictory findings to current practice patterns. For example, as Table 1 demonstrates, alternative stimulations to conventional stimulations are increasingly used with advancing female age; yet, as Figure 1 demonstrates, especially minimal stimulation and natural cycle IVF, while still producing lower live birth rates than conventional stimulation, are clearly more effective in younger women under age 35 than at older ages.

Especially minimal ovarian stimulation with a 26.1% live birth rate and natural cycle IVF with a 15.7% live birth rate in young women, may be considered potential alternatives to conventional stimulation, even though conventional IVF at 42.4% clearly produced higher live birth rates. Here observed live birth rates for minimal stimulation and natural cycles in women under age 35 are, indeed, surprisingly robust.

Though the DOR diagnosis was somewhat more common among patients undergoing alternative than conventional stimulations, this difference in DOR prevalence, at most, only partially explains the large difference in live birth rates (Figure 1) since restricting the analysis to only patients with DOR did not substantially alter the findings (Figure 2). We were not able to analyze other infertility diagnosis such as PCOS in the present study. It will be important to follow up this analysis for other infertility diagnoses, it is especially interesting to study efficacy of IVM protocols in PCOS patients. Such an approach may help to identify patients who are best candidates for various protocols.

Our study is particularly timely since it shows that national outcome data from routine clinical practice, contradicts observations from small clinical trials, which have recently been used to promote increased worldwide utilization of minimal stimulation IVF. [18]

We previously noted that, after female age, number of oocytes retrieved and embryos available for transfer are the most important predictors of live births in IVF cycles [5,23–25]. Since implantation rates decline and aneuploidy rates increase with advancing female age, the importance of oocyte and embryo

numbers increases because more embryos can be safely transferred into the uterus to compensate for lower implantation rates. Younger women with high implantation rates, in contrast, will often, even with only few embryos, still conceive.

Here presented findings, therefore, make clinical sense but are not reflected in how these alternative stimulations are currently clinically utilized in the U.S. Cumulative live birth rates (per embryo cohort in a single cycle) would, likely, favor conventional stimulation even more profoundly, since these protocols are more likely to result in surplus transferable embryos than any of the alternative protocols.

This analysis is limited by lack of a standardized definition of minimal stimulation IVF; SART permits individual fertility centers to designate the most fitting stimulation type for each cycle. Additionally, because this analysis is based on aggregate data we were, except for age and diagnosis of DOR, not able to assess confounding patient characteristics, including number of prior IVF attempts and repeat cycles. We, therefore, cannot rule out undiscovered patient selection biases for individual stimulation protocols. It is possible that some patients undergoing stimulation with alternative protocols had prior conventional stimulation with very low oocyte and embryo yields. Moreover, a retrospective study design does not permit to control for various factors which led to the selection of a stimulation protocol by a physician for each patient. We also note that there is an imbalance in the size of the study groups in our analysis with more than 90% of cycles in all age groups receiving conventional stimulation. However, it is important to note that by analyzing aggregate national data for the entire population of patients rather than a sample of the population the risk of selection bias is somewhat mitigated. Despite above noted limitations it is unlikely that adjustments for such biases would substantially change the principal findings given the large sample size and that live birth rates were 1.6 to 6.6-fold higher with conventional stimulation than all other protocols. We also note that most minimal stimulation and natural IVF cycles were performed by only two fertility centers, where selection of these protocols is

likely more a reflection of practice patterns than biased patient selection of poor prognosis patients. Indeed, while these two centers reported marginally lower live birth rates than other centers, excluding their data from the analysis did not substantially alter the principal findings.

Here presented data are, in addition, also consistent with other reports: Silber et al, for example, recently reported in a large number of natural cycles that the chance of live birth per oocyte was 26% under age 35 but only 1% above age 42 years. [8] González-Foruria et al also concluded that natural cycle IVF should be restricted to younger women under age 35, [26] while Check et al reported similar outcomes for conventional and minimal stimulation cycles under age 35 years but clearly superior outcomes for conventional stimulation at older ages. [27]

The literature also supports our observation that conventional ovarian stimulation at all ages, including in women under age 36, produces higher live birth rates than here investigated alternative stimulations. A recent randomized controlled trial over a 6-months period demonstrated clearly lower cumulative live birth rates with minimal stimulation IVF than conventional stimulation. [15] When paired with strict single embryo transfer policy, a recent European analysis of cost effectiveness found that three to six minimal stimulation cycles were comparable in cost to one conventional stimulation cycle. [28] This observation is relevant regarding the recently reported observation that the wide acceptance by Japanese IVF centers of minimal ovarian stimulation (with blastocyst-stage elective single embryo transfer) has resulted in a loss of two-thirds of the national fresh IVF cycle live birth rate over the last decade, while concomitantly tripling the number of IVF cycle starts. [19]

Conclusions

Because live birth rates are significantly lower with minimal stimulation IVF than conventional IVF in this analysis of national data, cautious use of minimal stimulation protocols in carefully selected patients rather than their universal application is warranted. Alternative stimulation protocols including minimal

stimulation, natural cycle IVF and in vitro maturation (IVM) appear relatively ineffective in women older than 40 and younger women with DOR. Despite these observations, such protocols maybe still be useful in patients with severe DOR who previously did not respond to conventional stimulation.

Table 1. IVF cycle characteristics for each ovarian stimulation protocol stratified by female age group.

Female Age Group		<35	35-37	38-40	41-42	>42
Conventional Stimulation IVF	Cycle starts	83,637 (98.5%)	43,661 (97.7%)	41,661 (96.0%)	21,809 (93.7%)	14,937 (87.1%)
	Cancelled cycles	5.5%	8.3%	11.0%	13.6%	16.4%
	Retrievals with no embryos suitable for transfer	4.0%	6.8%	11.2%	17.9%	24.8%
	Mean number of embryos transferred	1.6	1.8	2	2.4	2.7
	Elective single embryo transfer	37.0%	27.1%	17.9%	11.4%	7.3%
	Diminished ovarian reserve	5.4%	11.7%	21.2%	34.0%	44.2%
Minimal Stimulation IVF	Cycle starts	678 (0.8%)	627 (1.4%)	1,050 (2.4%)	922 (4.0%)	1,120 (6.5%)
	Cancelled cycles	10.0%	12.9%	11.5%	15.9%	15.7%
	Retrievals with no embryos suitable for transfer	18.2%	24.5%	34.1%	44.3%	39.8%
	Mean number of embryos transferred	1.5	1.5	1.5	1.6	1.7
	Elective single embryo transfer	36.6%	35.8%	39.6%	36.9%	29.6%
	Diminished ovarian reserve	14.0%	30.3%	46.4%	64.1%	66.8%
Natural Cycle IVF	Cycle starts	451 (0.5%)	314 (0.7%)	574 (1.3%)	443 (1.9%)	1,003 (5.8%)
	Cancelled cycles	21.1%	26.8%	22.1%	20.8%	24.1%
	Retrievals with no embryos suitable for transfer	12.1%	20.4%	21.3%	29.9%	31.4%
	Mean number of embryos transferred	1.2	1.2	1.2	1.2	1.2

	Diminished ovarian reserve	14.9%	17.3%	29.1%	41.3%	48.6%
In Vitro Maturation (IVM)	Cycle starts	120 (0.1%)	82 (0.2%)	130 (0.3%)	93 (0.4%)	89 (0.5%)
	Cancelled cycles	1.7%	0.0%	0.0%	0.0%	1.1%
	Retrievals with no embryos suitable for transfer	28.8%	22.0%	18.5%	25.8%	21.6%
	Mean number of embryos transferred	1.8	1.9	2	1.8	1.7
	Diminished ovarian reserve	11.7%	25.6%	42.3%	47.3%	51.7%

Cycle number is based on combined final 2014 and preliminary 2015 U.S. national data reported by Society for Assisted Reproductive Technology,

Proportion of patients with diminished ovarian reserve (DOR) diagnosis are significantly different between ovarian stimulation protocols in all age groups ($P < 0.0001$).

Mean number of embryos transferred is based on final 2014 data

Table 2. IVF pregnancy outcome for each ovarian stimulation protocol stratified by female age group.

Female Age Group		<35	35-37	38-40	41-42	>42
Conventional Stimulation IVF	Miscarriage	11.7%	15.2%	21.8%	31.5%	46.1%
	Live Birth	42.4%	33.1%	22.1%	11.7%	3.9%
	Confidence Range	(42.1-42.8)	(32.7-33.6)	(21.7-22.5)	(11.3-12.1)	(3.6-4.3)
	Singleton	32.5%	26.7%	18.2%	10.2%	3.6%
	Twins or more	9.9%	6.4%	3.9%	1.5%	0.3%
	Term	77.5%	79.2%	80.1%	81.8%	84.7%
	Pre-term	22.5%	20.8%	19.9%	18.2%	15.3%
Minimal Stimulation IVF	Miscarriage	10.1%	21.2%	16.7%	30.4%	47.6%
	Live Birth	26.1%	14.0%	8.9%	3.3%	0.9%
	Confidence Range	(22.9-29.5)	(11.5-17.0)	(7.3-10.7)	(2.3-4.6)	(0.5-1.6)
	Singleton	21.8%	11.5%	8.4%	3.3%	0.8%
	Twins or more	4.3%	2.6%	0.5%	0.0%	0.1%
	Term	85.3%	75.0%	86.0%	80.0%	70.0%
	Pre-term	14.7%	25.0%	14.0%	20.0%	30.0%
Natural Cycle IVF	Miscarriage	18.4%	16.2%	22.6%	32.0%	53.8%
	Live Birth	15.7%	9.9%	7.1%	3.8%	0.6%
	Confidence Range	(12.7-19.4)	(7.0-13.7)	(5.3-9.6)	(2.4-6.1)	(0.3-1.3)
	Singleton	13.7%	8.6%	6.8%	3.4%	0.5%
	Twins or more	2.0%	1.3%	0.3%	0.5%	0.1%
	Term	88.7%	80.6%	85.4%	88.2%	100.0%
	Pre-term	11.3%	19.4%	14.6%	11.8%	0.0%
In Vitro Maturation (IVM)	Miscarriage	27.8%	20.0%	20.0%	100.0%	100.0%
	Live Birth	10.8%	9.8%	11.5%	0.0%	0.0%
	Confidence Range	(6.4-17.7)	(5.0-18.1)	(7.1-18.2)	-	-
	Singleton	10.0%	8.5%	9.2%	-	-
	Twins or more	0.8%	1.2%	2.3%	-	-
	Term	76.9%	100.0%	80.0%	-	-
	Pre-term	23.1%	0.0%	20.0%	-	-

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Figure 1. Primary live birth rate per oocyte retrieval cycle for the whole study population stratified by ovarian stimulation protocol.

-Based on combined final 2014 and preliminary 2015 U.S. national data reported by Society for Assisted Reproductive Technology. Conventional Stimulation IVF served as the reference for all statistical comparisons. * P-value of < 0.05

Figure 2. Primary live birth rates per oocyte retrieval cycle for patients with diminished ovarian reserve (DOR) diagnosis stratified by ovarian stimulation protocol.

-Based on combined final 2014 and preliminary 2015 U.S. national data reported by Society for Assisted Reproductive Technology. Conventional Stimulation IVF served as the reference for all statistical comparisons. * P-value of < 0.05

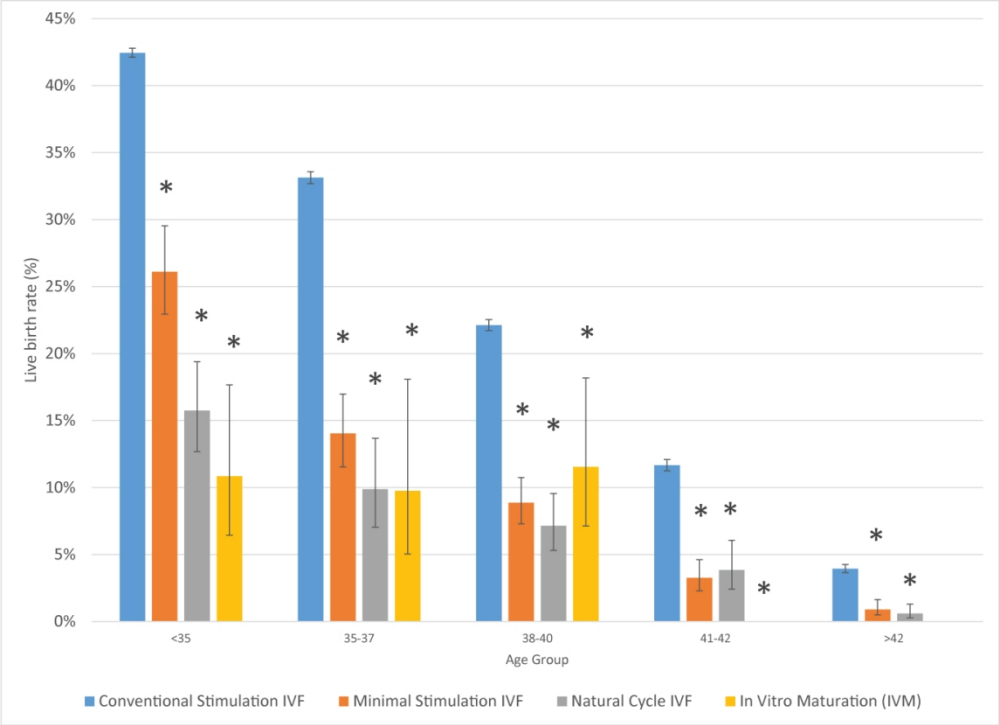

Figure 1: Primary live birth rate per oocyte retrieval cycle for the whole study population stratified by ovarian stimulation protocol.

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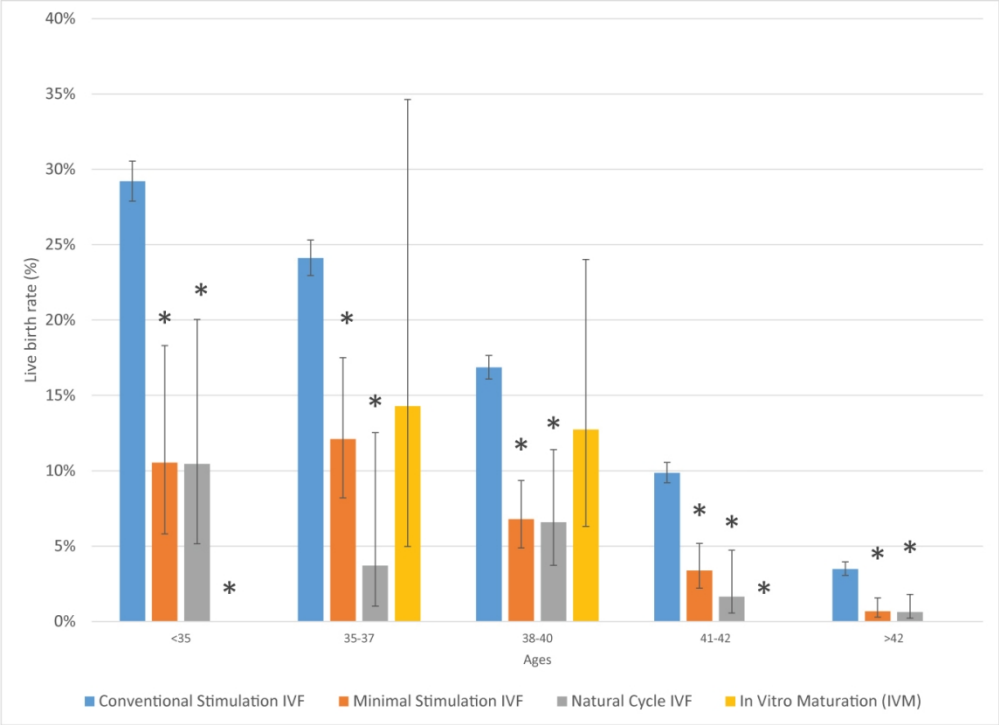

Figure 2: Primary live birth rates per oocyte retrieval cycle for patients with diminished ovarian reserve (DOR) diagnosis stratified by ovarian stimulation protocol.

115x84mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any pre-specified hypotheses	5,6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6,7*
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	6

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6, table, figures
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table, figures
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6,7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table, figures
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8,9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.