Low-technology assisted reproduction and the risk of preterm birth in a hospital-based cohort

Carmen Messerlian, Ph.D.,[a] Robert W. Platt, Ph.D.,[b] Seang-Lin Tan, M.D.,[c] Robert Gagnon, M.D.,[c] and Olga Basso, Ph.D.[a,c]

[a] Department of Epidemiology, Biostatistics and Occupational Health, McGill University; [b] Departments of Pediatrics and of Epidemiology and Biostatistics, McGill University Health Centre Research Institute; and [c] Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital, Montreal, Quebec, Canada

Objective: To estimate the risk of preterm birth in singleton infants conceived through low-technology assisted reproduction (intrauterine insemination and/or ovulation induction/stimulation).
Design: Hospital-based cohort study.
Setting: University-affiliated hospital.
Patient(s): Singleton babies born between 2001 and 2007 to 16,712 couples with no reported infertility (reference category), 378 babies conceived with low-technology treatment; 437 conceived with high-technology treatment; and 620 conceived naturally after a period of infertility.
Intervention(s): None. Treatment data were obtained from couples undergoing standard infertility investigation and care.
Main Outcome Measure(s): Preterm birth, defined at three clinical endpoints: <37, <35, and <32 weeks of completed gestation.
Result(s): After adjustment for age, parity, education, smoking, alcohol/drug use, and body mass index, the risk ratios and 95% confidence intervals (CI) of preterm birth for low technology were: 1.49 (CI: 1.12–2.00); 2.02 (CI: 1.30–3.13); and 2.93 (CI: 1.63–5.26) at <37, <35, and <32 weeks gestation, respectively, not dissimilar from the estimates for in vitro fertilization. Restricting the analysis to primiparas strengthened the association between treatment and preterm birth at the lower gestational endpoints. The increased risk persisted when the untreated group was used as the reference category, although the estimates were attenuated.
Conclusion(s): In this large hospital-based cohort study, low-technology assisted reproduction appeared to be a moderately strong predictor of preterm birth, with similar associations observed in the high-technology treatment group. After adjusting for confounders, as well as the shared characteristics of infertile couples, associations were attenuated but remained significant, suggesting that part of the risk is likely attributable to the treatment. (Fertil Steril® 2015;103: 81–8. ©2015 by American Society for Reproductive Medicine.)
Key Words: Assisted reproduction, infertility, intrauterine insemination, ovulation induction, preterm birth

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/messerlianc-low-technology-art-preterm-birth/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Worldwide, nearly 5 million babies have been born through assisted reproductive technology (ART) since 1978, representing between 1% and 4% of all births (1, 2). Although many more infants are conceived with non-ART procedures, such as ovulation induction and intrauterine insemination (IUI), the population surveillance is uncommon, and the full extent of their use is unknown (3). It has, however, been estimated that ovulation induction alone accounts for two to six times more births than ART in the United States (3), making medically assisted reproduction an important public health issue.

Extensive research has been performed on the health of ART-conceived children over the last two decades. Findings have consistently shown that babies born as a result of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are at increased risk of adverse outcomes, including preterm birth (4–18). Although more recent studies suggest that the overall risks associated with ART have declined in younger cohorts (14), singleton pregnancies remain at a higher risk of

Received August 10, 2014; revised and accepted October 2, 2014; published online November 21, 2014.
C.M. has nothing to disclose. R.W.P. reports personal fees from Oxford Outcomes and from Novartis. S.-L.T. has nothing to disclose. R.G. has nothing to disclose. O.B. has nothing to disclose.
Supported by a Canadian Institutes of Health Research Doctoral Award at the time of this study (to C.M.). The views expressed in this submitted article belong to the author and are not an official position of the institution or funder.
Reprint requests: Carmen Messerlian, Ph.D., Harvard School of Public Health, 665 Huntington Avenue, FXB 102A, Boston, Massachusetts 02115 (E-mail: cmesser@hsph.harvard.edu).

Fertility and Sterility® Vol. 103, No. 1, January 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.10.006

complication (7, 10, 13, 14, 17–19). Furthermore, a substantial body of evidence suggests that couples conceiving naturally after a long time to pregnancy (TTP) are also at increased risk of preterm birth (14, 20). Most research has focused on IVF-based technologies, but studies examining the risk of infertility itself by examining the naturally conceived pregnancies have not always been able to rule out non-IVF based treatment, and in particular, the use of pharmacotherapeutic ovulation induction agents prescribed outside a reproductive clinic setting (3, 14, 20).

"Low" technology treatments, such as ovulation induction or ovarian stimulation protocols (OS), alone or combined with IUI, are extensively relied upon as first-line methods in assisted reproduction (21, 22). Considering their widespread use and the number of babies born as a result of these procedures (3), there is comparatively little research examining their effect on pregnancy outcomes (14).

In this study, we estimate the risk of preterm birth in singleton infants conceived after different categories of treatment exposure compared with a reference group with no reported infertility. In particular, we investigate the risk associated with low-technology assisted reproduction (IUI and/or OS) as fewer studies exist on their potential effect on perinatal outcomes such a preterm birth.

MATERIALS AND METHODS

Study Population and Data

We assembled a hospital-based cohort of births from women residing in Montreal, Canada, who delivered at a large tertiary-care hospital from April 2001 to September 2007. Data were based on the hospital's extensive maternal and neonatal database (MOND) with virtually complete records for all live births and stillbirths (the latter recorded only if >500 g). The MOND included 25,198 records during the study period. We used a priori exclusion and inclusion criteria to reduce bias and confounding due to the hospital-based design. We excluded the following: high-risk referral pregnancies and births, women residing outside the city, women ≤20 and ≥45 years of age, and those with comorbidities known to be associated with both ART and preterm birth (see Supplemental Fig. 1, available online, for cohort formation). Twins and higher order multiples were also excluded, as preterm birth is very common among twins.

To complement the infertility information in MOND, we identified those women who had attended the hospital's reproductive clinic and had given birth within 36 months of their initial clinic appointments. We only requested a sample of charts (908 of 1,382) as the primary objective of the selection process was to obtain only those charts whereby we had missing information on the underlying cause of infertility in MOND. We obtained 839 of the requested medical charts, resulting in 1,050 births, and we abstracted information on diagnosis and treatment blindly with respect to the outcome (see Supplemental Fig. 2, available online, for medical chart identification and the abstraction process).

The final cohort comprised 18,147 singleton pregnancies. The reference group (n = 16,712) consisted of all pregnancies for which we had no indication of infertility based on either the MOND or the reproductive clinic data. The infertility exposed group (n = 1,435) comprised pregnancies conceived after a period of infertility, either naturally or after treatment. The study was approved by the McGill University Health Centre Institutional Ethics Review Board.

Classification of Exposure Status

We determined the infertility status for each pregnancy by using all relevant variables in MOND, complemented with the data collected from the medical chart. Time to pregnancy (TTP) was only available for women attending the infertility clinic and whose chart was obtained, so we relied on the infertility variable in MOND to determine eligibility in the exposed group. Among pregnancies with recorded TTP, those conceived after at least 12 months of trying were included as part of the infertile group. Those with <12 months and no record of treatment were included in the reference group (n = 14). Instances where we did not have TTP were classified in the reference group if there was no record of infertility or treatment in MOND (n = 268).

To determine treatment status, we first estimated the date of conception (calculated by subtracting gestational age from the infant's birth date). Based on this, a pregnancy was considered positive for treatment if the last recorded clinic cycle listed any form of treatment or if treatment was reported in MOND.

We separated pregnancies by type of treatment: low-technology (IUI or OS, alone or in combination) and high-technology (IVF, ICSI, or other procedures whereby gametes were manipulated in vitro). If present, the treatment information reported in the medical chart was considered as the gold standard in the event of discrepancies between the clinic and MOND data. When only the MOND data were available, these were considered valid. A pregnancy was considered naturally conceived if it was conceived within 90 days of the last recorded cycle and no treatment was indicated in either MOND or the clinic chart, or if it was conceived after 90 days of the last recorded/available cycle and there was no indication of treatment in MOND.

Outcome Definition

Preterm birth was defined as any pregnancy that ended between 20 and <37 gestational weeks, either as a live- or stillbirth. Pregnancies ending before 20 weeks were considered miscarriages and were excluded from the analysis (see Supplemental Fig. 1). Gestational age at birth in the hospital's database was estimated by an algorithm based on the first day of the last known menstrual period when confirmed by early ultrasound within ± 10 days. In cases where the last known menstrual period and early ultrasound estimates differed by more than 10 days, the latter was used. When the last known menstrual period was unknown, gestational age was based on ultrasound alone. We examined preterm birth at three clinical end points: [1] overall preterm birth: <37 weeks versus ≥37 weeks; [2] moderate preterm birth: <35 weeks versus ≥37 weeks; [3] very preterm birth: <32 weeks versus ≥37 weeks.

Covariates

Covariates were selected a priori, based on risk factors for both infertility/treatment and preterm birth. Maternal age and education, parity, smoking, and alcohol or drug use during pregnancy as well as reported prepregnancy weight and height were obtained from MOND. Maternal age at delivery was categorized into five groups (ages 21–28, 29–32, 33–35, 36–39, and 40–44), and maternal education (<12 years; 12 to 16 years; ≥16 years) and parity (0, 1, 2, or higher) were also noted. Body mass index (BMI) was calculated using the prepregnancy weight in kilograms divided by the square of height in meters, categorized as <18.5, 18.5–25, 25–30, and >30. Because of the high proportion of missing weight and height data, we used multiple imputation and re-estimated BMI for further analysis. Smoking and alcohol/drug use were self-reported during pregnancy and entered as binary variables.

Statistical Analyses

All statistical analyses were performed using Stata statistical software, version 12 (Stata Corporation). We first examined the characteristics of the study population and the frequency of the outcome by treatment exposure group compared with the reference category with no reported infertility. We estimated crude and adjusted risk ratios using generalized linear models with a log-link and binomial distribution for each definition of preterm birth by categories of treatment exposure. We selected a minimum set of covariates—age, parity, education, alcohol/drug use, and smoking—for the base model and subsequent models.

The fraction of missing information was 0.30 for weight, 0.48 for height, and 0.11 for education, and we thus show the nonimputed BMI-adjusted analysis in a separate model, as these produced less stable estimates. To address the missing BMI and education data, we used multiple imputation via chained equations (MICE) procedures to impute missing values for continuous height and weight variables, and we generated 10 imputed data sets (23). We used imputed height and weight values to recalculate BMI, and fitted multiple-imputed-models, with complete BMI and education values for the study population.

We performed these analyses on all singleton births and then restricted the analysis to only first births. Restricting on parity allowed us to examine the effect of primary infertility and to additionally address the potential effect of clustering of pregnancies by mother. For models that did not restrict to first births, we adjusted for clustering to account for the lack of independence between pregnancies to the same mother.

Sensitivity Analyses

Several investigators have recommended that to assess the "pure" effect of treatment, an untreated infertile population should serve as the reference category against different treatment groups (14, 24–26). Such an approach results in partially controlling for the effect of the underlying pathologies that cause infertility, and estimates an effect of treatment that is potentially unconfounded by the shared characteristics of infertile couples. We performed this analysis in an attempt to separate the effect of treatment from that of the underlying infertility.

In addition, as during the study period the province of Quebec had not yet implemented a publicly funded ART program, we were concerned that infertile couples with a lower socioeconomic status may have opted for low-technology treatment rather than paying for more expensive IVF treatment. Thus, using years of education as a proxy for socioeconomic status, we excluded the lowest education group (<12 years). We also wanted to determine whether there were differences by type of low-technology treatment, so we stratified our analysis by OS-only, OS with IUI, and IUI-only to assess this possibility. Finally, as we did not request or obtain every chart from the reproductive clinic (see Supplemental Fig. 2), we initially considered those births with no recorded infertility in MOND (n = 268) as belonging to the reference category. In a sensitivity analysis, we removed this subset from the reference category and included them in the untreated infertile group under the assumption that these pregnancies were conceived spontaneously after a period of infertility.

RESULTS

The study cohort comprised 18,147 singleton pregnancies with 1,435 (7.9%) classified in the infertile group (see Supplemental Fig. 1). Among the infertile, 620 (43.2%) conceived naturally without treatment, 378 (26.3%) conceived with low-technology and 437 (30.5 %) with high-technology treatment. In Table 1, we describe the study characteristics by treatment exposure group. The incidence of preterm birth varied by mode of conception. The untreated naturally conceived had the highest frequency of obesity and smoking during pregnancy. The low-technology group was younger and less educated compared with the other infertile categories and also had a high frequency of obesity. Women in the high-technology group were older and more educated, and were mainly nulliparous.

We report the crude and adjusted risk ratios (RR) and 95% confidence intervals (CI) for each of the three preterm birth end points by exposure group, in all pregnancies, and restricted to first pregnancies only (Tables 2 and 3, respectively). The relative risk of preterm birth increased as the threshold for defining preterm birth became more stringent, irrespective of the model, and was strongest in the low-technology group. The relative risk of birth before 32 weeks was most pronounced among primiparas in all three infertility-exposed groups (see Table 3).

In models taking into account missing data by multiple imputation (model 3), we observed a similar trend of increasing risk of preterm birth with decreasing gestational age, with the low-technology treatment group having the highest relative risk, although not statistically significantly different from high-technology treatment. Adjusting for BMI attenuated the effect most markedly in the treated groups. Primiparas had a marginally lower risk of preterm birth at <37 weeks compared with all pregnancies, but their

TABLE 1

Characteristic of singleton births by treatment exposure group.

Characteristics	Reference category (n = 16,712)	Treatment exposure group: Untreated (n = 620)	Low technology (n = 378)	High technology (n = 437)
Age group (y)				
21–28[a]	4,320 (25.9)	57 (9.2)	70 (18.5)	21 (4.8)
29–32	5,315 (31.8)	140 (22.6)	109 (28.8)	68 (15.6)
33–35	3,672 (22.0)	161 (26.0)	97 (25.7)	107 (24.5)
36–39	2,630 (15.7)	193 (31.1)	77 (20.4)	166 (38.0)
40–44	775 (4.6)	69 (11.1)	25 (6.6)	75 (17.2)
Parity				
0	7,754 (46.4)	325 (52.4)	245 (64.8)	327 (74.8)
1[a]	6,252 (37.4)	226 (36.4)	110 (29.1)	100 (22.9)
2	2,706 (16.2)	69 (11.1)	23 (6.1)	10 (2.3)
Education (y)				
<12	1,794 (10.7)	55 (8.9)	41 (10.8)	29 (6.6)
12–16	5,160 (30.9)	124 (32.3)	124 (32.8)	121 (27.7)
≥16[a]	7,949 (47.6)	310 (50.0)	171 (45.2)	246 (56.3)
Missing	1,809 (10.8)	55 (8.9)	42 (11.1)	41 (9.4)
BMI[b]				
<18.5	317 (1.9)	18 (2.9)	11 (2.9)	7(1.6)
18.5 to <25[a]	3,803 (22.8)	301 (48.6)	172 (45.5)	214 (48.9)
25 to <30	1,445 (8.6)	129 (20.8)	67 (17.7)	55 (12.6)
30+	793 (4.7)	83 (13.4)	49 (13.0)	40 (9.1)
Missing	10,354 (62.0)	89 (14.3)	79 (20.9)	121 (27.7)
Smoking	956 (5.7)	83 (13.4)	29 (7.7)	28 (6.4)
Alcohol/drug use	384 (2.3)	12 (1.9)	4 (1.1)	6 (1.4)
TTP median[c]		46 (29–67)	41 (27–62)	51 (34–87)
Preterm birth (wk)				
<37	1,202 (7.2)	53 (8.6)	42 (11.1)	51 (11.7)
<35	395 (2.5)	15 (2.6)	20 (5.6)	17 (4.2)
<32	161 (1.0)	9 (1.6)	12 (3.4)	9 (2.3)

Note: All values are n (%). Total singleton study cohort: 18,147.
[a] Reference category.
[b] Body mass index (BMI) reported in N = 7,504: untreated (n = 531); low tech (n = 299); high tech (n = 316).
[c] TTP (time to pregnancy) was known only for the women seen at the reproductive clinic (n = 957; 8.8% did not report TTP). We present median (25% to 75%) total TTP, which includes reported number of months trying to conceive before seeking treatment plus time until conception.

Messerlian. Low-technology treatment and preterm birth. Fertil Steril 2015.

risk in the fully adjusted BMI models increased at <35 and <32 weeks in all three exposure groups.

As expected, using the untreated infertile group as the reference category resulted in weaker relative risks among treated pregnancies, especially in the crude estimates (Table 4). Adjusting for clustering (data not shown) and time to pregnancy (see Table 4) did not materially change the estimates. Moreover, the sensitivity analyses suggested that primarily the IUI, and OS with IUI groups, rather than the OS group alone, were driving the observed association, although power in this analysis was limited. Restricting to pregnancies among women with at least a high school education did not change the results (see Table 4). When the 268 pregnancies that were identified as having uncertain infertility exposure were moved from the reference category to the untreated infertile group, the results were virtually unchanged (data not shown).

DISCUSSION

Our results suggest that singleton pregnancies conceived using low-technology treatment are at risk of moderate and very preterm birth, after adjusting for relevant covariates. Using multiple imputed data to further adjust for BMI attenuated the association, but the conclusions remained unchanged. Associations were strongest in first births, suggesting that primary infertility is a stronger risk factor for preterm birth. We observed similar results in the high-technology treatment group, suggesting that both forms of assisted reproduction are associated with an elevated risk of the outcome. We presented the main analysis using a general obstetric population as the reference to highlight the potential risks in singletons associated with this common form of treatment. Nevertheless, we also observed an increased risk when using untreated infertile couples as a reference category. To our knowledge, this is the first study to examine three potential modes of conception after a period of infertility on the risk of preterm birth using a hospital's administrative database complemented by primary clinical data.

Our results were robust to sensitivity analyses that explored whether the observed risk was driven by either infertility itself or by a subset of pregnancies within the low-technology treatment group. By using the untreated naturally conceived infertile group as the reference, we were able to partly control for underlying and common characteristics among infertile couples. Although this method does not account for the differences among infertile groups, such as distribution of causes of infertility, we were nevertheless

TABLE 2

Risk ratios of preterm birth by treatment exposure group: all singleton births.

Exposure group (wk)	Preterm n (%)[a,b]	Crude RR (95% CI)	Model 1 Base covariates RR (95% CI)	Model 2 Base + BMI RR (95% CI)	Model 3 MI: Base + BMI RR (95% CI)
Untreated					
<37	53 (8.5)	1.19 (0.91–1.55)	1.12 (0.83–1.50)	1.18 (0.85–1.63)	1.10 (0.84–1.43)
<35	15 (2.6)	1.04 (0.62–1.73)	0.95 (0.52–1.72)	1.02 (0.54–1.95)	0.89 (0.54–1.48)
<32	9 (1.6)	1.52 (0.78–2.96)	1.46 (0.64–3.35)	1.69 (0.71–4.01)	1.30 (0.66–2.56)
Low technology					
<37	42 (11.1)	1.54 (1.16–2.06)	1.46 (1.05–2.04)	1.68 (1.18–2.40)	1.49 (1.12–2.00)
<35	20 (5.6)	2.26 (1.46–3.50)	2.26 (1.35–3.77)	2.32 (1.32–4.10)	2.02 (1.30–3.13)
<32	12 (3.5)	3.36 (1.88–5.97)	4.27 (2.23–8.17)	3.92 (1.83–8.39)	2.93 (1.63–5.26)
High technology					
<37	51 (11.7)	1.62 (1.25–2.11)	1.47 (1.08–2.00)	1.44 (0.98–2.12)	1.53 (1.16–2.01)
<35	17 (4.2)	1.70 (1.06–2.73)	1.55 (0.89–2.70)	1.87 (1.01–3.47)	1.40 (0.86–2.29)
<32	9 (2.3)	2.22 (1.14–4.31)	2.07 (0.89–4.82)	2.08 (0.79–5.51)	1.77 (0.89–3.53)

Note: Model 1 includes age, parity, education, smoking, and alcohol/drug use. Model 2 includes all covariates in model 1 plus body mass index (BMI) (nonimputed, complete data). Model 3 uses multiple imputation (MI) with Model 2 covariates (age, parity, smoking, alcohol/drug use, and imputed BMI and education). CI = confidence interval; RR = risk ratio.

[a] Reference category. Preterm birth proportions: <37 weeks: 1,201 (7.2%); <35 weeks: 395 (2.5%); <32 weeks: 161 (1.0%).

[b] Preterm birth comparisons: <37 vs. ≥37; <35 vs. ≥37; <32 vs. ≥37.

Messerlian. Low-technology treatment and preterm birth. Fertil Steril 2015.

able to control for the characteristics that were shared. In this analysis, we observed a reduction in the relative risks at all three preterm birth end points, suggesting that part of the increased risk in babies born after infertility treatment may be attributable to these underlying factors.

This finding is consistent with previous studies that have used various approaches to control for underlying infertility (27–29). We furthermore adjusted for duration of infertility prior to treatment and observed a slight reduction in associations, similar to the findings by Källén et al. (30). Despite some attenuation, our results remained statistically significant, suggesting that pharmacologically induced or stimulated cycles and/or insemination procedures, irrespective of in vitro gamete manipulation, are likely to independently increase the risk of preterm birth. Furthermore, the increased risk of preterm birth did not appear to be driven by an economically underprivileged subgroup, as estimates were relatively unaffected when we examined only pregnancies to women with at least 12 years of education. Finally, the risk may potentially be more pronounced in the OS/IUI group rather than the OS-only group, although our power was limited in these subanalyses.

Our findings from the high-technology treatment group show similar trends to the low-technology group. Our results are consistent with the recent observation made by Pinborg et al. (14) and supported by findings in Källén et al. (30), Sazonova et al. (16), and Pandey et al. (13) that younger ART cohorts have an overall lower risk compared with older ART populations. This may be explained by the fact that fresh and frozen cycles were not differentiated, with the latter

TABLE 3

Risk ratios for preterm birth by treatment exposure group: first births only.

Exposure group (wk)	Preterm n (%)[a,b]	Crude RR (95% CI)	Model 1 Base covariates RR (95% CI)	Model 3 MI: Base + BMI RR (95% CI)
Untreated				
<37	26 (8.0)	1.17 (0.80–1.70)	1.02 (0.66–1.56)	1.04 (0.71–1.52)
<35	12 (3.9)	1.63 (0.92–2.90)	1.66 (0.84–3.27)	1.46 (0.82–2.62)
<32	7 (2.3)	2.45 (1.14–5.30)	2.89 (1.12–7.46)	2.19 (1.00–4.81)
Low technology				
<37	25 (10.2)	1.49 (1.02–2.18)	1.35 (0.88–2.07)	1.38 (0.94–2.02)
<35	13 (5.6)	2.36 (1.36–4.08)	2.50 (1.32–4.71)	2.10 (1.21–3.66)
<32	8 (3.5)	3.76 (1.83–7.73)	4.62 (1.95–10.91)	3.35 (1.62–6.93)
High technology				
<37	39 (11.9)	1.74 (1.28–2.36)	1.32 (0.91–1.92)	1.46 (1.06–2.01)
<35	15 (4.9)	2.09 (1.25–3.50)	1.97 (1.04–3.75)	1.79 (1.04–3.08)
<32	8 (2.7)	2.90 (1.41–5.97)	2.64 (0.98–7.10)	2.39 (1.10–5.18)

Note: Model 1: includes age, education, smoking, alcohol/drug use; restricted to first births only. Model 3: multiple imputation model (MI) includes all covariates in model 1, plus imputed body mass index (BMI) and education; restricted to first births only. CI = confidence interval; RR = risk ratio.

[a] Reference category: Preterm birth proportions: <37 weeks: 531 (6.8%); <35 weeks: 175 (2.4%); <32 weeks: 68 (0.9%).

[b] Preterm birth comparisons: <37 vs. ≥37; <35 vs. ≥37; <32 vs. ≥37.

Messerlian. Low-technology treatment and preterm birth. Fertil Steril 2015.

TABLE 4

Sensitivity analyses: risk of preterm birth in low technology assisted reproduction.

	Low-technology treatment		
	< 37 wk	< 35 wk	< 32 wk
Untreated infertile reference[a]			
Crude	1.30 (0.89–1.91)	2.18 (1.13–4.20)	2.21 (0.94–5.18)
Adjusted	1.32 (0.85–2.04)	2.16 (1.00–4.67)	2.65 (0.96–7.30)
Adjusting for TTP[b]			
Crude	1.46 (1.05–2.04)	2.26 (1.35–3.76)	4.27 (2.23–8.17)
Adjusted	1.42 (0.99–2.05)	2.16 (1.21–3.84)	3.33 (1.52–7.29)
Stratified by type of treatment			
IUI only[c]	2.16 (1.18–3.94)	3.04 (1.18–7.84)	3.82 (0.97–14.97)
OS and IUI[d]	1.92 (1.29–2.87)	3.12 (1.75–5.55)	4.94 (2.36–10.33)
OS alone[e]	1.00 (0.58–1.72)	1.25 (0.52–2.98)	1.84 (0.60–5.69)
Restricted to higher education[f]			
Crude	1.64 (1.21–2.22)	2.30 (1.46–3.67)	3.44 (1.88–6.28)
Adjusted	1.55 (1.10–2.19)	2.30 (1.33–3.97)	4.44 (2.25–8.74)

Note: IUI = intrauterine insemination; OS = ovarian stimulation; TTP = time to pregnancy.
[a] Untreated infertile reference: crude model estimates the risk of preterm birth in low-technology group compared to the untreated infertile group (used as the reference category) with no additional covariates. Adjusted model included all base covariates.
[b] Adjusting for TTP as a binary variable at ≥24 months versus ≤24 months: crude model estimates the risk of preterm birth in low-technology group adjusting for all base covariates. Adjusted model includes all base covariates plus TTP.
[c] IUI only: 58 pregnancies.
[d] OS with IUI: 152 pregnancies.
[e] OS alone: 168 pregnancies.
[f] Restricting to ≥12 years of education: crude model estimates the risk of preterm birth in low-technology group restricted to ≥12 years of education. Adjusted model includes all base covariates.

Messerlian. Low-technology treatment and preterm birth. Fertil Steril 2015.

generally having better outcomes. These recent trends may be due to a multitude of other factors, including perhaps a less severe and shorter duration of infertility before seeking treatment, and improvements in ovarian stimulation protocols and IVF techniques and procedures (14).

Overall, our findings from the untreated naturally conceived group show more modest results; associations were statistically significant only among primiparous births at <32 weeks gestation. Our findings are somewhat consistent with other published work in this area, albeit with a lower overall effect in this category than what is reported in recent meta-analyses (14, 20). Our lower estimates may be explained by the fact that we applied strict criteria to define the untreated infertile group, thus potentially reducing the number of treated women misclassified as untreated. Furthermore, a rebound spontaneous pregnancy—a pregnancy conceived immediately after a recent failed treatment cycle (31, 32)—would have been classified under either low-technology or high-technology treatment, depending on the last reported cycle.

A degree of misclassification within the exposure groups may have also influenced our results. We set an a priori index period of 90 days based on the fact that it was unlikely that a couple would have received treatment and conceived elsewhere within a 90-day period of leaving the clinic. A recent study on the clinical profile of an infertile population recruited during the same time period as our study reported that 42% of couples seeking treatment conceived spontaneously (33). The former estimate of natural conception among couples seeking treatment is comparable to our estimated 43%. Further evidence supporting our classification of treatment is provided by the fact that the frequency of twin pregnancies within each treatment category was consistent with what is reported in the literature. The twin rate was 1.1% in the untreated group, similar to that of the reference group and consistent with absence of treatment. Among the low- and high-technology treatment groups, twin rates were 9.6% and 32%, respectively, with comparable estimates reported elsewhere (18, 34–37). Although this was a hospital-based cohort from a tertiary care center, the preterm birth rate after applying exclusions was similar to that of the overall Montreal population (38).

Only few studies have examined the effect of low-technology assisted reproduction on the risk of preterm birth, with some heterogeneity in the methods and sources of data: two studies relied exclusively on countrywide registry-based data (27, 39); three studies used a combination of hospital-based data linked with various national databases (22, 35, 40); and one study used prospectively recruited primary data linked with outcome data from a national registry (41). Despite the differences in methods, our results are in general agreement: low-technology treatment is associated with an increased risk of preterm birth (22, 27, 35, 39, 40). Among the studies that additionally examined high-technology treatment, the conclusions were generally consistent with ours. Although our effect estimates on low-technology treatment are overall higher, the study by Ombelet et al. (35), using hospital-based registry data from 80 different obstetrics departments in Belgium, shares strong consistency with our results (<32 weeks: OR 3.26, 95% CI, 2.32–4.59). Only the results of the Wisborg et al. (41) study differ substantially from ours, despite examining all infertile exposure groups compared with a noninfertile reference.

Although low-technology treatment involves no manipulation of embryos, the use of pharmacologic agents to stimulate the production of oocytes is associated with poorer quality embryos (12, 37). Both in vivo and in vitro animal studies point to detrimental effects of exogenous hormones to the quality and viability of the developing embryo, which can result in chromosomal abnormalities (21) as well as changes to implantation (42) and placentation (37). Furthermore, hyperproliferated cycles have been reported to cause oxidative stress, which impacts both oocyte development and endometrial conditions (37). Meanwhile, other studies report that the treatment of sperm for IUI procedures also leads to oxidative stress, with potential chromosomal damage or changes to the quality of the sperm (43–47). Until recently, the latter procedure was assumed to be innocuous to the health of the embryo and neonate.

CONCLUSION

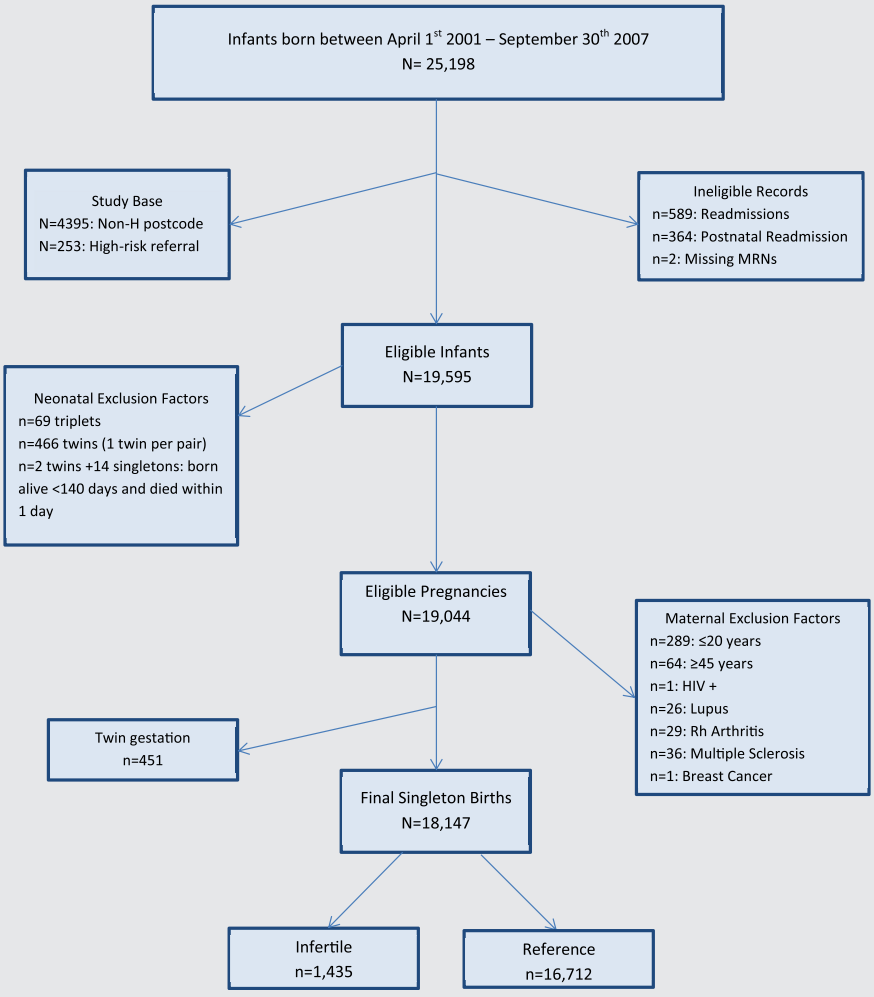
In this study, low-technology assisted reproduction was associated with a higher risk of preterm birth compared with untreated women with no reported infertility giving birth at the same hospital. This effect persisted after adjustment for confounders as well as for the shared characteristics among infertile couples, suggesting that part of the risk is likely attributable to treatment itself.

REFERENCES

1. ESHRE Capri Workshop GroupBaird DT, Bhattacharya S, Devroey P, Diedrich K, Evers JL, et al. Failures (with some successes) of assisted reproduction and gamete donation programs. Hum Reprod Update 2013;19:354–65.
2. Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil Steril 2009;92:1520–4.
3. Schieve LA, Devine O, Boyle CA, Petrini JR, Warner L. Estimation of the contribution of non-assisted reproductive technology ovulation stimulation fertility treatments to US singleton and multiple births. Am J Epidemiol 2009;170:1396–407.
4. Buckett WM, Tan SL. Congenital abnormalities in children born after assisted reproductive techniques: how much is associated with the presence of infertility and how much with its treatment? Fertil Steril 2005;84:1318–9.
5. Chen X-K, Wen SW, Bottomley J, Smith GN, Leader A, Walker MC. In vitro fertilization is associated with an increased risk for preeclampsia. Hypertens Pregnancy 2009;28:1–12.
6. Chen Y-H, Lin H-C, Chen S-F, Lin H-C. Increased risk of preterm births among women with uterine leiomyoma: a nationwide population-based study. Hum Reprod 2009;24:3049–56.
7. De Geyter C, De Geyter M, Steimann S, Zhang H, Holzgreve W. Comparative birth weights of singletons born after assisted reproduction and natural conception in previously infertile women. Hum Reprod 2006;21:705–12.
8. Filicori M, Cognigni GE, Gamberini E, Troilo E, Parmegiani L, Bernardi S. Impact of medically assisted fertility on preterm birth. BJOG 2005;112(Suppl 1):113–7.
9. Helmerhorst FM, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ 2004;328:261–4.
10. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol 2004;103:551–63.
11. McDonald SD, Han Z, Mulla S, Murphy KE, Beyene J, Ohlsson A. Preterm birth and low birth weight among in vitro fertilization singletons: a systematic review and meta-analyses. Eur J Obstet Gynecol Reprod Biol 2009;146:138–48.
12. Mitchell AA. Infertility treatment—more risks and challenges. N Engl J Med 2002;346:769–70.
13. Pandey S, Shetty A, Hamilton M, Bhattacharya S, Maheshwari A. Obstetric and perinatal outcomes in singleton pregnancies resulting from IVF/ICSI: a systematic review and meta-analysis. Hum Reprod Update 2012;18:485–503.
14. Pinborg AA, Wennerholm UB, Romundstad LB, Loft AA, Aittomaki KK, Söderström-Anttila VV, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. Hum Reprod Update 2013;19:87–104.
15. Reubinoff BE, Samueloff A, Ben-Haim M, Friedler S, Schenker JG, Lewin A. Is the obstetric outcome of in vitro fertilized singleton gestations different from natural ones? A controlled study. Fertil Steril 1997;67:1077–83.
16. Sazonova A, Källen K, Thurin-Kjellberg A. Factors affecting obstetric outcome of singletons born after IVF. Hum Reprod 2011;26:2878–86.
17. Sazonova A, Källen K, Thurin-Kjellberg A, Wennerholm UB, Bergh C. Obstetric outcome in singletons after in vitro fertilization with cryopreserved/thawed embryos. Hum Reprod 2012;27:1343–50.
18. Shevell T, Malone FD, Vidaver J, Porter TF, Luthy DA. Assisted reproductive technology and pregnancy outcome. Obstet Gynecol 2005;106:1039–45.
19. Davies MJ, Moore VM, Willson KJ, Van Essen PP, Priest KK, Scott HH, et al. Reproductive technologies and the risk of birth defects. N Engl J Med 2012;366:1803–13.
20. Messerlian C, Maclagan L, Basso O. Infertility and the risk of adverse pregnancy outcomes: a systematic review and meta-analysis. Hum Reprod 2013;28:125–37.
21. Ertzeid GG, Storeng RR. The impact of ovarian stimulation on implantation and fetal development in mice. Hum Reprod 2001;16:221–5.
22. Gaudoin M. Ovulation induction/intrauterine insemination in infertile couples is associated with low-birth-weight infants. Am J Obstet Gynecol 2003;188:611–6.
23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30:377–99.
24. Basso O, Baird D. Infertility and preterm delivery, birthweight, and caesarean section: a study within the Danish National Birth Cohort. Hum Reprod 2003;18:2478–84.
25. Allen VM, Wilson RD, Cheung A. Pregnancy outcomes after assisted reproductive technology. J Obstet Gynaecol Can 2006;28:220–50.
26. Reddy UM, Wapner RJ, Rebar RW, Tasca RJ. Infertility, assisted reproductive technology, and adverse pregnancy outcomes: executive summary of a National Institute of Child Health and Human Development workshop. Obstet Gynecol 2007;109:967–77.
27. Källén B, Olausson PO, Nygren KG. Neonatal outcome in pregnancies from ovarian stimulation. Obstet Gynecol 2002;100:414–9.
28. Romundstad LB, Romundstad PR, Sunde A, During von V, Skjaerven R, Gunnell D, et al. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. Lancet 2008;372:737–43.
29. Henningsen A-K, Pinborg A, Lidegaard Ø, Vestergaard C, Forman JL, Andersen AN. Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. Fertil Steril 2011;95:959–63.
30. Källén BB, Finnström OO, Lindam AA, Nilsson EE, Nygren KG, Olausson PP. Trends in delivery and neonatal outcome after in vitro fertilization in Sweden: data for 25 years. Hum Reprod 2010;25:1026–34.
31. van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 1999;5:483–92.
32. Bidet M, Bachelot A, Bissauge E, Golmard JL, Gricourt S, Dulon J, et al. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. J Clin Endocrinol Metab 2011;96:3864–72.
33. Donckers J, Evers JL, Land JA. The long-term outcome of 946 consecutive couples visiting a fertility clinic in 2001–2003. Fertil Steril 2011;96:160–4.
34. Fauser BC, Devroey P, Macklon NS. Multiple birth resulting from ovarian stimulation for subfertility treatment. Lancet 2005;365:1807–16.
35. Ombelet W. Perinatal outcome of 12,021 singleton and 3108 twin births after non-IVF-assisted reproduction: a cohort study. Hum Reprod 2005;21:1025–32.
36. Peterson CM, Hatasaka HH, Jones KP, Poulson AM, Carrell DT, Urry RL. Ovulation induction with gonadotropins and intrauterine insemination compared with in vitro fertilization and no therapy: a prospective, nonrandomized, cohort study and meta-analysis. Fertil Steril 1994;62:535–44.
37. Santos F, Hyslop L, Stojkovic P, Leary C, Murdoch A, Reik W, et al. Evaluation of epigenetic marks in human embryos derived from IVF and ICSI. Hum Reprod 2010;25:2387–95.
38. Kramer MS, Wilkins R, Goulet L, Séguin L, Lydon J, Kahn SR, et al. Investigating socio-economic disparities in preterm birth: evidence for selective study participation and selection bias. Paediatr Perinat Epidemiol 2009;23:301–9.
39. Klemetti R, Sevón T, Gissler M, Hemminki E. Health of children born after ovulation induction. Fertil Steril 2010;93:1157–68.
40. Wang JX, Norman RJ, Kristiansson P. The effect of various infertility treatments on the risk of preterm birth. Hum Reprod 2002;17:945–9.
41. Wisborg K, Ingerslev HJ, Henriksen TB. In vitro fertilization and preterm delivery, low birth weight, and admission to the neonatal intensive care unit: a prospective follow-up study. Fertil Steril 2010;94:2102–6.
42. Deng S, Xu J, Zeng J, Hu L, Wu Y. Ovarian stimulation leads to a severe implantation defect in mice. Reprod Biomed Online 2013;27:172–5.
43. Tremellen K. Oxidative stress and male infertility—a clinical perspective. Hum Reprod Update 2008;14:243–58.

44. Guz J, Gackowski D, Foksinski M, Rozalski R, Zarakowska E, Siomek A. Comparison of oxidative stress/DNA damage in semen and blood of fertile and infertile men. PLoS One 2013;8:e68490.
45. Saleh RA, Agarwal A. Oxidative stress and male infertility: from research bench to clinical practice. J Androl 2002;23:737–52.
46. Aitken RJ. Falling sperm counts twenty years on: where are we now? Asian J Androl 2013;15:204–7.
47. Borini A, Tarozzi N, Bizzaro D, Bonu MA, Fava L. Sperm DNA fragmentation: paternal effect on early post-implantation embryo development in ART. Hum Reprod 2006;21:2876–81.

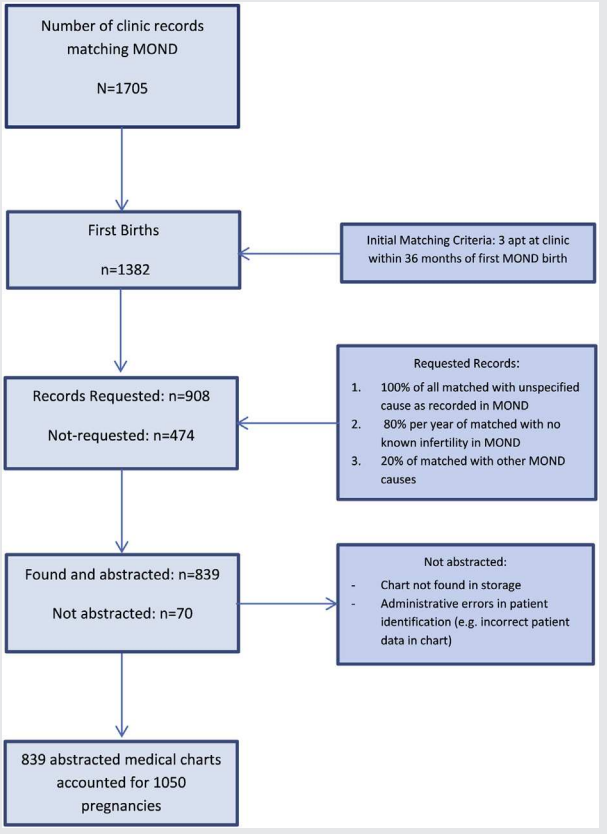
SUPPLEMENTAL FIGURE 1



Participant flow chart.

Messerlian. Low-technology treatment and preterm birth. Fertil Steril 2015.

SUPPLEMENTAL FIGURE 2



Identifying reproductive clinic patients in the maternal and neonatal database (MOND). Process of selecting medical charts to abstract.

Messerlian. Low-technology treatment and preterm birth. Fertil Steril 2015.