Research Article

iMedPub Journals
http://wwwimedpub.com

Journal of Reproductive Endocrinology & Infertility
ISSN 2476-2008

2018
Vol.3 No.1:3

DOI: 10.21767/2476-2008.100029

Do Fertility Outcomes Differ in an Underinsured Urban Predominantly Hispanic population? A Single Center Experience

Katherine LP[1]*, Rogerio A[1], Nataki CD[1], Jessica S[1], Arielle G[1] and Ralf CZ[2]

1 Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, USA
2 Neway Fertility, New York, USA

***Corresponding author:**
Katherine L Palmerola

Department of Obstetrics and Gynecology, Columbia University Medical Center, New York, USA.

Kdl2112@cumc.columbia.edu

Tel: (215) 499-1069
Fax: (212) 305-4672

Citation: Katherine LP, Rogerio A, Nataki CD, Jessica S, Arielle G et al. (2018) Do Fertility Outcomes Differ in an Underinsured Urban Predominantly Hispanic population? A Single Center Experience. J Reproductive Endocrinol & Infert. Vol.3 No.1:4

Abstract

Background: Racial disparities persist in many aspects of modern healthcare, including the diagnosis and treatment of patients with infertility. These measures are particularly understudied in Hispanic women. The objective of this study is to compare fertility outcomes of an underinsured, largely Hispanic population to outcomes from national cohorts.

Capsule: Conception rates following controlled ovarian stimulation in underinsured minority populations are poor providers should be proactive in encouraging patients to pursue *in vitro* fertilization when possible.

Methods: A retrospective review of women with polycystic ovary syndrome (PCOS) or unexplained infertility undergoing controlled ovarian stimulation (COS) cycles from 2012-2016 at an underinsured fertility clinic was undertaken. Patients underwent COS with clomiphene citrate or letrozole. Ovulation was detected with ovulation predictor kits (OPK) or induced with Ovidrel®. Patients underwent timed intercourse (TIC) or intrauterine insemination (IUI). A group of patients proceeded to *in vitro* fertilization (IVF). Patient demographics, conception rates, and ongoing pregnancy rates were noted and compared to national cohorts of women with PCOS and unexplained infertility undergoing COS.

Results: Two hundred thirty nine patients underwent 858 COS cycles. The mean age of patients was 34.5 years. Fifty two percent of patients were identified as Hispanic. Compared to the previously published PCOS cohorts, conception rates were lower. Ten patients with PCOS pursued IVF, undergoing 9 embryo transfers (ET), with 6 (66.7%) conceptions and 4 (44.4%) ongoing pregnancies. Compared to previously publish unexplained infertility cohorts, conception rates were lower. Five patients with unexplained infertility pursued IVF, undergoing 4 ET, with 4 (100%) conceptions and 2 (50%) ongoing pregnancies.

Conclusion: Conception rates in this underinsured, predominantly Hispanic population are poor and lower than rates described in multicenter trials with predominantly Caucasian populations. With access to IVF, conception and ongoing pregnancy rates are high and similar to national averages. Providers treating underserved populations should be proactive in encouraging patients to pursue IVF when possible.

Keywords: Hispanic; socioeconomic disparities; access to care; infertility; controlled ovarian stimulation.

Abbreviations: AMH: Anti-Müllerian Hormone; AFC: Antral Follicle Count; ART: Assisted Reproductive Technology; BMI: Body Mass Index; CWRC: Center for Women's Reproductive Care; CUMC: Columbia University Medical Center; COS: Controlled Ovarian Stimulation; ET: Embryo transfer; IUI: Intrauterine Insemination; IVF: *In vitro* fertilization; NSFG: National Survey of Family Growth; NEJM: New England Journal of Medicine; PCOS: Polycystic ovary Syndrome; REI: Reproductive Endocrinology and Infertility; RMN: Reproductive Medicine Network; TIC: Timed Inter Course

Received: January 31, 2018; **Accepted:** April 23, 2018; **Published:** April 30, 2018

Introduction

Infertility affects all racial, ethnic and socio-economic groups. According to the 2013 National Survey of Family Growth (NSFG), 12% of women in the United Sates experienced infertility in 2002, an increase from 8.4% of women in 1982 [1]. Delayed

childbearing undoubtedly contributes to the increasing incidence of infertility. Paralleling this trend, assisted reproductive technology (ART) has evolved considerably over this period. ART involves all procedures in which oocytes, sperm, or embryos are manipulated in a laboratory setting to achieve reproduction. Since the first ART birth reported in 1978 [2], many couples are now able to conceive and achieve desired family size because of advancements in this field.

Multiple studies have shown that only a fraction of the population has access to ART or other infertility treatments, leading to disparities in infertility prevalence by race and ethnicity [3-5]. NSFG reports (2010) demonstrate that while 15% of non-Hispanic white women sought infertility treatments to achieve pregnancy, only 8.0% of non-Hispanic black women and 7.6% of Hispanic women did so [4,5]. Furthermore, of those women with access to infertility services, the duration of infertility and treatment outcomes differed in minority groups compared to the rest of the population [4,5]. Using 2010 Society for Assisted Reproductive Technology reports, Fujimoto et al. highlighted that live birth rates following ART were lower in minority groups versus white women: 10% less for Asian women, 13% less for Hispanic women, and 38% less for black women [6]. The reasons for these differences remain unclear. In response to these findings, the Center for Disease Control and Prevention released the National Public Health Action Plan for the Detection, Prevention, and Management of Infertility, aspiring to eliminate disparities in access to high-quality infertility services [7]. Similarly, the Ethics Committee of the American Society for Reproductive Medicine recognizes the creation of a family as a basic human right and encourages all ART providers to strive to lessen barriers to infertility care [8].

Multiple factors may contribute to disparities in access to infertility treatment and differences in treatment outcomes. Disparities in education, especially health education, may limit understanding of their medical conditions and infertility diagnosis and treatment options [9]. Disparities in access and use of preventative care services contribute to disparities in general medical health and comorbid conditions, as well as delayed diagnosis and referral to specialists, including infertility providers [10]. Consequently fertility treatments begin at later age, with higher number of comorbid conditions, and lower overall prognosis. Furthermore, disparities in conditions known to cause infertility may account for differences in treatment outcomes when infertility services are accessible. For example, the incidence of tubal disease, Fragile X gene mutation, and obesity varies between women of different races, with minorities being disproportionately affected [4,11-15]. Similarly, Shuler et al. showed significant variation in infertility diagnoses according to ethnicity: Hispanic women have increased incidence of tubal factor infertility compared to non-Hispanic white women [16]. For many patients, the cost of infertility services is insurmountable, thus preventing adequate access to and use of care. According to 2016 estimates, the cost of one cycle of *in vitro* fertilization (IVF) may exceed 50% of the average American individual's annual disposable income if these services are not covered by insurance [17-19]. Consequently, cost limits the availability of infertility services to patients of lower socioeconomic status across all races and ethnicities.

The Columbia University Medical Center (CUMC) Reproductive Endocrinology and Infertility (REI) Clinic at Audubon Practice provides unique access to fertility treatments for uninsured and underinsured patients at an income-based, fee per appointment cost. Patients are self-referred or referred by ambulatory care providers within the New York Presbyterian Hospital network as well as providers from the greater tri-state area. The clinic is staffed by CUMC REI fellows and Obstetrics and Gynecology residents, under the supervision of a CUMC board-certified REI attending physician. The clinic provides complete infertility evaluation, including hormonal assays, ultrasonography, and saline infused sonohysterogram. Patients are referred for a hysterosalpingogram and semen analysis, as well as genetic testing and counseling, urology evaluation and gynecologic surgery, when indicated. In-person or telephone translator services are available for non-English speaking patients. A dedicated nurse with expertise in endocrinology and infertility coordinates patient care and facilitates communication between patients and physicians. The clinic offers ovulation induction and controlled ovarian stimulation (COS) with clomiphene citrate, letrozole, and gonadotropins. Cycles are monitored with serial ultrasounds and ovulation is timed with ovulation predictor kits or Ovidrel®. Conception is attempted with timed intercourse (TIC) or intrauterine insemination (IUI), including donor sperm IUI. IUIs are performed at the CUMC Center for Women's Reproductive Care (CWRC) with the assistance of the CWRC andrology team and under the supervision of a CWRC attending physician. Access to ART services is also possible for patients who desire or require these treatments. IVF approval is based on the qualifying criteria of the New York State Department of Health Infertility Demonstration Program [20].

The REI clinic at Audubon Practice attracts a wide range of patients from New York City and the surrounding region, as well as internationally. Based in Washington Heights, New York, a large proportion of patients are of Hispanic ethnicity, providing a unique opportunity to evaluate infertility outcomes in this population. The purpose of this study was to assess treatment outcomes of patients with polycystic ovary syndrome (PCOS) or unexplained infertility in this underinsured, majority Hispanic population. We hypothesized that with adequate access to infertility services, these women would experience conception rates and pregnancy outcomes similar to those previously reported for national cohorts of women with PCOS or unexplained infertility.

Methods

Study population

This retrospective study included women undergoing COS cycles at the CUMC REI Clinic at Audubon Practice between January 2012 and December 2016. A total of 239 patients collectively underwent 858 COS cycles between January 2012 and December 2016. Of these cycles, 449 (52.3%) were conducted in Hispanic patients. Based on diagnoses following infertility evaluation, two groups of women were identified: women with PCOS (n=38 women, 100 cycles) and women with unexplained infertility (n=47 women, 175 cycles). Women with alternative infertility

diagnoses or multiple diagnoses in combination with PCOS or unexplained infertility were excluded from our analysis. Cancelled cycles and cycles without known cycle outcomes were excluded from analysis **(Figure 1)**. The diagnosis of PCOS was based on Rotterdam Criteria [21], with laboratory exclusion of alternative diagnoses. The diagnosis of unexplained infertility was made following negative male and female infertility testing, which included normal ovarian reserve testing (as defined by antral follicle count (AFC), early follicular phase follicle stimulating hormone (FSH) and estradiol levels, and anti-Müllerian hormone levels), normal thyroid stimulating hormone and prolactin testing, patent fallopian tubes on hysterosalpingogram, normal uterine cavity assessment on saline infused sonohysterogram, and normal semen assessment according to 2010 World Health Organization guidelines [22].

Demographic information and baseline infertility testing information were collected, including age (years), body mass index (BMI, kg/m^2), race, ethnicity, anti-Müllerian hormone (AMH) level (ng/mL), baseline FSH level (mIU/mL), and AFC. Conception with TIC versus IUI was noted. Data points were obtained through abstraction from existing patient electronic records. The demographics of the Audubon Practice patients as well as PCOS and unexplained infertility cohorts are presented in **Table 1**. Cycle outcomes, including conception rate, biochemical pregnancy rate, miscarriage rate, and ongoing pregnancy rate were recorded. The Columbia University Medical Center Institutional Review Board approved this study, IRB #AAAR0502.

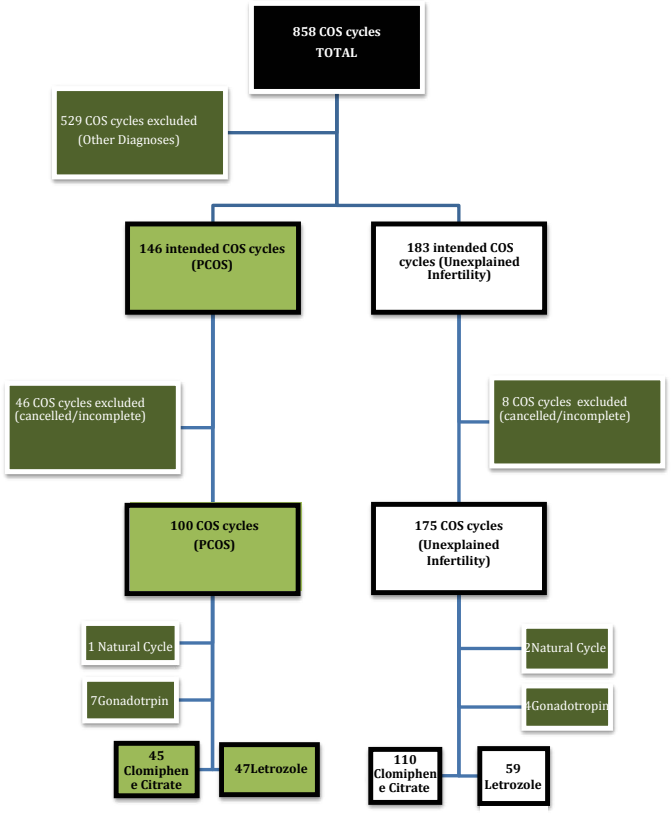

Figure 1 Infertility ministry survey. This figure represents the survey sent to participants to learn more about the availability and the details of their infertility ministry.

Controlled ovarian stimulation and intrauterine insemination

After spontaneous menstruation or induced withdrawal bleeding, patients initiated clomiphene citrate (50 mg, 100 mg, or 150 mg) or letrozole (2.5 mg, 5 mg, or 7.5 mg) between cycle days 2 to 5 for 5 days. Medication choice and medication dosage were determined by patient age, ovarian reserve testing, prior cycle outcomes, and provider or patient preference. Gonadotropin and natural cycles were excluded from analysis due to low number. Follicle growth was assessed with ultrasound 1 week after medication initiation and subsequently every two days as determined by follicle growth and patient availability. Cycles were cancelled if inadequate follicle growth was appreciated (with subsequent follow up ultrasounds), or if an inappropriately high number of follicles were identified. Ovulation was detected with use of ovulation predictor kits, or induced with Ovidrel® when follicle size reached a mean diameter of 22 mm and ovulation had not yet occurred. The infertility nurse provided patients with in-person training on ovulation predictor kit use. Following ovulation, couples initiated timed intercourse, or underwent IUI with partner or anonymous donor sperm. Timed intercourse was instructed to occur the evening of positive morning ovulation kit and the following evening. If ovulation was induced with Ovidrel®, couples were instructed to have intercourse the subsequent two evenings after administration. IUI was timed to the morning following a positive evening ovulation predictor kit or two mornings following Ovidrel® injection. Although IUI was advised for all couples with unexplained infertility, this treatment was not always possible due to patient financial constraints.

In vitro fertilization

Patients with PCOS or unexplained infertility who underwent IVF during the study period were identified. The cycle characteristics and fertility outcomes of these patients were evaluated.

Outcomes

The primary outcome was rate of conception. Conception was defined as a positive serum human chorionic gonadotropin level. Secondary outcomes included rate of biochemical pregnancy, miscarriage and ongoing pregnancy. Biochemical pregnancy was defined as conception with subsequent decline in human chorionic gonadotropin without ultrasound evidence of pregnancy (gestational sac with yolk sac). Miscarriage was defined as conception with ultrasound evidence of pregnancy and subsequent pregnancy loss. Ongoing pregnancy was defined as conception with ultrasound evidence of pregnancy and subsequent discharge from fertility practice.

Results

CUMC PCOS patient outcomes

Of 858 total COS cycles, 146 (17.0%) cycles were conducted in patients with a diagnosis of PCOS and 100 cycles were included in the analysis: 45 (45%) with clomiphene citrate, 47 (47%) with letrozole, 7 (7%) with gonadotropins and 1 (1%) using no ovulation induction medications **(Table 2)**. Fifty-nine percent of

Table 1 Audubon Practice Demographic Data.

		Audubon Practice ALL+ n= 858	Audubon Practice PCOS* n=100	Audubon Practice Unexplained Infertility* n=175
Age, years		34.5 ± 6.0	29.6 ± 6.2	33.9 ± 3.7
BMI, kg/m²		27.1 ± 5.32	28.6 ± 5.6	25.7 ± 4.6
Race	Asian	34 (4.0%)	3 (3%)	8 (4.6%)
	Black	49 (5.7%)	0	0
	White	131 (15.3%)	13 (13.0%)	16 (9.1%)
	NH/PI	9 (1.1%)	0	0
	Missing/Unknown	635 (80.2%)	84 (84%)	150 (85.7%)
Ethnicity	Hispanic	449 (52.3%)	59 (59%)	103 (58.9%)
	Not Hispanic	131 (15.3%)	3 (3%)	19 (10.9%)
	Missing/Unknown	278 (32.4%)	38 (38%)	53 (30.2%)
AMH, ng/mL		2.1 ± 2.88	6.2 ± 4.3	2.5 ± 1.5
FSH, mIU/mL		6.8 ± 3.74	5.4 ± 1.8	6.8 ± 2.3
AFC, follicle		16.7 ± 9.5	28.0 ± 5.6	16.3 ± 7.4
Ovulation Method	OPK	414 (48.3%)	36 (36%)	106 (60.6%)
	Ovidrel	243 (28.3%)	55 (55%)	52 (29.5%)
	Missing/Unknown	201 (23.4%)	9 (9%)	19 (10.9%)
Conception Method	TIC	501 (58.4%)	82 (82%)	124 (70.9%)
	IUI	184 (21.4%)	17 (17%)	50 (28.6%)
	dsIUI	59 (6.9%)	0	1 (0.6%)
	Missing/Unknown	114 (13.3%)	1 (1%)	0

Note BMI: Body Mass Index; NH/PI: Native Hawaiian/Pacific Islander; AMH : Anti-Müllerian Hormone; FSH: Follicle Stimulating Hormone; AFC: Antral Follicle Count; OPK: Ovulation Predictor Kit; TIC: Timed Inter Course; IUI: Intrauterine Insemination; dsIUI: Donor Sperm Intrauterine Insemination data are represented as mean ± standard deviation or n (% total).
+ Data includes patients will all infertility diagnoses treated with COS at the CUMC REI clinic at audubon practice between 2012 and 2016.
* All cycles included (clomiphene, letrozole, gonadotropin, natural cycles).

Table 2 Baseline characteristics of Columbia University Medical Center (CUMC) and Reproductive Medicine Network (RMN) cohorts with polycystic ovary syndrome (PCOS) and unexplained infertility.

PCOS PATIENTS								
		CUMC OVERALL+ n=100	CUMC Clomiphene n=45 (45%)	RMN Clomiphene n=376	p-value	CUMC Letrozole n=47 (47%)	RMN Letrozole n=374	p-value
Age (years)		29.6 ± 6.2	29.2 ± 4.8	28.8 ± 4.0	0.536[a]	29.2 ± 7.4	28.9 ± 4.5	0.693[a]
BMI (kg/m²)		28.6 ± 5.6	28.1 ± 5.6	35.1 ± 9.0	<0.001[a]	29.1 ± 5.6	35.2 ± 9.5	<0.001[a]
Hispanic		59 (59%)	30 (66.7%)	68 (18.1%)	<0.001[b]	24 (51.1%)	60 (16%)	<0.001[b]
Conception Method	TIC	83 (83%)	45 (100%)	376 (100%)		36 (76.6%)	374 (100%)	<0.001[b]
	IUI	17 (17%)	0	0		11 (23.4%)	0	<0.001[b]
	dsIUI	0	0	0		0	0	
UNEXPLAINED INFERTILITY PATIENTS								
		CUMC OVERALL+ n=175	CUMC Clomiphene n=110 (62.9%)	RMN Clomiphene n=300	p-value	CUMC Letrozole n=59 (33.7%)	RMN Letrozole n=299	p-value
Age (years)		33.9 ± 3.7	33.3 ± 3.8	32.0 ± 4.6	0.008[a]	34.8 ± 3.4	32.2 ± 4.3	<0.001[a]
BMI (kg/m²)		25.7 ± 4.6	25.9 ± 4.5	26.7 ± 6.4	0.229[a]	25.2 ± 4.9	27.3 ± 6.5	0.019[a]
Hispanic		103 (58.9%)	67 (60.9%)	30 (10.0%)	<0.001[b]	33 (55.9%)	35 (11.7%)	<0.001[b]
Conception Method	TIC	124 (70.9%)	80 (72.7%)	0	<0.001[b]	42 (71.2%)	0	<0.001[b]
	IUI	50 (28.6%)	29 (26.4%)	300 (100%)	<0.001[b]	17 (28.8%)	299 (100%)	<0.001[b]
	dsIUI	1 (0.6%)	1 (0.9%)	0	0.268[b]	0	0	

Note: BMI: Body Mass Index; TIC: Timed InterCourse; IUI: Intrauterine Insemination; dsIUI: Donor Sperm Intrauterine Insemination
Data are represented as mean ± standard deviation or n (% total).
+ All cycles included (clomiphene, letrozole, gonadotropin, natural cycles)
[a] Student's t-test
[b] Two-tailed Fisher's exact test

PCOS patients identified as Hispanic. Conception was attempted with TIC in 83 (83%) patients and with IUI in 17 (17%) patients. Conception was higher for PCOS patients following letrozole (19.1%) compared to clomiphene citrate (13.3%) **(Table 3)**. During the study period, 10 patients with PCOS pursued IVF, collectively undergoing 14 IVF cycles. These cycles resulted in 5 fresh embryo transfers and 4 frozen embryo transfers, with 6 (66.7%) transfers resulting in conception, and 4 (44.4%) ongoing pregnancies.

CUMC unexplained infertility patient outcomes

Of 858 total COS cycles, 183 (21.3%) cycles were conducted in patients with a diagnosis of unexplained infertility and 175 cycles were included for analysis: 110 (62.9%) with clomiphene citrate, 59 (33.7%) with letrozole, 4 (2.3%) with gonadotropins, and 2 (1.1%) using no COS medications. Fifty-nine percent of patients with unexplained infertility identified as Hispanic. Conception was attempted with TIC in 124 (70.9%) patients, with IUI in 50 (28.6%) patients, and with dsIUI in 1 (0.6%) patient. Conception was higher for unexplained infertility patients following clomiphene citrate (4.5%) compared to letrozole (0%). When analysis was limited to patients under age 35 receiving clomiphene citrate COS (n=66), conception rate remained low (n=3, 4.5%). When analysis was limited to patients undergoing clomiphene citrate COS with IUI or dsIUI (n=30), conception rate still remained low (n=2, 6.7%). During the study period, 5 patients with unexplained infertility pursued IVF, collectively undergoing 5 IVF cycles. These cycles resulted in 4 fresh embryo transfers, with 4 (100%) transfers resulting in conception, and 2 (50%) ongoing pregnancies.

Discussion

Critical analysis and reporting of current fertility outcomes in minority populations is a vital first step in order to address disparities in fertility health and infertility treatment. By contributing to the available knowledge on these populations, health care professionals, insurance providers and policy makers will have the data required to initiate and implement meaningful practice change. This study reports on the infertility treatment outcomes of an urban, predominantly Hispanic population, a minority group that is critically underrepresented in medical literature. We found that conception rates in this underinsured minority population were poor and were much lower than rates in multicenter trials using COS.

The PCOS patient cohort from the Reproductive Medicine Network (RMN) described in the 2014 New England Journal of Medicine (NEJM) trial [23] evaluated a predominantly (77-80%). Caucasian population that achieved a 27.4% conception rate following clomiphene citrate and a 41.2% conception rate following letrozole. Similarly, the unexplained infertility cohort from the Reproductive Medicine Network (RMN) described in the 2015 New England Journal of Medicine trial [24] evaluated a predominantly (79-81%) Caucasian population that achieved a 35.3% conception rate following clomiphene citrate and a 28.4% conception rate following letrozole. While there are many methodological differences between the RMN trials and our current study, the conception rates experienced by our predominantly Hispanic PCOS and unexplained infertility cohorts were far lower than expected, given these previously published cohorts.

In the RMN PCOS trial, TIC was used for all conception attempts, while in our patient population TIC was used 82% of the time. In the RMN unexplained infertility trial, IUI was used for all conception attempts, while in our patient population, only 29.1% of patients attempted conception with IUI or dsIUI. Even when

Table 3 Controlled ovarian stimulation (COS) cycle outcomes of Columbia University Medical Center (CUMC) and Reproductive Medicine Network in the polycystic ovary.

PCOS PATIENTS								
		CUMC OVERALL+ n=100	**CUMC Clomiphene n=45 (45%)**	**RMN Clomiphene n=376**	**p-value**	**CUMC Letrozole n=47 (47%)**	**RMN Letrozole n=374**	**p-value**
Conception		16 (16.0%)	6 (13.3%)	103 (27.4%)	0.047[a]	9 (19.1%)	154 (41.2%)	0.004[a]
Pregnancy Outcomes	Biochemical	1 (11.0%)	0	18 (9.7%)	0.587[a]	1 (11.1%)	29 (18.8%)	1.000[a]
	Ectopic	1 (11.0%)	1 (16.7%)	4 (3.9%)	0.251[a]	0	4 (2.6%)	1.000[a]
	Miscarriage	3 (18.8%)	0	30 (29.1%)	0.185[a]	2 (22.2%)	49 (31.8%)	0.721[a]
	Ongoing	11 (68.8%)	5 (83.3%)	81 (78.6%)	1.000[a]	6 (66.7%)	117 (76.0%)	0.690[a]
UNEXPLAINED INFERTILITY PATIENTS								
		CUMC OVERALL+ n=175	**CUMC Clomiphene n=110 (61.2%)**	**RMN Clomiphene n=300**	**p-value**	**CUMC Letrozole n=59 (33.7%)**	**RMN Letrozole n=299**	**p-value**
Conception		7 (4.0%)	5 (4.5%)	106 (35.3%)	<0.001[a]	0	85 (28.4%)	<0.001[a]
Pregnancy Outcomes	Biochemical	1 (14.3%)	1 (20.0%)	14 (4.7%)	0.224[a]	0	13 (4.3%)	1.000[a]
	Ectopic	0	0	5 (1.7%)	1.000[a]	0	5 (1.7%)	1.000[a]
	Miscarriage	0	0	10 (3.3%)	1.000[a]	0	8 (7.7%)	1.000[a]
	Ongoing	6 (85.7%)	4 (80.0%)	85 (28.3%)	1.000[a]	0	67 (22.4%)	1.000[a]

Syndrome (PCOS) and unexplained infertility cohorts.
Data are represented as n (% total).
+ All cycles included (clomiphene, letrozole, gonadotropin, natural cycles)
a Two-tailed Fisher's exact test

TIC cycles were excluded, conception rates remained poor. Patients in our unexplained infertility cohort were on average older than patients in the RMN cohort. When analysis was limited to patients under 35 years, outcomes remained poor, though the very low number of patients with conception limits this extrapolation. Interestingly, although our patient cohort demonstrated lower BMI than the RMN cohorts, often associated with improved conception rates, this did not portend favorable outcomes for our patients.

Reviewing our clinical experiences, we wondered if our practice patterns might have contributed to poorer outcomes. For example, our older patients with unexplained infertility did more COS cycles than would be recommend in standard practice. The Group Health Incorporated insurance provides ART coverage following 3 unsuccessful IUI if women are over 35 years of age. Our patients over the age of 35 years with unexplained infertility underwent a mean of 3.9 COS cycles during the study period. Numerous exceptions also occurred. For example, one patient underwent 11 COS cycles with clomiphene citrate, letrozole and gonadotropins before accruing enough resources to pursue IVF. Unfortunately, the vast majority of our patients ultimately never pursued IVF, or were lost to follow up, if no conception occurred after multiple cycles of COS. These additional cycles with poor prognosis may have altered our overall conception rates. It is well known that socioeconomic disparities contribute to limited access and use of infertility treatments, especially costly ART services [5,25-30]. Our patients were similarly limited by the expense of ART – while many patients desired or required IVF to achieve optimal fertility, few patients were ultimately able to pursue ART due to financial constraints. These restrictions are likely attributable to the limited access to care that affects all low socioeconomic populations.

Multiple other factors may account for the differences in outcomes between our underinsured minority population and the RMN cohorts. For example, while access to care limits healthcare for minorities living in remote locations [10,11]. Even a location within the metropolitan of New York City experienced similar disparities in access to care. Patients miss appointments due to lengthy commutes on public transportation, delays and cancellations in public transportation, uncompromising employers who limit work absences, and inadequate childcare coverage for appointments. We estimate that as many as one third of our patients were unable to comply with optimal cycle management – wither attending multiple appointments for improved follicle monitoring, using Ovidrel® instead of ovulation predictor kits, or undergoing IUI instead of timed intercourse – due to their socioeconomic status. Thus, patients attended fewer medical appointments, resulting in fewer opportunities for preventative intervention of general medical conditions, delayed or suboptimal treatment of existing medical conditions, and delayed referral to subspecialist providers. In addition to inadequate access to general medical care and fertility treatments, disparities in health literacy may also contribute to differences in treatment outcomes [9] Lower education and health literacy may limit these patients' comprehension of their medical condition, its overall health impact, and available treatment options. This limited comprehension impacts treatment compliance and may negatively influence treatment outcome. Language differences between providers and patients, even with the use of certified medical translation services, may compound these differences [31].

When our patients pursued IVF, conception and ongoing pregnancy rates were high and similar to national averages: 66.7% of PCOS patients and 100% of patients with unexplained infertility achieved conception following embryo transfer, though our low numbers limit generalizability. While the improved outcomes with IVF are expected compared to alternative fertility treatment methods, additional improved success may reflect closer ultrasound and serum monitoring that occurs during the IVF process, in addition to higher patient motivation and compliance with treatment and follow up. Herndon et al. [3] described a novel low-cost IVF program aiming to bridge the access and financial gaps in ART services for low resource populations. The group not only demonstrated feasibility of low-cost ART through four low-stimulation protocols, but also achieved promising pregnancy outcomes, citing a 29% cumulative live birth rate [3]. Thus, fertility providers treating underserved populations should be proactive in encouraging patients to pursue IVF when possible, and may consider cost-effective ART protocols to achieve pregnancy in low-resource populations. Moreover, healthcare networks and insurance providers will benefit from further evaluating the efficacy and cost-savings of alternative ART regimens for different socioeconomic populations.

The authors acknowledge there are limitations to this study. First, the inherent limitations as a retrospective review and the small sample size may limit the wider application of these study findings. We also note that a significant amount of racial demographic information for our patient cohort is either missing or unknown. We believe this is related to inadequate demographic surveys in which patients of Hispanic descent consider "Hispanic" to be their identifying race over "White," "Black," or "Other." In preparation for the 2020 Census, the United States Census Bureau is considering combining race and ethnicity divisions under the following categories: White, Hispanic/Latino/Spanish, Black/African American, Asian, American Indian/Alaskan Native, Middle Eastern/North African, Native Hawaiian/Other Pacific Islander, Other Race/Ethnicity/Origin [32,33]. This is supported by the fact that more patients identified as either "Hispanic" or "Not Hispanic" than a specific race. Additionally, the inclusion of patients undergoing greater than 3 COS cycles may be lowering the overall conception rate. If these patients were able to access IVF sooner, conception rates for the COS cohort may have been modestly higher.

This study highlights discrepancies in access to and use of care such as IVF in low-income, low-resource settings and potentially identifies ethnic differences in response to COS. It is our hope that these findings may prompt larger epidemiologic and prospective investigation to clarify ethnic differences in fertility care and outcomes. Providers should be cognizant of the limitations of COS in underserved populations. When possible, providers should consider encouraging these patients to proceed with IVF, or to

conserve resources to ultimately pursue IVF, if pregnancy has not been achieved within a predetermined number of COS cycles. Low-cost ART services offer a promising adjunct to traditional ART treatment that may bridge gaps in access and use of fertility care in minority populations.

References

1 Chandra A, Copen C, Stephen E (2013) Infertility and imparied fecundity in the United States: data from the national survey of family growth.

2 Steptoe P, Edwards R. (1978) Birth after the reimplantation of a human embryo. The Lancet 312: 366.

3 Herndon C, Anaya Y, Noel M, Cakmak H, Cedars M (2017) Outcomes from a university-based low-cost in vitro fertilization program providing access to care for a low-resource socioculturally diverse urban community. Fertil Steril 108: 642-649

4 Quinn M, Fujimoto V (2016) Racial and ethnic disparities in assisted reproductive technology access and outcomes. Fertil Steril 105: 1119-1123.

5 Dieke A, Zhang Y, Kissin D, Barfield W, Boulet S (2017) Disparities in assisted reproductive technology utilization by race and ethnicity, United States: a commentary. J Womens Health26: 605-608.

6 Fujimoto V, Luke B, Brown M (2010) Racial and ethnic disparities in assisted reproductive technology outcomes in the United States. Fertil Steril 93: 382-390.

7 Kissin D, Boulet S, Jamieson D (2016) Team ARTSaR Fertility treatments in the United States: improving access and outcomes. Obstet Gynecol 128: 387-390.

8 (2015) Medicine ECotASfR. Disparities in access to effective treatment for infertility in the United States: an Ethics Committee opinion. Fertil Steril 104: 1104-1110.

9 Healthy People 2020: An opportunitiy to address societal determinants of health in the United States (2010).

10 Prevention CfDCa. CDC health disparities and inequalities report — United States Morb Mortal Wkly Rep 62: 7-32 (2013).

11 Huddleston H, Cedars M, Sohn S, Giudice L, Fugimoto V (2010) Racial and ethnic disparities in reproductive endocrinology and infertility. Am J Obstet Gynecol 202: 413-419.

12 Kreisel K, Torrone E, Bernstein K, Hong J, Gorwitz R (2017) Prevalence of pelvic inflammatory disease in sexually experienced women of reproductive age -United States MMWR Morb Mortal Wkly Rep 66: 80-83.

13 (2015) Sexually transmitted diseases surveillance: STDs in racial and ethnic minorities.

14 Stephen E, Chandra A (2006) Declining estimates of infertility in the United States: Fertil Steril 86: 516-523.

15 Sutton M, Sternberg M, Zaidi A, Louis MS, Markowitz L (2005) Trends in pelvic inflammatory disease hospital discharges and ambulatory visits United States Sex Transm Dis 32.

16 Shuler A, Rodgers A, Budrys N, Holden A, Schenken R, et al. (2011) In vitro fertilization outcomes in Hispanics versus non-Hispanic whites. Fertil Steril 95: 2735-2737.

17 Boulet S, Crawford S, Zhang Y (2015) Embryo transfer practices and perinatal outcomes by insurance mandate status. Fertil Steril 104: 403-409.

18 Chambers G, Hoang V, Sullivan E (2014) The impact of consumer affordability on access to assisted reproductive technologies and embryo transfer practices: an international analysis. Fertil Steril 101: 191-198.

19 Chambers G, Sullivan E, Ishihara O, Chapman M, Adamson G (2009) The economic impact of assisted reproductive technology: a review of selected developed countries. Fertil Steril 91: 2281-2294.

20 Infertility Demonstration Program (2014).

21 Group REA-SPCW (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 81: 19-25.

22 Cooper TG, Noonan E, von Eckardstein S (2010) World Health Organization reference values for human semen characteristics. Hum Reprod Update 16: 231-245.

23 Legro R, Brzyski R, Diamond M (2014) Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med 371: 119-29.

24 Diamond M, Legro R, Coutifaris C (2015) Letrozole, gonadotropin, or clomiphene for unexplained infertility. N Engl J Med 373: 1230-1240.

25 Becker G, Castrillo M, Jackson R, Nachtigall R (2006) Infertility among low-income Latinos. Fertil Steril 85: 882-887.

26 Macaluso M, Wright-Schnapp T, Chandra A (2010) A public health focus on infertility prevention, detection, and management Fertil Steril 93: 1-10.

27 Nachtigall R (2006) International disparities in access to infertility services. Fertil Steril 85: 871-875.

28 Nargund G (2009) Natural/mild assisted reproductive technologies: reducing cost and increasing safety. Womens Health 5: 359-360.

29 Nargund G, Frydman R (2007) Toward a more physiologic approach to IVF. Reprod Biomed Online 14: 550-552.

30 Verberg M, Eijkemans M, Macklon N (2009) The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis. Hum Reprod Update 15: 5-12.

31 Napoles A, Santoyo-Olsson J, Karliner L, Gregorich S, Perez-Stable E (2015) Inaccurate language interpretation and its clinical signficance in the medical encounters of Spanish-speaking Latinos. Med Care 53: 940-947.

32 National Content Test: Race and Ethnicity Analysis Report. 2017

33 Harris P, Thielke R, Taylor R, Payne J, Gonzalez N, et al. (2009) Research Electronic Data Capture - a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42: 377-381.