GYNECOLOGY

The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization

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BACKGROUND: It is critical to evaluate the combined impact of age and body mass index on the cumulative likelihood of live birth following in vitro fertilization, as achieving a lower body mass index before infertility treatment often is recommended for women with overweight and obesity. It is important to consider whether achieving a particular body mass index, thus resulting in an older age at in vitro fertilization cycle start, is beneficial or harmful to the likelihood of live birth.

OBJECTIVES: To evaluate the combined impact of age and body mass index on the cumulative live birth rate following in vitro fertilization to inform when delaying in vitro fertilization treatment to achieve a lower body mass index may be beneficial or detrimental to the likelihood of live birth.

STUDY DESIGN: This is a retrospective study using linked fresh and cryopreserved/frozen cycles from January 2014 to December 2015 from the Society for Reproductive Technology Clinic Outcome Reporting System, representing >90% of in vitro fertilization cycles performed in the United States. The primary outcome was live birth as measured by cumulative live birth rate. Secondary outcomes included implantation rate, clinical pregnancy rate, and miscarriage rate. Poisson and logistic regression were used to calculate risk and odds ratios with 95% confidence intervals to determine differences in implantation, clinical pregnancy, and miscarriage, as appropriate, among first fresh in vitro fertilization cycles compared across age (years) and body mass index (kg/m^2) categories. Cox regression was used to calculate hazard ratios with 95% confidence intervals to determine differences in the cumulative live birth rate using fresh plus linked frozen embryo transfer cycles.

RESULTS: There were 51,959 first fresh cycles using autologous eggs and 16,067 subsequent frozen embryo transfer cycles. There were 21,395 live births, for an overall cumulative live birth rate of 41.2% per cycle start. The implantation rate, clinical pregnancy rate, and cumulative live birth rate decreased with increasing body mass index and age, and the miscarriage rate increased with increasing body mass index and age (linear trend $P<.001$ for all). Body mass index had a greater influence on live birth at younger ages as compared with older ages.

CONCLUSIONS: Age-related decline in fertility has a greater impact than body mass index on the cumulative live birth rate at older ages, suggesting that taking time to achieve lower body mass index before in vitro fertilization may be detrimental for older women with overweight or obesity. Delaying conception to lose weight before in vitro fertilization should be informed by the combination of age and body mass index.

Key words: body mass index, cumulative live birth rate, in vitro fertilization, infertility, maternal age, obesity

Obesity has become increasingly prevalent among women of reproductive age.[1–5] In addition to having greater risks of cardiovascular disease and diabetes, women with obesity are more likely than women of normal weight to experience sequelae of polycystic ovary syndrome, with menstrual cycle irregularity, delayed time to conception, and infertility.[6–12] Although data are mixed, most studies have found that among women undergoing in vitro fertilization (IVF), obesity has been associated with the need for greater doses of gonadotropins, as well as lower implantation, pregnancy, and live birth,

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and increased risks of cycle cancellation and miscarriage.[13–19] As a result, weight loss often is recommended for women with overweight and obesity who have difficulty conceiving, as data suggest that it may improve menstrual cyclicity and ovulation, reduce hyperinsulinemia, decrease leptin levels, and improve IVF outcomes.[9,20–23] Studies have found that modest weight loss of 5%–10% may improve fertility by increasing ovulation and spontaneous pregnancy rates.[24–26] In a prospective cohort study of 87 infertile women with obesity, those who decreased their BMI between 3 and 4 units over a 6-month period demonstrated improved fertility; however, women whose BMI remained greater than 40 after weight loss did not.[24]

It has been suggested that treatment for infertility in women with obesity be deferred pending weight loss to a BMI <35, or <30 for women with good prognosis (<37 years old with normal ovarian reserve parameters).[25] However, data have been mixed regarding the impact of weight loss on IVF outcomes, and a recent randomized controlled trial of weight reduction for women with obesity and infertility before IVF did not find that achieving a lower BMI significantly improved the live birth rate following IVF.[27,28] In that study, which only included women with BMI between 30 and 35, there were no improvements in the live birth rate following IVF among women who lost weight (average weight loss =14.5 pounds) compared with those who started IVF immediately, even among women who achieved BMI ≤25 or a 5-unit reduction in BMI over 4 months.[27] A recent randomized prospective pilot study found that among women with BMI 30–40, an average weight loss of 7% over 12 weeks improved the

AJOG at a Glance

Why was this study conducted?

Lowering body mass index before infertility treatment often is recommended for women with overweight and obesity. It is important to consider whether achieving a lower body mass index, thus resulting in an older age at in vitro fertilization cycle start, is beneficial or harmful to the likelihood of live birth.

Key findings

Cumulative live birth rate following in vitro fertilization is influenced by the combination of age and body mass index. Body mass index has a greater influence on live birth at younger ages.

What does this add to what is known?

If older patients with infertility and obesity desire childbearing, proceeding with in vitro fertilization rather than waiting to achieve a lower body mass index may increase the likelihood of live birth. The combination of age and body mass index should be considered.

cumulative pregnancy rate compared with women who started IVF treatment immediately; however, sample sizes were limited (n=41), there was no significant difference in BMI among groups after weight decrease in the intervention group, and BMI after weight loss was not clearly reported.[28]

There may be women with infertility for whom losing weight will ultimately be detrimental to their success with IVF due to the time it takes to achieve weight loss, resulting in an older age at IVF cycle start. Female age is directly related to embryonic aneuploidy, which rises steadily after age 30 years and exhibits a sharper increase after age 35.[29] As maternal age at IVF cycle start increases, pregnancy and live birth rates decrease, whereas the miscarriage rate increases.[30,31] For example, in 2015, the cumulative live birth rates (CLBRs) for women <35 years, 35−37 years, and 38−40 years were 42.4%, 32.7%, and 21.9%, respectively.[32]

It is important to consider whether achieving a particular BMI, thus resulting in an older age at IVF cycle start, is beneficial or harmful to the likelihood of live birth. The purpose of the present study is to determine the age and BMI combinations at which an age-related fertility decline may outweigh potential improvements in cumulative IVF live birth rates associated with lower BMIs, which typically takes months to years to achieve.

Materials and Methods

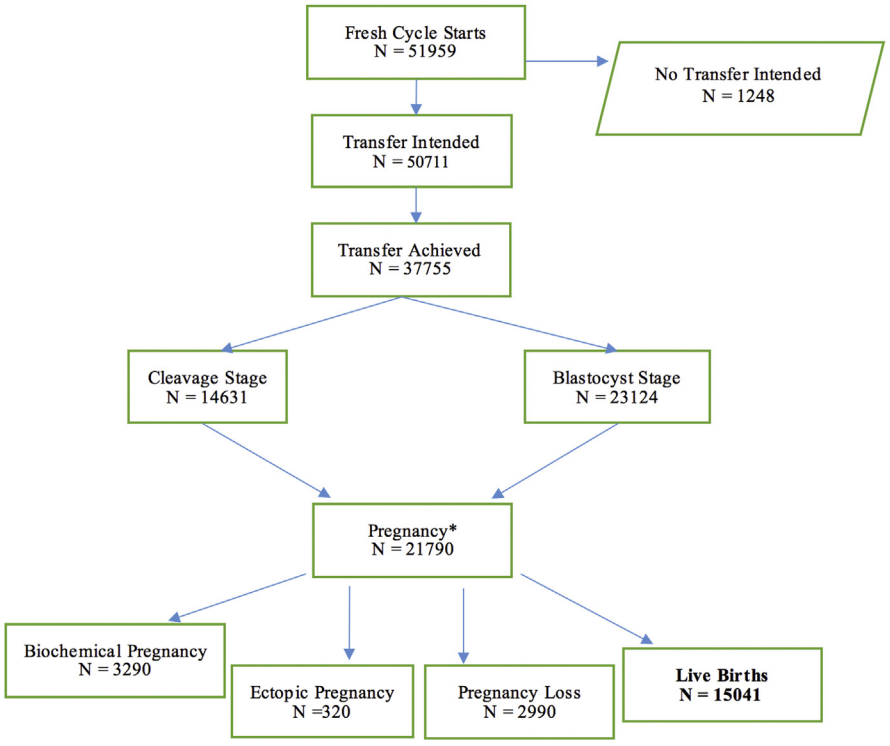
People-first language (eg, "women with overweight") will be used throughout this manuscript instead of condition-first language (eg, "overweight women"), as supported by American College of Obstetricians and Gynecologists and the Obesity Action Coalition, to support the mitigation of obesity bias within the medical literature.[33-35] Comprehensive demographic and outcome data from both fresh and frozen IVF cycles performed by infertility clinics in the United States and Puerto Rico between January 2014 to December 2015 were obtained from the Society for Reproductive Technology (SART) Clinic Outcome Reporting System. This includes data from 371 of all 464 infertility clinics in the United States and Puerto Rico in 2015, representing >90% of IVF cycles performed. Fresh IVF cycles and all subsequent frozen IVF cycles using embryos obtained from the fresh cycles were linked by SART and provided to the investigators to calculate cumulative live birth per fresh egg retrieval within the study's time frame. The 2014 reporting year was the first year that allowed for such linkages.

Inclusion criteria were the first fresh autologous IVF and intracytoplasmic sperm injection cycles that started in 2014 (N=51,959), plus all additional frozen embryo transfer (FET) cycles (N=16,067). Cycles were excluded if there was no diagnosis of infertility, including cycles that were performed for fertility preservation for a malignancy or other systemic disease, or for preimplantation genetic testing without infertility. Long-term oocyte or embryo banking cycles, donor egg, and gestational carrier cycles also were excluded.

Poisson regression was used to calculate risk ratios (RRs) with 95% confidence intervals (CIs) for implantation, and logistic regression was used to calculate odds ratios (ORs) with 95% CIs for clinical pregnancy, miscarriage, ectopic pregnancy, biochemical pregnancy, and multiple pregnancy among first fresh IVF cycles compared across age (years) and BMI (kg/m^2) categories at cycle start. For these analyses, cycles in which a fresh transfer was not planned at cycle start were excluded (eg, if a cycle was planned for embryo banking, preimplantation genetic testing, or subsequent FETs). The following variables were defined as per SART criteria. The implantation rate was defined as the number of fetal heartbeats/number of embryos transferred. Clinical pregnancy was defined as a documented intrauterine gestational sac. Biochemical pregnancy was defined as a positive pregnancy test without evidence of an intrauterine gestational sac. Miscarriage was defined as loss of a previously documented clinical pregnancy before 20 weeks' gestation. Ectopic pregnancy was defined as an ultrasound-documented gestational sac outside of the uterine cavity or pathologic evidence of an extrauterine pregnancy.

Cox regression was used to calculate hazard ratios (HRs) with 95% CIs to determine differences in the CLBR across age and BMI categories. Embryos created during a fresh IVF stimulation cycle can be transferred during that same fresh cycle, or can be cryopreserved for use in a future frozen/thawed embryo transfer (FET) cycle. The CLBR is defined as the live birth rate following a first fresh IVF cycle plus all additional frozen embryo cycles in which the transferred embryo was created at the time of the fresh IVF stimulation.[36,37] In other words, the CLBR captures the live birth rate over a treatment period by

FIGURE 1
Flowchart of IVF outcomes following 51,959 first fresh autologous cycles



IVF outcomes following the 51,959 first fresh cycles using autologous eggs in 2014, of which 50,711 were intended for a fresh transfer. There were 15,041 live births, resulting in an overall live birth rate of 39.8% among first fresh embryo transfers (29.7% among fresh cycle starts). There were 16,067 subsequent FET cycles from 2014 to 2015 resulting in 6354 additional live births, for an overall CLBR of 41.2% among fresh cycle starts. *Includes all pregnancies. This value includes cycles with missing pregnancy outcome data.

CLBR, cumulative live birth rate; *FET*, frozen embryo transfer; *IVF*, in vitro fertilization.

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

including outcomes from both fresh transfers and FETs, including cycles for which the primary transfer was an FET. Once a woman achieved a live birth, her future cycles were censored. For all analyses, age categories included: <30, 30−34, 35−37, 38−40, 41−42, and >42 years. BMI (kg/m^2) stratifications included: underweight (<18.5), normal weight (18.5−24.9), overweight (25.0−29.9) class I obesity (30.0−34.9), class II obesity (35.0−39.9), class III obesity (40.0−44.9), morbid obesity (45.0-49.9), and super obesity (≥50). Age <30 years and normal BMI (BMI=18.5−24.9) were considered referent groups. In multivariable models, statistical adjustments were made for age, BMI, smoking, history of previous IVF cycles, number of embryos transferred, blastocyst embryo transfer, and embryo grade, where indicated. Adjusting for anti-Müllerian hormone (AMH) had minimal impact on the results, and AMH data were missing for 43% of cycles; the final models were therefore not adjusted for AMH. A cross-tabulated referent table for CLBR by individual year of age and BMI category was created for patients and clinicians to gain insight into the possible detriment to the likelihood of live birth if IVF is delayed to achieve a lower BMI. All analyses were performed using Statistical Analysis Software (SAS), version 9.3 (SAS Institute, Inc, Cary, NC). The study was approved by the SART Research Committee and found to be institutional review board exempt by the Partners HealthCare Institutional Review Board.

Results

There were 51,959 first fresh cycles using autologous eggs in 2014, of which 50,711 were intended for a fresh transfer (Figure 1). Of 37,755 fresh transfers, 23,124 (61%) occurred at the blastocyst stage and 14,631 (39%) occurred at the cleavage stage. There were 15,041 live births, resulting in an overall live birth rate of 39.8% among first fresh embryo transfers (29.7% among fresh cycle starts). There were 16,067 subsequent FET cycles from 2014 to 2015, resulting in 6354 additional live births, for an overall CLBR of 41.2% among fresh cycle starts.

Demographic characteristics for patients undergoing a first fresh cycle in 2014 are shown in Table 1. In summary, most women undergoing IVF were between the ages of 30 and 40 years. The majority of women had a normal (n=27,304, 52.5%) or overweight BMI (25.0−29.9 kg/m^2; n=12,775 [24.6%]). Nearly one half (n=23,294, 44.8%) of women had overweight or obesity, with 1487 (2.9%) of women being classified as having Class III obesity (BMI ≥40), and 114 (0.2%) being classified as having super obesity (BMI ≥50). Infertility diagnoses, AMH values, and gravidity/parity were similar across BMI categories. Women with obesity had fewer oocytes retrieved and fewer zygotes (normally fertilized eggs) than women with normal weight, and women with BMI ≥40 had fewer blastocyst embryo transfers than women with lower BMIs. The number of embryos transferred did not vary by BMI category.

IVF outcomes stratified by BMI category are shown in Table 2. The implantation rate, clinical pregnancy rate, and CLBR decreased with increasing BMI (linear trend $P<.001$ for all). A significant decrease in implantation rate was seen among both cleavage and blastocyst transfers as BMI category increased, and this decrease became more pronounced among greater BMI categories. For example, compared with normal-weight women (referent), women with BMI 30.0−34.9, 40.0−44.9, and ≥50 had

TABLE 1
Demographic characteristics for 51,959 first fresh IVF cycles started in 2014, representing data from >90% of IVF cycles in the United States and Puerto Rico

	BMI, kg/m^2							
Variables	<18.5 Underweight n=1379	18.5–24.9 Normal weight n=27,304	25.0–29.9 Overweight n=12,775	30.0–34.9 Class I obesity n=6030	35.0–39.9 Class II obesity n=2984	40.0–44.9 Class III obesity n=1027	45.0–49.9 morbid obesity n=346	≥50.0 super obesity n=114
Age at IVF cycle start, y								
<30 (n=6883)	199 (14.4%)	3606 (13.2%)	1654 (12.9%)	823 (13.6%)	419 (14.0%)	128 (12.5%)	42 (12.1%)	12 (10.5%)
30–34 (n=17,449)	518 (37.6%)	9501 (34.8%)	4154 (32.5%)	1859 (30.8%)	942 (31.6%)	331 (32.2%)	110 (31.8%)	34 (29.8%)
35–37 (n=11,080)	297 (21.5%)	5751 (21.1%)	2742 (21.5%)	1299 (21.5%)	640 (21.4%)	229 (22.3%)	93 (26.9%)	29 (25.4%)
38–40 (n=9229)	202 (14.6%)	4644 (17.0%)	2359 (18.5%)	1165 (19.3%)	583 (19.5%)	193 (18.8%)	55 (15.9%)	28 (24.6%)
41–42 (n=4402)	104 (7.5%)	2258 (8.3%)	1140 (8.9%)	533 (8.8%)	242 (8.1%)	89 (8.7%)	29 (8.4%)	7 (6.1%)
>42 (n=2916)	59 (4.3%)	1544 (5.7%)	726 (5.7%)	351 (5.8%)	158 (5.3%)	57 (5.6%)	17 (4.9%)	4 (3.5%)
Infertility diagnosis								
Unexplained	250 (16.6%)	5060 (17.1%)	1926 (14.1%)	770 (12.1%)	343 (10.9%)	103 (9.6%)	39 (10.8%)	13 (11.0%)
Male factor	537 (35.6%)	11195 (37.8%)	5471 (40.1%)	2529 (39.6%)	1253 (39.9%)	432 (40.3%)	133 (36.7%)	51 (43.2%)
Tubal factor	157 (10.4%)	3847 (13.0%)	2483 (18.2%)	1292 (20.2%)	646 (20.5%)	179 (16.7%)	58 (16.0%)	21 (17.8%)
OD/PCOS	207 (13.7%)	3830 (12.9%)	1978 (14.5%)	1372 (21.5%)	919 (29.2%)	379 (35.3%)	140 (38.7%)	42 (35.6%)
Endometriosis	200 (13.2%)	3292 (11.1%)	1386 (10.2%)	519 (8.1%)	241 (7.7%)	68 (6.3%)	18 (5.0%)	6 (5.1%)
DOR	498 (33.0%)	9133 (30.8%)	3914 (28.7%)	1685 (26.4%)	738 (23.5%)	259 (24.1%)	83 (22.9%)	28 (23.7%)
Uterine	77 (5.1%)	1685 (5.7%)	845 (6.2%)	421 (6.6%)	210 (6.7%)	76 (7.1%)	13 (3.6%)	5 (4.2%)
Gravidity	0.89 (1.28)	0.95 (1.28)	1.08 (1.41)	1.15 (1.47)	1.1 (1.46)	1.02 (1.43)	0.94 (1.34)	0.85 (1.36)
Parity	0.71 (0.82)	0.68 (0.81)	0.75 (0.94)	0.8 (1.01)	0.69 (0.92)	0.7 (0.90)	0.56 (0.72)	0.74 (0.96)
AMH, ng/mL	2.57 (2.59)	2.48 (2.71)	2.47 (2.65)	2.53 (2.74)	2.72 (2.98)	2.42 (2.91)	2.34 (2.46)	2.11 (2.47)
Protocol								
Antagonist	358 (25.9%)	7404 (26.8%)	3549 (27.5%)	1655 (27.2%)	809 (26.9%)	284 (27.7%)	91 (26.2%)	33 (28.9%)
Agonist	161 (11.6%)	2917 (10.6%)	1391 (10.8%)	676 (11.1%)	314 (10.5%)	125 (12.2%)	57 (16.4%)	11 (9.6%)
Flare	864 (62.5%)	17319 (62.7%)	7946 (61.7%)	3751 (61.7%)	1880 (62.6%)	615 (60.1%)	199 (57.3%)	70 (61.4%)
Gonadotropin dose	31.97 (23.54)	33.16 (31.73)	33.71 (25.45)	34.03 (18.36)	35.37 (23.59)	36.59 (17.05)	38.01 (16.71)	40.08 (19.89)
ICSI (yes)	1044 (69.1%)	20368 (68.7%)	9482 (69.5%)	4338 (67.9%)	2129 (67.7%)	752 (70.1%)	248 (68.5%)	81 (68.6%)
No. eggs retrieved	12.78 (8.81)	13.06 (8.63)	12.87 (8.34)	13.03 (8.30)	12.66 (8.20)	11.73 (8.06)	10.62 (7.52)	9.65 (6.21)
No. 2PN embryos	7.61 (5.80)	7.84 (21.53)	7.44 (5.61)	7.57 (5.53)	7.26 (5.49)	6.75 (5.02)	5.92 (4.92)	5.69 (3.88)

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

(continued)

TABLE 1
Demographic characteristics for 51,959 first fresh IVF cycles started in 2014, representing data from >90% of IVF cycles in the United States and Puerto Rico
(continued)

Variables	BMI, kg/m^2							
	<18.5 Underweight n=1379	18.5–24.9 Normal weight n=27,304	25.0–29.9 Overweight n=12,775	30.0–34.9 Class I obesity n=6030	35.0–39.9 Class II obesity n=2984	40.0–44.9 Class III obesity n=1027	45.0–49.9 morbid obesity n=346	≥50.0 super obesity n=114
Transfer								
Cleavage-stage	292 (37.2%)	6105 (37.7%)	2882 (37.8%)	1353 (36.7%)	700 (38.7%)	277 (46.2%)	99 (48.8%)	41 (53.9%)
Blastocyst	492 (62.8%)	10071 (62.3%)	4746 (62.2%)	2330 (63.3%)	1107 (61.3%)	322 (53.8%)	104 (51.2%)	35 (46.1%)
No. embryos transferred	1.79 (0.78)	1.86 (0.79)	1.92 (0.78)	1.95 (0.81)	1.93 (0.79)	2.03 (0.83)	1.93 (0.80)	1.98 (0.74)

AMH, anti-mullerian hormone; *BMI*, body mass index; *DOR*, diminished ovarian reserve; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization; *OD*, ovulatory dysfunction; *PCOS*, polycystic ovary syndrome.
Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

progressively lower implantation rates (RR, 0.96; CI, 0.88–0.96; RR, 0.82; CI, 0.74–0.91; RR, 0.51; CI, 0.35–0.74), respectively. No statistically significant difference in implantation rate was seen between women with normal weight and underweight. Similar trends were seen for clinical pregnancy rates when data were analyzed per cycle start and per embryo transfer. The clinical pregnancy rate per cycle start was lower among women with underweight compared with women with normal weight (OR, 0.87; CI, 0.77–0.98). The likelihood of miscarriage increased with BMI. For example, compared with women with normal weight, women with BMI 40.0-44.9 had an OR (CI) of miscarriage of 1.71 (1.31–2.25). No differences in ectopic pregnancy or multiple pregnancy rates were seen. The CLBR decreased progressively as BMI category increased above normal. For example, compared with women of normal weight, women with overweight (BMI 25.5–29.9), Class III obesity (BMI 40.0–44.9), and super obesity (BMI ≥50) had progressively lower CLBR (hazard ratio [HR], 0.96; CI, 0.93–0.99; HR, 0.76; CI, 0.68–0.85; and HR, 0.41; CI, 0.26–0.63), respectively.

IVF outcomes stratified by age category are shown in Table 3. The implantation rate, clinical pregnancy rate, and CLBR decreased with age, and the miscarriage rate increased with age (linear trend $P<.001$ for all) for both cleavage-stage and blastocyst embryo transfers. Statistically significant decreases in implantation, clinical pregnancy, and cumulative live birth as well as increases in miscarriage were seen in each age category beyond the youngest group (<30 years: referent). The multiple pregnancy rate decreased with age. There were no differences in ectopic pregnancy or biochemical pregnancy among cycles resulting in a transfer.

The CLBR for each age and BMI combination is shown in Table 4. Within each BMI category, the CLBR decreased with age. Similarly, for any given age, the CLBR decreased as the BMI category increased above normal (18.5–24.9 kg/m^2: referent). For example, a 30-year-old woman with normal BMI, Class II

TABLE 2
IVF outcomes by BMI category among 51,959 first fresh IVF cycles started in 2014, representing data from >90% of IVF cycles in the United States and Puerto Rico

	BMI, kg/m^2								
	<18.5 Underweight	18.5–24.9 Normal weight	25.0–29.9 Overweight	30.0–34.9 Class I obesity	35.0–39.9 Class II obesity	40.0-44.9 Class III obesity	45.0-49.9 Morbid obesity	≥50 Super obesity	*P*value test for linear trend
Implantation rate[a,b]									
Cleavage-stage	118/361 (32.7%)	2477/7498 (33.0%)	1144/3636 (31.5%)	562/1728 (32.5%)	246/877 (28.1%)	102/360 (28.3%)	29/123 (23.6%)	9/48 (18.8%)	
Blastocyst	310/593 (52.3%)	6576/12,083 (54.4%)	2962/5750 (51.5%)	1355/2792 (48.5%)	671/1339 (50.1%)	185/396 (46.7%)	52/130 (40.0%)	14/41 (34.2%)	
RR (95% CI)									
Crude	0.99 (0.91–1.08)	ref	0.94 (0.91–0.97)	0.89 (0.85–0.93)	0.87 (0.82–0.93)	0.78 (0.71 -0.87)	0.69 (0.57–0.83)	0.50 (0.35–0.73)	<.001
Adjusted	0.96 (0.88–1.05)		0.95 (0.92–0.99)	0.92 (0.88–0.96)	0.88 (0.83–0.94)	0.82 (0.74–0.91)	0.70 (0.58–0.84)	0.51 (0.35–0.74)	
Clinical pregnancy rate[a]									
Cleavage-stage	127/361 (35.2%)	2739/7498 (36.5%)	1257/3636 (34.6%)	605/1728 (35.0%)	275/877 (31.4%)	110/360 (30.6%)	35/123 (28.5%)	9/48 (18.8%)	
Blastocyst	336/593 (56.7%)	7028/12,083 (58.2%)	3171/5750 (55.2%)	1476/2792 (52.9%)	728/1339 (54.4%)	207/396 (52.3%)	57/130 (43.9%)	15/41 (36.6%)	
OR (95% CI)									
Crude	0.95 (0.83–1.08)	ref	0.90 (0.85–0.94)	0.86 (0.80–0.91)	0.83 (0.76–0.91)	0.73 (0.63–0.84)	0.57 (0.44–0.74)	0.37 (0.23–0.59)	<.001
Adjusted	0.93 (0.81–1.07)		0.90 (0.85–0.95)	0.85 (0.80–0.91)	0.83 (0.75–0.91)	0.76 (0.65–0.89)	0.60 (0.46–0.79)	0.39 (0.24–0.64)	
Miscarriage rate[c]									
Cleavage-stage	28/127 (22.1%)	573/2739 (20.9%)	261/1257 (20.8%)	122/605 (20.2%)	77/275 (28.0%)	27/110 (24.6%)	11/35 (31.4%)	1/9 (11.1%)	
Blastocyst	46/336 (13.7%)	911/7028 (13.0%)	492/3171 (15.5%)	251/1476 (17.0%)	126/728 (17.3%)	49/207 (23.7%)	9/57 (15.8%)	4/15 (26.7%)	
OR (95% CI)									
Crude	1.06 (0.83–1.37)	ref	1.14 (1.04–1.26)	1.22 (1.08 -1.38)	1.42 (1.20 -1.67)	1.76 (1.35–2.29)	1.55 (0.94–2.55)	1.47 (0.55–3.94)	<.001
Adjusted	1.14 (0.88–1.48)		1.12 (1.02–1.24)	1.19 (1.04–1.35)	1.41 (1.19–1.67)	1.72 (1.31–2.25)	1.50 (0.90–2.50)	1.42 (0.52–3.87)	

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019. *(continued)*

TABLE 2
IVF outcomes by BMI category among 51,959 first fresh IVF cycles started in 2014, representing data from >90% of IVF cycles in the United States and Puerto Rico *(continued)*

	BMI, kg/m^2								
	<18.5 Underweight	18.5–24.9 Normal weight	25.0–29.9 Overweight	30.0–34.9 Class I obesity	35.0–39.9 Class II obesity	40.0-44.9 Class III obesity	45.0-49.9 Morbid obesity	≥50 Super obesity	*P* value test for linear trend
Biochemical pregnancy[a]									
Cleavage-stage	23/361 (6.4%)	586/7498 (7.8%)	295/3636 (8.1%)	150/1728 (8.7%)	77/877 (8.8%)	41/360 (11.4%)	9/123 (7.3%)	3/48 (6.3%)	
Blastocyst	48/593 (8.1%)	1108/12,083 (9.2%)	474/5750 (8.2%)	274/2792 (9.8%)	145/1339 (10.8%)	34/396 (8.6%)	16/130 (12.3%)	7/41 (17.1%)	
OR (95% CI)									
Crude	0.85 (0.66–1.09)	ref	0.94 (0.86–1.03)	1.09 (0.98–1.22)	1.18 (1.02–1.36)	1.16 (0.91–1.48)	1.16 (0.76–1.76)	0.34 (0.69–2.59)	.004
Adjusted	0.86 (0.67–1.10)		0.94 (0.86–1.03)	1.08 (0.97–1.21)	1.17 (1.01–1.36)	1.16 (0.91–1.49)	1.18 (0.78–1.80)	0.39 (0.72–2.69)	
Multiple pregnancy rate[d]									
Cleavage-stage	24/99 (24.2%)	435/2145 (20.3%)	214/985 (21.7%)	116/475 (28.3%)	44/197 (22.3%)	22/82 (26.8%)	8/23 (34.8%)	1/8 (12.5%)	
Blastocyst	66/287 (23.0%)	1464/6048 (21.4%)	715/2644 (27.0%)	295/1202 (24.5%)	134/589 (22.8%)	43/156 (27.6%)	14/48 (29.2%)	3/10 (30.0%)	
OR (95% CI)									
Crude	1.01 (0.79–1.28)	ref	1.14 (1.04–1.25)	1.08 (0.95–1.22)	0.97 (0.82–1.16)	1.25 (0.93–1.66)	1.49 (0.90–2.47)	0.95 (0.31–2.88)	.068
Adjusted	1.04 (0.80–1.34)		1.10 (1.00–1.21)	1.02 (0.89–1.16)	0.92 (0.77–1.11)	1.13 (0.83–1.54)	1.35 (0.77–2.35)	0.80 (0.25–2.56)	
Cumulative live birth rate[e]									
Cleavage-stage	114/361 (31.6%)	2398/7498 (32.0%)	1118/3636 (30.8%)	540/1728 (31.3%)	232/877 (26.5%)	90/360 (25.0%)	25/123 (20.3%)	8/48 (16.7%)	
Blastocyst	361/593 (60.9%)	7649/12,083 (63.3%)	3336/5750 (58.0%)	1552/2792 (55.6%)	729/1339 (54.4%)	198/396 (50.0%)	62/130 (47.7%)	12/41 (29.3%)	
HR (95% CI)[f]									
Crude	1.03 (0.95–1.12)	ref	0.95 (0.92–0.98)	0.93 (0.89–0.97)	0.85 (0.80–0.90)	0.76 (0.68–0.84)	0.73 (0.60–0.88)	0.40 (0.26–0.62)	<.001
Adjusted	1.07 (0.98–1.16)		0.96 (0.93–0.99)	0.94 (0.90–0.99)	0.85 (0.81–0.91)	0.76 (0.68–0.85)	0.73 (0.60–0.89)	0.41 (0.26–0.63)	

Multivariable models adjusted for age, smoking, and history of previous fresh and frozen cycles (Y/N). Additional adjustments were made for number of embryos transferred, blastocyst transfer (Y/N), and embryo grade when an embryo transfer occurred.

BMI, body mass index; *CI*, confidence interval; *FET*, frozen embryo transfer; *HR*, hazard ratio; *IVF*, in vitro fertilization; *OR*, odds ratio; *RR*, risk ratio.

[a] Among cycles resulting in transfer; [b] Numbers represent percent of cycles with any implantation. RRs refer to the implantation rate (number of fetal heartbeats/number of embryos transferred); [c] Among clinical pregnancies; [d] Among live births following first fresh cycle; [e] Numbers represent raw percentage of live births as of the last cycle; [f] Cox regression uses first fresh cycles + 16,067 subsequent FET cycles.

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

TABLE 3
IVF outcomes by age category among 51,959 first fresh IVF cycles started in 2014, representing data from >90% of IVF cycles in the United States and Puerto Rico

	Age, y						*P* value test for linear trend
	<30	30–34	35–37	38–40	41–42	>42	
Implantation rate[a,b]							
Cleavage-stage	549/1257 (43.7%)	1576/3973 (39.7%)	1193/3288 (36.3%)	954/3342 (28.6%)	327/1703 (19.2%)	88/1068 (8.2%)	
Blastocyst	2437/4053 (60.1%)	5458/9562 (57.1%)	2637/4996 (52.8%)	1247/3066 (40.7%)	287/1010 (28.4%)	59/437 (13.5%)	
RR (95% CI)	ref						<.001
Crude		0.90 (0.87–0.93)	0.72 (0.69–0.75)	0.45 (0.43–0.47)	0.23 (0.21–0.25)	0.09 (0.07–0.10)	
Adjusted		0.92 (0.88–0.95)	0.76 (0.73–0.79)	0.48 (0.46–0.51)	0.26 (0.24–0.28)	0.10 (0.08–0.11)	
Clinical pregnancy rate[a]							
Cleavage-stage	575/1257 (45.7%)	1682/3973 (42.3%)	1306/3288 (39.7%)	1073/3342 (32.1%)	394/1703 (23.1%)	127/1068 (71.0%)	
Blastocyst	2564/4053 (63.3%)	5757/9562 (60.2%)	2835/4996 (56.8%)	1430/3066 (46.6%)	348/1010 (34.5%)	84/437 (19.2%)	
OR (95% CI)	ref						<.001
Crude		0.84 (0.79–0.90)	0.69 (0.65–0.74)	0.44 (0.41–0.48)	0.26 (0.24–0.29)	0.11 (0.10–0.13)	
Adjusted		0.86 (0.81–0.92)	0.71 (0.66–0.76)	0.44 (0.41–0.48)	0.24 (0.22–0.27)	0.10 (0.09–0.12)	
Miscarriage rate[c]							
Cleavage-stage	59/575 (10.3%)	243/1682 (14.5%)	244/1306 (18.7%)	306/1073 (28.5%)	168/394 (42.6%)	80/127 (63.0%)	
Blastocyst	253/2564 (9.9%)	655/5757 (11.4%)	443/2835 (15.6%)	362/1430 (25.3%)	132/348 (37.9%)	43/84 (51.2%)	
OR (95% CI)	ref						<.001
Crude		1.24 (1.09–1.43)	1.80 (1.56–2.08)	3.30 (2.85–3.82)	6.15 (5.10–7.41)	12.67 (9.41–17.05)	
Adjusted		1.23 (1.07–1.41)	1.76 (1.53–2.04)	3.29 (2.82–3.83)	6.26 (5.11–7.67)	13.26 (9.64–18.23)	
Biochemical pregnancy[a]							
Cleavage-stage	105/1257 (8.4%)	313/3973 (7.9%)	235/3288 (7.2%)	291/3342 (8.7%)	154/1703 (9.0%)	86/1068 (8.1%)	
Blastocyst	358/4053 (8.8%)	817/9562 (8.5%)	452/4996 (9.1%)	314/3066 (10.2%)	111/1010 (11.0%)	54/437 (12.4%)	
OR (95% CI)	ref						.027
Crude		0.95 (0.85–1.07)	0.95 (0.84–1.07)	1.09 (0.96–1.24)	1.13 (0.97–1.33)	1.07 (0.88–1.31)	
Adjusted		0.95 (0.85–1.06)	0.92 (0.82–1.05)	1.04 (0.91–1.18)	1.05 (0.89–1.24)	0.98 (0.80–1.21)	
Multiple pregnancy rate[d]							
Cleavage-stage	138/510 (27.1%)	360/1427 (25.2%)	208/1051 (19.8%)	124/760 (16.3%)	32/220 (14.6%)	2/46 (4.4%)	
Blastocyst	599/2278 (26.3%)	1255/5043 (24.9%)	599/2355 (25.4%)	245/1055 (23.2%)	32/213 (15.0%)	4/40 (10.0%)	

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

(continued)

TABLE 3
IVF outcomes by age category among 51,959 first fresh IVF cycles started in 2014, representing data from >90% of IVF cycles in the United States and Puerto Rico *(continued)*

	Age, y						*P* value test for linear trend
	<30	30–34	35–37	38–40	41–42	>42	
OR	ref						<.001
Crude		0.93 (0.84–1.02)	0.86 (0.77–0.97)	0.71 (0.62–0.82)	0.48 (0.37–0.64)	0.21 (0.09–0.48)	
Adjusted		0.90 (0.81–1.00)	0.66 (0.59–0.75)	0.27 (0.23–0.32)	0.05 (0.04–0.08)	0.01 (0.00–0.02)	
Cumulative live birth rate[e]							
Cleavage-stage	583/1257 (46.4%)	1635/3973 (41.2%)	1190/3288 (36.2%)	825/3342 (24.7%)	239/1703 (14.0%)	53/1068 (5.0%)	
Blastocyst	2877/4053 (71.0%)	6475/9562 (67.7%)	2957/4996 (59.2%)	1304/3006 (42.5%)	246/1010 (24.4%)	40/437 (9.2%)	
HR (95% CI)[f]	ref						<.001
Crude		0.90 (0.87–0.94)	0.75 (0.72–0.79)	0.50 (0.47–0.53)	0.26 (0.24–0.28)	0.08 (0.06–0.09)	
Adjusted		0.91 (0.89–0.95)	0.79 (0.75–0.82)	0.53 (0.50–0.56)	0.28 (0.25–0.30)	0.08 (0.06–0.11)	

Multivariable models adjusted for BMI, smoking, and history of previous fresh and frozen cycles (Y/N). Additional adjustments were made for number of embryos transferred, blastocyst transfer (Y/N), and embryo grade when an embryo transfer occurred.

BMI, body mass index; *CI*, confidence interval; *FET*, frozen embryo transfer; *HR*, hazard ratio; *IVF*, in vitro fertilization; *OR*, odds ratio; *RR*, risk ratio.

[a] Among cycles resulting in transfer; [b] Numbers represent percent of cycles with any implantation. RRs refer to the implantation rate (number of fetal heartbeats/number of embryos transferred); [c] Among clinical pregnancies; [d] Among live births following first fresh cycle; [e] Numbers represent raw percentage of live births as of the last cycle; [f] Cox regression uses first fresh cycles + 16,067 subsequent FET cycles.

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

obesity, and Class III obesity had a CLBR of approximately 63%, 54%, and 48%, respectively. A 34-year-old woman with the same BMI categories had a CLBR of approximately 51%, 44%, and 40%, respectively. At most ages, women with underweight or overweight had slightly lower CLBRs compared with women with normal weight. Decreases in the CLBR with increasing BMI were less pronounced at older ages. For example, a 33-year-old woman with normal BMI as compared with Class III obesity had a CLBR of approximately 56% rather than 37%, whereas a 39-year-old woman with normal BMI as compared with Class III Obesity had a CLBR of 25% rather than 23%. In general, there were smaller differences in CLBR across BMI categories older than age 38 years compared with in younger women. The number of women in the highest BMI categories was small, particularly at higher ages. There were no live births among women with BMI $\geq$50 older than age 39 years, or for women with morbid obesity (BMI 45.0—49.9) older than age 42 years.

Comment

Principal findings

The results of this study suggest that the cumulative live birth rate with IVF should take into account the combination of age and BMI, and that delaying conception to attempt to achieve a lower BMI may be detrimental to IVF success at older ages. A 2015 committee opinion from the American Society for Reproductive Medicine states that the benefits of weight loss must be balanced with the decline in fertility that comes with advancing age.[38] To our knowledge, this is the first study that considers the combined impact of age and BMI on cumulative live birth rates. BMI has a greater influence on live birth at younger ages as compared with older ages. Age-related aneuploidy has a greater impact than BMI on the likelihood of live birth at older ages. Findings suggest that physicians should discuss with patients whether taking time to achieve a particular BMI, thus

TABLE 4

Cumulative likelihood of live birth (%) based on maternal age and BMI among 51,959 first fresh IVF cycles started in 2014 + 16,067 frozen embryo cycles between 2014 and 2015, representing data from >90% of IVF cycles in the United States and Puerto Rico

	BMI, kg/m^2							
Age, y	<18.5 Underweight	18.5–24.9 Normal weight	25.0–29.9 Overweight	30.0–34.9 Class I obesity	35.0–39.9 Class II obesity	40.0-44.9 Class III obesity	45.0-49.9 Morbid obesity	≥50 Super obesity
<30	129/199 (65%)	2299/3606 (64%)	980/1654 (59%)	491/823 (60%)	208/419 (50%)	61/128 (48%)	17/42 (40%)	3/12 (25%)
30	50/83 (60%)	979/1550 (63%)	355/619 (57%)	156/265 (59%)	91/168 (54%)	25/52 (48%)	5/25 (20%)	2/10 (20%)
31	63/104 (61%)	1040/1761 (59%)	436/766 (57%)	179/329 (54%)	78/163 (48%)	26/65 (40%)	6/20 (30%)	0/1 (0%)
32	61/100 (61%)	1122/1945 (58%)	477/872 (55%)	197/369 (53%)	77/179 (43%)	26/59 (44%)	8/23 (35%)	2/9 (22%)
33	55/122 (45%)	1144/2053 (56%)	472/914 (52%)	243/453 (54%)	89/203 (44%)	28/75 (37%)	9/21 (43%)	1/6 (17%)
34	48/109 (44%)	1126/2192 (51%)	470/983 (48%)	188/443 (42%)	101/229 (44%)	32/80 (40%)	9/21 (43%)	1/8 (13%)
35	60/127 (47%)	1056/2100 (50%)	414/931 (44%)	207/450 (46%)	102/241 (42%)	32/73 (44%)	9/24 (38%)	2/12 (17%)
36	34/83 (41%)	819/1927 (43%)	379/936 (40%)	197/472 (42%)	89/207 (43%)	32/82 (39%)	12/36 (33%)	2/7 (29%)
37	34/87 (39%)	669/1724 (39%)	333/875 (38%)	133/377 (35%)	73/192 (38%)	18/74 (24%)	11/33 (33%)	3/10 (30%)
38	21/69 (30%)	542/1711 (32%)	281/863 (33%)	118/393 (30%)	52/212 (25%)	11/56 (20%)	5/20 (25%)	3/14 (21%)
39	14/74 (19%)	389/1546 (25%)	216/814 (27%)	115/423 (27%)	61/215 (28%)	18/80 (23%)	2/19 (11%)	1/8 (13%)
40	11/59 (19%)	280/1387 (20%)	128/682 (19%)	73/349 (21%)	27/156 (17%)	7/57 (12%)	5/16 (31%)	0/6 (0%)
41	6/71 (8%)	167/1238 (13%)	94/613 (15%)	33/267 (12%)	24/125 (19%)	6/44 (14%)	1/15 (7%)	0/4 (0%)
42	1/33 (3%)	108/1020 (11%)	46/527 (9%)	29/266 (11%)	10/117 (9%)	5/45 (11%)	2/14 (14%)	0/3 (0%)
>42	0/59 (0%)	43/1544 (3%)	32/726 (4%)	17/351 (5%)	3/158 (2%)	3/57 (5%)	0/17 (0%)	0/4 (0%)

BMI, body mass index; *IVF*, in vitro fertilization.

Goldman et al. The combined impact of maternal age and body mass index on cumulative live birth following in vitro fertilization. Am J Obstet Gynecol 2019.

leading to older age at IVF cycle start, is likely to be beneficial or harmful to the cumulative likelihood of live birth.

Results

For some age and BMI combinations, taking time to achieve a lower BMI before IVF may be beneficial: for example, a 31-year-old woman with Class III Obesity was shown to have a CLBR of 40%, whereas a 33-year-old woman with Class I Obesity had a CLBR of 54%; if it takes 2 years for a 31-year-old woman with BMI 40.0−44.9 to lose weight and achieve a BMI of 30−34.9, she may substantially increase her likelihood of live birth. However, for others, taking time to lose weight may be detrimental: a 39-year-old woman with Class III obesity had a CLBR of 23%, whereas a 41-year-old woman with Class I obesity had a CLBR of 12%. Given that it takes time to achieve a lower BMI, a 39-year-old woman with overweight or obesity would potentially be compromising her likelihood of success with IVF, as she would be older at cycle start if she delayed fertility treatment for 1−2 years to lose weight. Generally, infertile women <35 years old with BMI ≥40 may increase their CLBR if they are able to achieve a BMI <35 over 1−2 years before treatment. In contrast, older women with overweight or obesity may actually decrease their likelihood of live birth if they delay attempting conception to lose weight. A reference table was created based on age and BMI category to inform patients and physicians about the impact of BMI on the cumulative live birth rate following IVF.

Importantly, this study reports IVF success at very high BMI categories, including super obesity (BMI ≥50). The number of women in this BMI category is relatively small in our database, despite the association of infertility with obesity.[13-16,20−23] This is likely due to IVF programs imposing a treatment cutoff above a certain BMI due to safety concerns (mean ± standard deviation BMI cutoff among programs imposing a restriction is 38.4 ± 5.2 kg/m^2).[39] Nonetheless, we felt it important to evaluate the CLBR for women with these greater BMIs, as most previous studies excluded women above a certain BMI or have grouped the largest BMIs together.[40,41] The largest IVF outcomes study evaluating the association of obesity and live birth did include BMI ≥50 as the heaviest category, but only looked at live birth following fresh transfer and did not evaluate the CLBR.[15] We found that while live births are possible with IVF for women with super obesity (CLBR = 17.5%), no patient in her 40s in this BMI category achieved a live birth, though numbers were small. Successfully losing weight for women >40 years with BMI ≥50 may therefore result in an increase in the likelihood of birth.

The results of this study support the seemingly conflicting results in the existing literature regarding the impact that achieving a lower BMI has on IVF outcomes.[24,27,28] For example, in findings by Clark et al,[24] the average patient age was 31.9 years, and there was no upper limit of BMI for inclusion; the authors found that achieving a lower BMI within 6 months resulted in improvements in IVF outcomes, except among women whose BMI remained above 40. Consistent with previous findings, in this present study, a 33-year-old woman with BMI 40−44.9 had a CLBR of 37%, whereas a 34-year-old woman with BMI <35−39.9 had a CLBR of 44%. However, we found that for many women, particularly those ≤35 years old with BMI >45, achieving a lower BMI may increase the CLBR even if BMI remained above 40. A more recent randomized controlled study by Einarsson et al[27] only included women <38 years old with BMI 30-35 and failed to demonstrate improved live birth rates with achievement of lower BMIs. In this present study, a 35-year-old with a BMI of 35 and a 36-year-old woman with a BMI of 30 had the same CLBR of 42%. It is likely that disparate findings regarding the benefit of weight loss exist due to the constricted patient eligibility in many studies, as well as the profound relationship between age and fertility.

Clinical implications

Obesity can have devastating health consequences, and the benefits of losing weight on overall well-being cannot be overstated.[42,43] In the United States, a majority of men and women have overweight or obesity, including approximately one half of women of reproductive age.[38,44,45] Obesity is detrimental to fertility and is associated with increased risk of ovulatory disorders, decreased responsiveness to fertility medications, and reduced oocyte and endometrial quality.[13−15,24,40] It is also critical to keep in mind the elevated maternal-fetal risks in pregnancies complicated by obesity[46]; however, many women are unwilling to delay conception attempts to lose weight.[47] Time to achieve weight loss is variable and for some women, it may take years to lower BMI. Although exercise and medication management are typical first-line weight loss interventions, the only treatment proven to result in long-term, rapid, and sustained weight loss is bariatric surgery.[6,8,48−50] Women generally are advised to wait 12−18 months after bariatric surgery to conceive, although data to support this delay are limited.[8,51−53] Exercise and weight-management programs are likely to require more time to achieve weight loss and are less likely to be sustained.[54] All interventions, which have variable likelihoods of success in lowering BMI, lead to older age at IVF cycle start. Interestingly, the number of embryos transferred was not, on average, lower among obese patients, despite obese women having greater maternal-fetal risks that may be compounded by multi-fetal gestations.[55,56] Implantation rates were lower among obese women, and it is possible that clinicians chose to transfer more than one embryo to compensate for the lower likelihood of pregnancy. Given the risks associated with multiple gestation and obesity in pregnancy, strong consideration should be given to single embryo transfer in patients with elevated BMI.

Strengths and limitations and research implications

Strengths of this study include use of the SART Clinic Outcome Reporting System database and the resultant large sample size that captures data from most IVF clinics in the United States, increasing

generalizability. Our main outcome was cumulative live birth rate, which is arguably the most important outcome to patients, and was obtained using linked fresh plus frozen cycles. This study evaluated the joint impact of age and BMI, and included women in the highest BMI categories (including BMI ≥50). Limitations of this study include its retrospective nature and potential inaccuracies in registries that are difficult to measure. As each SART-affiliated clinic inputs cycles on an individual basis and are not always prospectively reported, it is possible that some cycles with intent for freeze-all were misidentified. This would result in lower reported implantation and clinical pregnancy rates from those analyses, but would not impact CLBR analyses. Further, it is possible that patients with an unsuccessful initial transfer and subsequent weight loss, followed by a successful transfer, were not captured within this study's time frame. Importantly, achieving a certain BMI after losing weight may be physiologically different from starting out at that same BMI for a given age. If an elevated initial BMI has a persistent negative effect on the likelihood of live birth following IVF, then the CLBR after achieving a lower BMI may be overestimated here. It is possible that IVF with embryo freeze-all followed by weight loss and delayed transfer would be a beneficial strategy for some patients; however, this study is not designed to answer that specific question, and it may be inaccurate to extrapolate the true benefits of weight loss on CLBR from this study. Future research may determine the direct impact of weight loss on the CLBR; however, a large and meaningful study would be challenging given the large sample size required and the sensitive nature of age and fertility treatment, which many subjects would not voluntarily defer long-term. Until such a study is undertaken, the present work can provide a valuable counseling resource.

Conclusions

We have shown that age has a greater impact on the CLBR than BMI at older ages, and our results suggest that if a patient with infertility and obesity desires childbearing, delaying weight loss to attempt conception with IVF rather than taking time to lose weight may increase her likelihood of live birth. As the impact of BMI on the likelihood of live birth is dependent on age, the benefit of losing weight is likely related to the rapidity with which weight loss could be achieved—a difficult variable to predict. This study is not meant to deter weight loss in women who would otherwise benefit from it, but rather to help ascertain the age and BMI combinations at which delaying weight loss to achieve a live birth may or may not be advisable.

When counseling women about weight before IVF, physicians should consider the combination of age and BMI and should include a discussion about the overall benefits of weight loss on health, fertility, and pregnancy. Realistic expectations of the success of various weight loss interventions should be considered along with childbearing goals. ■

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