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Smaller fetal size in singletons after infertility therapies: The influence of technology and the underlying infertility

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Abstract

Objective—To determine whether fetal size differences exist between matched fertile and infertile women and among women with infertility achieving pregnancy through various treatment modalities.

Design—Retrospective cohort study with propensity score analysis

Setting—Tertiary care center and affiliated community hospitals

Patients—1246 fertile and 461 infertile healthy women with singleton live-births over a ten-year period. Infertile women conceived 1) without medical assistance (WMA), 2) with ovulation induction (OI), or 3) with *in vitro* fertilization (IVF).

Main Outcome Measure(s)—Birthweight; secondary outcomes included crown rump length, second trimester estimated fetal weight, and incidence of low birth weight (LBW) and preterm delivery.

Results—Compared to matched fertile women, infertile women had smaller neonates at birth (3375±21 vs. 3231±21 grams; p<0.0001) and more LBW infants (RR=1.68, 95% CI 1.06, 2.67). Neonates conceived via OI were the smallest of infertility subgroups compared to those of fertile women (3092 ± 46 vs. 3397 ± 44 grams; p<0.001). First trimester fetal size was smaller in infertile

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vs. fertile women (CRL 7.9±0.1 vs. 8.5±0.1 mm, p<0.01). Within infertility subgroups, no differences in fetal or neonatal size were found.

Conclusions—The inherent pathologic processes associated with infertility may have a larger impact on fetal growth than infertility therapies.

Keywords

IVF or ART; fetal size; birthweight; infertility; ovulation induction

INTRODUCTION

More than 25% of women 18–44 years of age have impaired fecundity. (1) Recent advances in assisted reproductive technologies (ART) have revolutionized the treatment armamentarium for these women. As a result of increasing ART use, over 1% of children in the United States and up to 4–5% in some countries are born every year as a result of ART. (2, 3) Thus, ensuring healthy outcomes in these children remains crucial.

Though ART is regarded as generally safe, there continues to be a heightened risk of adverse perinatal outcomes among singleton gestations from ART as compared to spontaneous conceptions.(4–8) Three meta-analyses of the data have supported these conclusions and a consensus statement from the National Institutes of Health suggests we warn patients of such.(9–12)

Past research has focused on the relationship between ART technologies and modifications in fetal health. Micromanipulation techniques, extended culture systems and medications utilized in IVF have been linked to alterations in gene expression patterns in gametes and early embryos.(13–18) Yet, comparisons between ART patients and the general “fertile” population do not address the pathologic contribution of the underlying subfertility/ infertility or alterations in the hormonal milieu with superovulation.

We undertook this study to evaluate fetal growth in singleton live-births among otherwise healthy matched infertile and fertile cohorts of women. Due to the inherent biases in observational studies and the multifactorial issues underlying infertility we further sought to address this research question with a more complex analytical approach. We tested the primary hypothesis that offspring from women with underlying infertility are smaller *in utero* and at delivery when compared with fertile women, independent of the use of ART.

MATERIALS AND METHODS

Participant identification and characteristics

Infertile and fertile cohorts of women, 18–45 years of age, with singleton live-births between 01/01/1999 and 02/01/2009 were identified. Infertility patients were defined as those who initiated care within our Division with inability to conceive for 12 months or greater in women under 35, or six months or greater in someone 35 years or older (19, 20). The Washington University prenatal ultrasound database was utilized to select both infertile patients with complete pregnancy follow up data and fertile controls. This database was initiated in 1990 and is managed by dedicated coordinators who obtain detailed information from patients through self-reported questionnaires, medical record acquisition, prospective communication with patients, and physician contact for out-of-network deliveries.

The process of selecting infertile women included an electronic query to identify patients with live-births as a result of in vitro fertilization (IVF) from our unit and established patients with CPT codes for early obstetrical ultrasounds (76817) who were not IVF

patients. They were subdivided into three groups based on mode utilized to achieve pregnancy after medical record review: 1) Conceptions without medical assistance (WMA), 2) conception by ART (20)-(specifically IVF +/− intracytoplasmic sperm injection (ICSI)), and 3) conception by ovulation induction (OI); clomiphene citrate or injectable gonadotropins) alone. Precise gestational dating for conceptions from IVF or OI was by the date of the oocyte retrieval, intrauterine insemination, or ovulation predictor kit (OPK). Patients who conceived WMA were required to have a known last menstrual period (LMP) documented in the chart in addition to self-reported previously regular cycles or have a recorded date of OPK surge. Infertility diagnoses were obtained from the medical records. Other exclusions were pregnancies with selective reduction, fetal chromosomal or major congenital anomalies or maternal pre-gestational diabetes, pre-existing hypertension, renal disease, sickle cell disease or other major medical conditions, and tobacco use. All infertile women in our office had a first trimester ultrasound regardless of method of conception. Patients with a first trimester spontaneous reduction of a second gestational sac were included but this was controlled for in multivariate analyses.

The fertile cohort, identified from a query of our institutional prenatal genetics ultrasound database, had: 1) Record of a first and second trimester ultrasound, 2) No database conception coding associated with infertility including the phrases artificial or intrauterine insemination, OPK, clomiphene or gonadotropins, IVF, or an “other” category with descriptive details suggestive of infertility therapy, 3) A known LMP, confirmed by first trimester ultrasound dating, and 4) The same exclusionary criteria as the infertile group. In the latter half of the study period first trimester ultrasounds were ordered routinely by our generalist groups to confirm dating and viability of the pregnancy. In order to assure appropriate inclusion/exclusion criteria, indications for first trimester ultrasound in the fertile cohort were also analyzed throughout the study period.

IVF pregnancies were all fresh embryo cycles. Frozen embryo, donor oocyte, and cycles utilizing testicular sperm extraction were excluded. All IVF cycles were done using standard controlled-ovarian hyperstimulation protocols with gonadotropins and GnRH agonist or antagonist pituitary suppression, ultrasound-guided transvaginal oocyte aspiration, and transcervical embryo transfer as previously described.(21) Number and timing of embryo transfer was individualized based on clinical indications.

A singleton live-birth was defined as a viable infant delivered at 23 completed weeks or later in gestation with a fetal weight more than 500 grams. Maternal age was recorded as age at the time of delivery. Race/ethnicity was self-reported information with patients subdivided into white, black and other for analyses.

The primary outcome was birthweight. Secondary outcomes included *in utero* fetal size in the first trimester as measured by crown rump length (CRL; transvaginal ultrasound), size in the second trimester as measured by a composite estimated fetal weight (EFW) in grams, low birthweight (LBW; <2500 grams) and preterm delivery (PTD <37 weeks gestation). If patients had more than one ultrasound, the earliest first trimester ultrasound that recorded a CRL was used and the second trimester scan most approximate to 20 weeks gestation was selected for comparison.

Data analysis/Statistics

Descriptive statistics were done using student’s t-tests and chi-square tests. Because infertility patients differ systematically from fertile patients on a host of factors important to fetal growth, we implemented a propensity score approach to identify fertile patients who were most similar to the infertile patients. Propensity score analyses are used in observational studies to reduce selection bias and balance population characteristics when

randomized control trials are not feasible. For each patient, the probability of being an infertility patient (i.e. propensity score) was estimated from a logistic regression model that considered multiple maternal and fetal variables associated with fetal/neonatal size (maternal age at delivery, maternal race, fetal gender, gestational diabetes, preterm labor, premature rupture of membranes, and pre-eclampsia/eclampsia). We then implemented one-to-one matching of fertile and infertile patients using the greedy matching algorithm - this algorithm seeks to maximize exact propensity score matches while minimizing the number of unmatched subjects, reducing matching bias.(22) While this matching reduces the sample size of the comparison groups it balances the potential loss of precision with the improvement in control of bias.

All fetal and neonatal size variables were examined for normality using estimates of skew and kurtosis and were within the ranges of normal, −0.8 to 0.8 for skewness and −3 to 3 for kurtosis. Adjusted means were estimated using generalized linear models. All fetal and neonatal size analyses were adjusted for the exact gestational age at the time of the ultrasound or delivery measurement.

Comparisons of individual infertility populations to other infertility populations (e.g. OI v. IVF) were adjusted for maternal age at delivery, maternal race, fetal gender and history of gestational diabetes, preterm labor, premature rupture of membranes and pre-eclampsia/eclampsia, and presence of a second gestational sac in regression analyses. Analyses were performed using SPSS v. 16.0 and SAS v. 9.2 (SAS Corporation, Cary, NC) and the study was IRB approved.

RESULTS

A total of 1707 women (461 infertile and 1246 fertile) were included in the study (Table 1). Initial query for IVF live-births, cross-referenced with our perinatal database, resulted in 498 patients of which 182 (37%) were excluded for multiple gestations and 65 (13%) for other reasons (frozen embryos, oocyte donors, maternal/fetal indications). In the OI and WMA infertile subgroups, 374 patients were initially identified but 21 (6%) excluded for multiple gestations and 143 (38%) for other reasons (undocumented LMP and maternal/fetal indications). Indications for first trimester ultrasound in the fertile cohort were for: confirmation of viability or gestational age (63.1%), first trimester bleeding (17.1%), advanced maternal age (8.8%), prior loss (8.7%), rule out ectopic (1.3%), or other (1%).

After propensity score matching, confounding variables were more balanced between the fertile and infertile groups (Table 2). Only small differences remained in the few covariates with the fewest number of events in both cohorts. Compared to fertile women, neonates from infertile women were smaller at birth (3375 ± 21 vs. 3231 ± 21 grams; $p<0.0001$; Table 3). Women who underwent OI therapies had smaller infants at delivery than fertile women compared to other infertile subgroups (Table 3). A smaller fetal size was also found in the first trimester in the infertile group. This difference was also seen in women who conceived through OI and WMA, but not with IVF conceptions. There were no fetal size differences seen in the second trimester. The number of LBW infants was significantly higher in the infertile patients as compared to the fertile patients (RR=1.68, 95% CI 1.06, 2.67) although there was no increase in PTD. The risk for a LBW delivery persisted among infertility patients who utilized IVF (RR=2.0, 95% CI 1.12–3.67), but not in other subgroups, as compared to the fertile women.

When comparing conceptions in women with underlying infertility in a multivariate regression analysis, we found no difference in birthweight between those that conceived WMA and those that utilized IVF (3311 ± 42 vs. 3273 ± 26 grams; $p=0.45$) (Table 4).

However, neonates conceived with OI were significantly smaller than those from IVF (3106 ± 41 vs. 3269 ± 26 grams; p=0.001) and WMA (3120 ± 40 vs. 3324 ± 40 grams; p<0.001). There were no statistical differences in the second trimester in fetal size between any of the infertile groups, nor a difference in LBW or PTD.

To further assess the fetal size discrepancies, we subdivided infertility patients and analyzed the most common infertility diagnoses (male factor, unexplained, ovulation disorder, and polycystic ovarian syndrome (PCOS)). Mean CRL size in infertile women with PCOS were smaller than infertile women without PCOS and fertile women. In a generalized linear model controlling for maternal age, fetal gender, and gestational age at ultrasound, infertile women with PCOS had significantly smaller fetuses in the first trimester as compared to women without PCOS (p=0.001). There was no further size difference in the second trimester or at birth in patients with PCOS, nor were there differences in fetal/neonatal size in the other listed infertility diagnoses at any time point (data not shown).

DISCUSSION

Our data show that fetal size is significantly smaller at delivery and in early gestation in singleton live-births from infertile women compared to fertile women. This is the first reported comparison of fetal size both *in utero* and at birth between infertile and fertile women. Furthermore, this is the first ART study to our knowledge utilizing propensity scores to reduce inherent bias in observational, non-randomized studies. Comparing pregnancies in patients with multiple infertility diagnoses, who require ovulation induction therapies and *in vitro* technology to women who conceive without any assistance, is difficult. Although a randomized controlled study would be ideal, such an approach is nearly impossible. While still with limitations associated with retrospective studies, the propensity score matching algorithm offers a stronger analytical approach than a regression analysis in this study. It balances population characteristics and controls both known and unrecognized confounding variables that would not otherwise be controlled for in unmatched patient cohorts.

The similar neonatal size findings in offspring from infertile women who conceived with IVF as compared to WMA suggest that the mechanisms underlying the infertility may have a larger impact on alterations in fetal growth than the use of ART. This study supports previous studies suggesting that reductions in birthweight and adverse fetal outcomes are more likely in women who report prolonged times to conception, and differences between ART and spontaneous conceptions disappear when siblings born to the same mother are compared.(23–28)

The specific findings of this study also imply that differing aspects of embryonic and *in utero* growth warrant further consideration. Important size discrepancies were found in both the first trimester and at delivery but not in the mid-gestation. Alterations in fetal development in the first trimester could be significantly influenced by the underlying mechanisms of infertility. Differences in CRL size between fertile and infertile groups appeared to be most represented by the OI treatment group which may be attributed to a selection bias, demonstrated by a larger proportion of PCOS and ovulatory dysfunction patients in this group. The lack of a difference in the IVF patients could be due different infertility diagnoses, enhanced growth in *in vitro* culture systems, or a potential benefit of removing the oocyte from a negative follicular environment (14, 29, 30) though these hypothesis generating findings warrant follow-up. Finally, we believe that there are also likely differences in patients and outcomes within the infertility cohort based on the underlying pathologic reason for the subfertility/infertility. This may explain some of the findings within the secondary infertility subgroup comparisons. Our cohort size was too

small to perform the comparisons based on infertility diagnosis and this warrants further research. Regardless of the cause, size impairments during this critical time of fetal development and the potential catch-up growth in the second trimester could be predictive of long-term health and disease later in life as previously suggested.(31–36)

Neonatal size differences at birth may be more of a placental-mediated mechanism of growth restriction. Whether the influence comes primarily from the underlying infertility or therapies on the trophectoderm of the embryo is largely unknown. Our matched comparisons demonstrate a reduction in birthweight and higher incidence of LBW infants in pregnant women with a history of infertility as compared to fertile women. We controlled for gestational ages and excluded frozen embryo transfers, both of which could influence alternate conclusions from similar studies.(37, 38) The higher prevalence of LBW in infertile women, especially those who underwent IVF, could be due to selection bias of patients who required IVF (i.e. diminished ovarian reserve) as compared to other therapies, or an additive technological or therapeutic impact on gamete and fetal health.(39–43) This increase in LBW infants warrants further investigation since these rates are higher than the CDC's reported prevalence (2002 report: 7.7%) of LBW infants in the US.(44).

Ultimately one could argue that differences in neonatal weight at delivery in the range of 150–300 grams, while statistically significant, may not be clinically significant. Yet, similar differences in birthweight have been reported in epidemiologic studies highlighting the powerful influence of neonatal size differences on developmental origins of disease in later life including reports from the Dutch Famine, maternal tobacco use, and studies by David Barker of populations followed from birth to adulthood. (34–36, 45–51) Equally relevant to the findings in our study, some of these studies demonstrated that fetal effects in early pregnancy could have long lasting impacts on health in later life independent of birthweight differences.

Our study was limited by the inability to obtain complete historical information from the patients due to the retrospective design, such as time to conception in the fertile cohort and potential iatrogenic deliveries. Exclusionary and institutional selection criteria could increase selection bias in the study, yet the database includes patients from both tertiary care and affiliated community hospitals which improves generalizability. Specifically, inclusion of only fertile controls that had both a first and second trimester ultrasound could be inherently selecting a "higher risk" control group. However, use of first trimester ultrasound by our obstetric groups has become more routine over the last decade to confirm dating and viability and we excluded patients with a more concerning indication for first trimester ultrasound. Yet, if we do assume that this control group is at higher risk of adverse outcomes, especially due to a higher preterm birth rate found, we could postulate that the differences found between infertile women and a lower risk fertile control could be even greater. Lack of BMI and weight gain in pregnancy data could also have an unappreciated role in fetal size discrepancies. Finally, we attempted to include a well-matched geographically-similar fertile control group and utilized propensity scores to account for as much unrecognized bias as possible. Our inability to find a difference in birthweight between fertile women and infertile patients who conceived spontaneously is likely due to a lack of power due to smaller numbers of patients with infertility who present for therapy but conceive spontaneously during testing or between other treatments, though we cannot exclude a true finding. Finally while we feel that the pathologic processes that underlie infertility diagnoses have a key role in fetal/neonatal health, we still cannot completely exclude a role of these therapies of interest.

Practitioners and organizations must continue to monitor the outcomes of ART pregnancies, recognizing that the technology may not be the sole reason for adverse findings. An

increasing number of couples will continue to pursue IVF for a multitude of reasons. The oldest offspring from IVF in the US are nearing the age of 30 and the health of this young generation warrants our attention.

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Table 1

Patient and infertility demographics[a]

	Infertile Cohort			Fertile Cohort
	Without Medical Assistance	**Ovulation Induction**	**In Vitro Fertilization**	**Spontaneous Conception**
N	104	106	251	1246
Mean Age (SD)	34.1 (4.5)	33.4 (4.3)	34.7 (4.2)	30.6 (5.2)
Race (%)				
White	87.5	91.5	84.9	65.3
Black	7.7	1.9	5.2	16.5
Other	4.8	6.6	10.0	18.2
Female Fetal Gender (%)	47.1	47.6	46.4	49.1
Gestational DM (%)	3.9	7.6	6.0	5.1
Preterm Labor (%)	14.4	9.4	10.0	18.0
Premature Rupture Of Membranes (%)	3.9	1.9	1.6	3.2
Pre-eclampsia/Eclampsia (%)	10.6	14.2	8.8	8.1
Preterm Deliveries (<37 weeks) (%)	14.9	10.5	17.1	17.2
Low Birth Weight (<2500 grams) (%)	7.2	9.1	12.1	7.8
Ultrasound Measurements (Mean +SD)				
Gestation (1st trimester US) (weeks)	6.7 (1.0)	6.9 (1.0)	6.9 (0.7)	7.0 (0.7)
Crown Rump Length (mm)	6.6 (4.7)	6.9 (6.1)	8.2 (4.6)	8.7 (5.0)
Gestation (2nd trimester US) (weeks)	19.9 (3.1)	19.6 (2.5)	19.1 (3.4)	19.5 (1.4)
Estimated Fetal Weight (grams)	360 (231)	340 (203)	359 (367)	334 (100)
Gestational Age at Delivery (weeks)	38.8 (1.7)	38.6 (2.1)	38.4 (2.3)	38.3 (2.0)
Birth weight (grams)	3326 (521)	3118 (601)	3251 (664)	3278 (580)
	Infertility Demographics			
Infertility Diagnosis (%)[b]				
Male Factor	17.9	21.1	33.4	
PCOS	12.3	18.3	4.4	
Ovulation Disorder	17.9	29.4	19.0	
Tubal Factor	7.5	10.1	23.5	
Unexplained	35.8	29.4	18.7	
Endometriosis	4.7	4.5	16.7	
Diminished Ovarian Reserve	0.9	2.7	5.2	
Other	6.5	2.7	7.6	
Intracytoplasmic Sperm Injection (%)			49.2	
Assisted Hatching (%)			44.4	

	Infertile Cohort			Fertile Cohort
	Without Medical Assistance	**Ovulation Induction**	**In Vitro Fertilization**	**Spontaneous Conception**
Oocytes retrieved (Mean + SD)			12.3 (6.1)	
Embryos transferred (Mean + SD)			2.5 (0.8)	
Peak Estradiol (Mean + SD) pg/ml			2115 (963)	

[a] All data is unmatched and unadjusted

[b] Totals are not 100% due to patients with more than one diagnosis

Table 2

Comparison of fertile and infertile groups before and after propensity score matching

	BEFORE MATCHING				AFTER MATCHING							
	Fertile	**OI**	**IVF**	**WMA**	**Fertile**	**Infertile**	**Fertile**	**OI**	**Fertile**	**IVF**	**Fertile**	**WMA**
N	1246	106	251	104	430	430	105	105	251	251	102	102
Mean Age (SD)	30.6 (5.2)	33.4 (4.3)	34.7 (4.2)	34.1 (4.5)	33.9 (4.5)	34.0 (4.3)	33.4 (4.6)	33.4 (4.3)	34.7 (4.2)	34.7 (4.2)	34.3 (4.8)	34.0 (4.5)
Race												
White	65.3	91.5	84.9	87.5	87.0	86.3	91.4	92.4	86.5	84.9	86.3	87.3
Black	16.5	1.9	5.2	7.7	4.7	5.1	1.0	1.0	4.4	5.2	7.8	7.8
Other	18.2	6.6	10.0	4.8	8.4	8.6	7.6	6.7	9.2	10.0	5.9	4.9
Female Sex	49.1	47.6	46.4	47.1	49.5	47.9	46.7	47.6	51.8	46.6	49.0	47.1
Gestational diabetes	5.1	7.6	6.0	3.9	5.1	5.4	9.5	7.6	4.4	6.0	2.0	3.9
Preterm labor	18.0	9.4	10.0	14.4	11.4	11.6	7.6	9.5	8.8	10.0	11.8	14.7
Premature rupture of membranes	3.2	1.9	1.6	3.9	2.3	2.1	1.0	2.0	2.4	1.6	3.9	3.9
Preeclampsia/Eclampsia	8.1	14.2	8.8	10.6	10.0	7.9	14.3	14.3	6.0	8.8	5.9	10.8

OI=Ovulation Induction; IVF=In vitro fertilization; Spont=Spontaneous conceptions within an infertile cohort; WMA=Without medical assistance

Table 3

Infertile vs Fertile Cohorts: First trimester, second trimester and delivery outcomes for matched OI, IVF and spontaneous versus fertile cohorts

	Fertile	Infertile	p-value	Fertile	OI	p-value	Fertile	IVF	p-value	Fertile	WMA	p-value
N	430	430		105	105		251	251		102	102	
1st Trimester												
CRL[a]	8.5 (0.1)	7.9 (0.1)	<0.01	8.7 (0.3)	7.5 (0.3)	0.01	8.5 (0.1)	8.4 (0.1)	0.40	8.2 (0.3)	7.1 (0.3)	0.01
2nd trimester												
EFW[b]	331 (3.2)	324 (3.4)	0.10	339 (6.6)	335 (6.6)	0.66	318 (2.6)	320 (2.7)	0.59	351 (6.9)	334 (7.1)	0.10
Birthweight, grams[b]	3375 (21)	3231 (21)	<0.0001	3397 (44)	3092 (46)	<0.0001	3368 (27)	3268 (28)	0.01	3386 (42)	3293 (43)	0.13
LBW, %	6.3	10.6	0.02	5.7	9.1	0.36	6.0	12.1	0.02	4.9	7.2	0.49
PTD, %	15.1	14.7	0.86	11.4	10.5	0.83	13.6	17.1	0.27	15.7	14.9	0.87

[a] Adjusted for gestational age at delivery and number of gestational sacs

[b] Adjusted for gestational age at delivery

CRL=crown rump length (mm), EFW=estimated fetal weight (grams), LBW=low birth weight (<2500 grams), PTD=preterm delivery (<37 weeks); WMA=Without medical assistance

Measurements displayed are mean (SE) unless otherwise noted

Table 4

Infertility Subgroup Comparison: First trimester, second trimester and delivery outcomes for infertility subgroups of patients

	OI	IVF	p-value	IVF	WMA	p-value	OI	WMA	p-value
1st Trimester									
CRL[a]	8.0 (0.2)	7.2 (0.3)	0.03	7.9 (0.2)	7.3 (0.3)	0.09	6.7 (0.4)	6.8 (0.4)	0.89
2nd trimester									
EFW[b]	301 (6.2)	311 (4.2)	0.17	306 (4.4)	311 (6.8)	0.52	347 (10.5)	332 (10.9)	0.33
Birthweight, grams[b]	3106 (41)	3269 (26)	0.001	3273 (26)	3311 (42)	0.45	3120 (40)	3324 (40)	<0.001
LBW, %	9.1	12.1	0.42	12.1	7.2	0.19	9.1	7.2	0.63
PTD, %	10.5	17.1	0.11	17.1	14.9	0.60	10.5	14.9	0.34

[a] Adjusted for gestational age at delivery, maternal age, maternal race, fetal gender, prior diagnosis of gestational diabetes, preterm labor, premature rupture of membranes, or pre-eclampsia/eclampsia, and number of gestational sacs

[b] Adjusted for gestational age at delivery, maternal age, maternal race, fetal gender, and prior diagnosis of gestational diabetes, preterm labor, premature rupture of membranes, or pre-eclampsia/eclampsia

CRL=crown rump length (mm), EFW=estimated fetal weight (grams), LBW=low birth weight (<2500 grams), PTD=preterm delivery (<37 weeks); WMA=Without medical assistance

Measurements displayed are mean (SE) unless otherwise noted