

Original Article



Effects of Antiretroviral Therapy and HIV Exposure in Utero on Adverse Pregnancy and Infant Outcomes: A Prospective Cohort Study in Guangzhou, China*

HU Fang¹, LIANG Jing Jing¹, LU Jian Jun^{2,3}, HU Yi Fei⁴, HU Yan¹, YU Jia⁵,
ZOU Xing Wen⁵, MA Ying Hua^{6,#}, and LIN Sui Fang^{1,#}

1. Department of Child Health Care, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China; 2. Medical Affairs Department of the First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong, China; 3. Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China; 4. Department of Child, Adolescent and Maternal Health, School of Public Health, Capital Medical University, Beijing 100069, China; 5. Department of Woman Health Care, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, Guangdong, China; 6. Institute of Child and Adolescent Health, Health Science Center, Peking University, Beijing 100191, China

Abstract

Objective This study aimed to evaluate the effects of in-utero exposure to HIV and ART on pregnancy outcome and early growth of children.

Methods This cohort study enrolled 802 HIV-infected pregnant women between October 2009 and May 2018 in Guangzhou, China. The women were assigned to receive combination ART (cART) or mono/dual ART or no treatment. The primary outcomes were the combined endpoints of any adverse pregnancy outcome [including ectopic pregnancy, spontaneous abortion, stillbirth, preterm birth, small for gestational age (SGA)] and adverse early growth outcome (including infant death, HIV infection of mother-to-child transmission, and underweight, wasting and stunting of infants at 4 weeks of age).

Results Adverse pregnancy outcomes occurred in 202 (35.1%) of all enrolled HIV-infected women, and 121 (31.3%) of all infants exhibited adverse effects on early growth at 4 weeks of age. The rates of adverse pregnancy outcomes, spontaneous abortion, ectopic pregnancy, stillbirth, infant death and perinatal HIV infection were higher among women not receiving ART, compared to those treated with cART or mono/dual ART ($P < 0.05$). However, women treated with cART had a higher rate of SGA, compared to untreated women ($P < 0.05$). No differences in early infant growth were observed among the different treatment regimens.

Conclusion Our findings underscore the essentiality of prioritizing HIV-positive pregnant women for ART, as even mono/dual ART available in resource-limited countries could improve pregnancy outcomes and infant survival.

Key words: HIV; Adverse pregnancy outcome; Adverse infant outcome; Mother-to-child transmission (MTCT); Antiretroviral therapy (ART)

Biomed Environ Sci, 2019; 32(10): 719-729 doi: 10.3967/bes2019.092

ISSN: 0895-3988

www.besjournal.com (full text)

CN: 11-2816/Q

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*Transmission of HIV-Chinese Association of STD and AIDS Prevention and Control [PMTCT2018-001]; National Center for Women and Children's Health, China, CDC (He Sheng Yuan Maternal and Infant's Nutrition and Health Program) [2018FYH008]; and the National Natural Science Foundation of China [81673245, 81673232].

#Correspondence should be addressed to Prof. MA Ying Hua, PhD, Tel: 86-10-82802861, E-mail: yinghuama@bjmu.edu.cn; Dr. LIN Sui Fang, BSc, Tel: 86-20-38367683, E-mail: suifanglin@163.com

Biographical note of the first author: HU Fang, female, born in 1984, MSc, Attending Physician, majoring in preventing mother-to-child transmission of HIV, HBV, and syphilis.

INTRODUCTION

Approximately 1.5 million HIV-infected women become pregnant every year in the world^[1]. Additionally, 1.8 million new infections reported globally in 2016, of which 160,000 were children younger than 15 years who infected through mother-to-child transmission (MTCT)^[2]. The number of people living with HIV is increasing in developing countries, where this infection predominantly affects younger people who desire to bear children^[3]. Data from the HIV/AIDS Comprehensive Response Information Management System in China demonstrate a rapid increase in the population of female patients aged 15-49 years in Guangdong Province^[4]. The largest number of HIV-infected pregnant women resides in Guangzhou, the capital city of Guangdong Province.

In the 1994 ACTG 076 trial demonstrated that administration of the single antiretroviral drug zidovudine could reduce perinatal HIV transmission in infants by nearly 70%^[5]. Accordingly, World Health Organization (WHO) began to recognize the importance of using antiretroviral therapy (ART) during pregnancy to block HIV perinatal transmission. Programs intended to prevent perinatal HIV transmission subsequently updated the maternal ART regimens every few years. Compared with mono-therapy, a 3-drug ART more effectively reduced the vertical transmission of HIV^[6,7] without readily triggering the emergence of viral resistance^[8], which was more conducive to maternal health. Thus, mono-therapy has been classified as alternative rather than first-line regimen^[9]. WHO updated the indications and programs for ART administration to pregnant women in 2010, 2013, and 2015^[10-12].

The increasing availability of combination antiretroviral therapy (cART) has significantly reduced the number of new pediatric HIV infections and improved both maternal and infant survival^[13]. Accordingly, such regimens represent one of the most successful public health responses to HIV. Still, the success of these programs has led to new problems regarding the potential adverse effects of fetal exposure to antiretroviral drugs and HIV^[14,15]. Although the association between untreated advanced AIDS and adverse pregnancy outcomes is well documented^[16], some studies^[17-22] also suggest the risks of ART during pregnancy, including possible increases in the rates of preterm delivery, low birth weight and other adverse pregnancy outcomes. However, other studies found no significant differences in associations of ART regimens with

serious adverse fetal outcomes^[23,24]. In other words, the safety evidence is insufficient and conflicting, and the findings vary by the class of antiretroviral agents, which exhibit different placental and pharmacokinetic transference characteristics^[25].

Until recently, birth data of ART-exposed pregnancies were mostly derived from studies conducted in developed countries and African populations. In addition, most studies investigated antiretroviral agents not widely used in low-and middle-income countries, and many focused only on pregnancy outcomes but did not monitor the effects of these drugs on early infant growth. It is critical to monitor the rates of adverse outcomes among HIV-infected pregnant women receiving various ART regimens to determine whether adverse outcomes differ among regimen types^[15]. Therefore, we examined the effects of in utero HIV and ART exposure on adverse birth outcomes and early infant growth (4 weeks postpartum) in Guangzhou, China.

METHODS

Study Design and Participants

This prospective cohort study was conducted within the Integrated Prevention of MTCT (IPMTCT) program, a national system of HIV, syphilis and hepatitis B testing, treatment and surveillance that includes all pregnant women in China. This system covers all medical institutions, and all pregnant women are offered free opt-out HIV testing during their first prenatal visit in Guangzhou. If a patient is diagnosed with HIV, more detailed information is retrieved from the system and double-checked. Pregnant women living with HIV are offered free ART and follow-up care until delivery.

Infants born to HIV-infected mothers are subjected to high-risk neonatal management and are followed by pediatricians at 1, 3, 6, 9, 12, and 18 months of age. These infants are provided with free antiretroviral prophylaxis, HIV testing during early infancy, HIV-antibody testing and physical examinations involving standard procedures to establish the infection status. Infants undergo early-infant HIV testing and a physical examination by pediatricians at 1 and 3 months of age, respectively.

The present study included all HIV-infected pregnant women reported to the IPMTCT system in Guangzhou between October 2009 and May 2018. HIV-infected pregnant women who elected to terminate their pregnancy were excluded. Any adverse pregnancy outcomes of women with

singleton pregnancy were analyzed.

The study was conducted in accordance with the China IPMTCT guidelines. All study protocols were approved by the Center for National Women's and Children's Health, China CDC. Informed consent was obtained from all participating mothers.

Interventions for the Prevention of MTCT of HIV

The treatment regimen for the prevention of MTCT of HIV in Guangzhou was updated three times. By 2015, all HIV-positive pregnant women began receiving zidovudine-based cART (zidovudine, lamivudine and lopinavir/ritonavir) or efavirenz-based cART (tenofovir, lamivudine and efavirenz). Before 2015, two regimens were provided: a preventive antiviral regimen and a therapeutic antiviral regimen according to the maternal condition. The specific medication plans are listed in [Table 1](#). After ART initiation, clinical follow-ups were conducted through an integrated primary care service that provided antenatal and HIV care.

All HIV-exposed infants were prescribed once-daily nevirapine or twice-daily zidovudine within 6-12 hours after birth, which continued for 4-12 weeks depending on the MTCT risk assessment. All infants included in this study were fed artificially.

The study participants were categorized into three groups based on the medication regimens used by the pregnant women: (1) cART, a combination of three or more antiretroviral drugs; (2) ART comprising one or two antiviral drugs, referred to as 'mono/dual ART' or (3) no treatment.

Adverse Outcomes and Definitions

The outcomes of interest were the composite adverse pregnancy outcomes, including at least one of the following: (1) preterm birth, defined as a live birth before a gestational age of 37 weeks; (2) small for gestational age (SGA), defined as a live infant birthweight of less than the 10th percentile by gestational age and sex (based on the Intergrowth-21st Project Standards^[26]); (3) congenital anomaly detected by the nurse midwife during neonatal examination or structural screening *via* B-ultrasound; (4) stillbirth, defined as fetal death occurring before/during labor (based on a 1-min Apgar score of 0); (5) spontaneous abortion, defined as a spontaneous pregnancy loss at or before 20 weeks of gestation and (6) ectopic pregnancy.

The following main outcomes were used to evaluate the adverse effects of *in utero* HIV and ART exposure on early infants: (1) infant mortality, defined as the death of live-born infant within 1 year

old. (2) MTCT of HIV: as per the China IPMTCT guideline, HIV-exposed infants are diagnosed *via* virological testing at 4 and 12 weeks of age. A positive virological test indicates that the infant is HIV-infected, whereas a negative test indicates the need for repeated serological HIV antibody testing at 12 and 18 months of age. If both subsequent HIV antibody tests are positive, the child is considered HIV-infected. (3) Stunting, defined as a length-for-age Z score (LAZ) by sex of less than -2. (4) Underweight, defined as a weight-for-age Z score (WAZ) by sex of less than -2. (5) Wasting, defined as a weight-for-length Z score (WLZ) by sex of less than -2. We calculated the infant LAZ, WAZ, and WLZ based on Fenton^[27] and WHO^[28] growth reference standards, using a corrected age for infants born prior to 37 completed weeks of gestation.

Data Collection and Laboratory Procedures

The socio-demographic and clinical characteristics of HIV-positive mothers, including age, parity, educational level, occupation, marital status, household registration, maternal CD4 count and HIV viral load during the third trimester, mode of delivery and ART regimens, were collected. Information about their infants, including birthdate, gestational age, sex, birthweight, birthlength, birth defects, neonatal diseases, antiretroviral prophylaxis, early infant diagnosis and HIV antibody testing, weights and heights at all follow-up time-points were recorded using a national standardized format with assistance from medical professionals. All maternal CD4 counts and HIV viral loads during the third trimester were tested at Guangzhou No. 8 People's Hospital, a single specialized infectious disease hospital in Guangdong Province.

The accuracy of all case cards was evaluated. The gestational age at birth was expressed as completed weeks and based on the first- or second-trimester ultrasound test. In the absence of a recorded ultrasound result, the last menstrual period was used to calculate gestational age. The infant birthlength and birthweight were abstracted from clinical records. Trained nurses used a firm recumbent stadiometer to measure infant lengths to the nearest 0.1 cm and weights to the nearest 10 grams at all subsequent study visits.

Statistical Analysis

A descriptive analysis was used to describe the socio-demographic information of the study participants. The chi-square test was used to describe and compare categorical socio-

demographic data and clinical characteristics between different groups of participants receiving different treatment regimens. The *t*-test, analysis of variance and non-parametric test were used to compare continuous data and characteristics among different groups according to the results of normal distribution tests. The risks of adverse pregnancy outcomes and early infant growth outcomes associated with the treatment regimens were

estimated using a logistic regression adjusted for the mother's education level (primary or no education, junior high school, senior high school and higher, missing or unknown), ethnicity (Han, Others), parity (primiparous, parous), residence registration (Guangdong Province, other province/country), gestational age (weeks) at the first antenatal care visit and number of antenatal care visits. The mode of delivery (spontaneous labor, elective caesarean

Table 1. Description of the three maternal medication plans

Year	Prophylaxis regimen			Treatment regimen	
	Regimen / medication period	Regimen	Eligibility	Regimen	Eligibility
From Feb. 2011, to Aug. 2011	Recommended regimen	From gestational week 28 to labor: AZT 300 mg bid At labor: immediately AZT 300 mg + NVP 200 mg + 3TC 150 mg oral, and then AZT 300 mg every 3 hours, 3TC 150 mg every 12 hours Postpartum: AZT 300 mg bid + 3TC 150 mg bid for 1 week	No indication for ART, and did not receive ART previously	AZT + 3TC + NVP/EFV	Viral load > 1,000 copies/mL
	Minimum-level plan	NVP 200 mg post-labor, once			
From Sep. 2011 to June 2015	Pregnancy (≥ 14 w) and labor	AZT 300 mg + 3TC 150 mg + LPV/r 400/100 mg, bid or AZT 300 mg + 3TC 150 mg, bid, +EFV 600 mg, qd	CD4 cell count > 350 cells/mL and/or WHO stage I/II disease	AZT 300 mg + 3TC 150 mg, bid, + EFV 600 mg, qd, as early as possible	CD4 cell count ≤ 350 cells/mL and/or WHO stage III/IV disease
	Postpartum	1. Artificial feeding, stop ART after delivery 2. Breastfeeding, continue ART till 1 week after stopping breastfeeding			
	Labor	A single dose of NVP 200 mg, and AZT 300 mg + 3TC 150 mg, bid, until the end of delivery	Pregnant women with confirmed HIV infection during labor who fed their babies artificially		
	Postpartum	AZT 300 mg + 3TC 150 mg, bid, for 7 days		AZT 300 mg + 3TC 150 mg + NVP 200 mg, bid, as early as possible	CD4 cell count < 250 cells/mL and/or WHO stage III/IV disease
	Option 1	AZT + 3TC + LPV/r or AZT + 3TC + EFV (usage and dosage as listed above), 1 week after breastfeeding cessation	Pregnant women with confirmed HIV infection during labor who breastfed their babies		
	Option 2	A single dose of NVP 200 mg, and AZT 300 mg + 3TC 150 mg, bid, until the end of delivery; Continued AZT 300 mg + 3TC 150 mg, bid, post-labor for 7 days.			
After July 2015				AZT 300 mg bid + 3TC 300 mg qd + LPV/r 400/1,000 mg bid	Pregnant women who did not receive ART during pregnancy or labor, regardless of CD4 level and stage; start ART immediately.
				TDF 300 mg qd + 3TC 300 mg qd + EFV 600 mg qd 1. If virus suppression is ideal, retain the original regimen. 2. If virus suppression is not ideal, adjust the ART regimen.	Pregnant women who have received ART before pregnancy; evaluate effect based on the viral load.

Note. ART, antiretroviral therapy; AZT, Zidovudine; NVP, evirapine; 3TC, Lamivudine; EFV, efavirenz; LPV/r, Lopinavir/ritonavir; TDF, Tenofovir; qd, once-daily; bid, twice-daily.

section, emergency caesarean section), gestational age at delivery (days), birthweight (grams) and infant antiretroviral prophylaxis (nevirapine, zidovudine, unmedicated) were also included as covariates when analyzing the risks of early infant growth outcomes. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC, USA) and the Statistical Package for Social Sciences version 20 software package for Windows (SPSS Inc, Chicago, IL, USA). All reported *P* values are based on a two-sided test with a significance level of $\alpha = 0.05$.

RESULTS

From October 2009 to May 2018, 802 pregnant women with HIV were recruited in this study. Of these women, 361 received cART during pregnancy, 91 received mono/dual ART and 133 did not receive

ART. Of the 562 total live births, 6 infants were infected with HIV *via* MTCT (Figure 1).

No significant differences in the maternal age, marital status and newborn's sex were observed between the treatment regimens (Table 2). However, pregnant women who had not received ART were more likely to exhibit the following characteristics: non-Han ethnicity, lower education level, residence in another province/country, multiparous, first antenatal care at a later date, less antenatal care, a lower CD4 count during pregnancy, lower rate of selective cesarean section, later delivery, heavier birthweight of her baby and reduced likelihood of infant antiretroviral prophylaxis. HIV pregnant women receiving cART and those with mono/dual drug therapy began ART at similar gestational ages and had similar durations of ART during pregnancy.

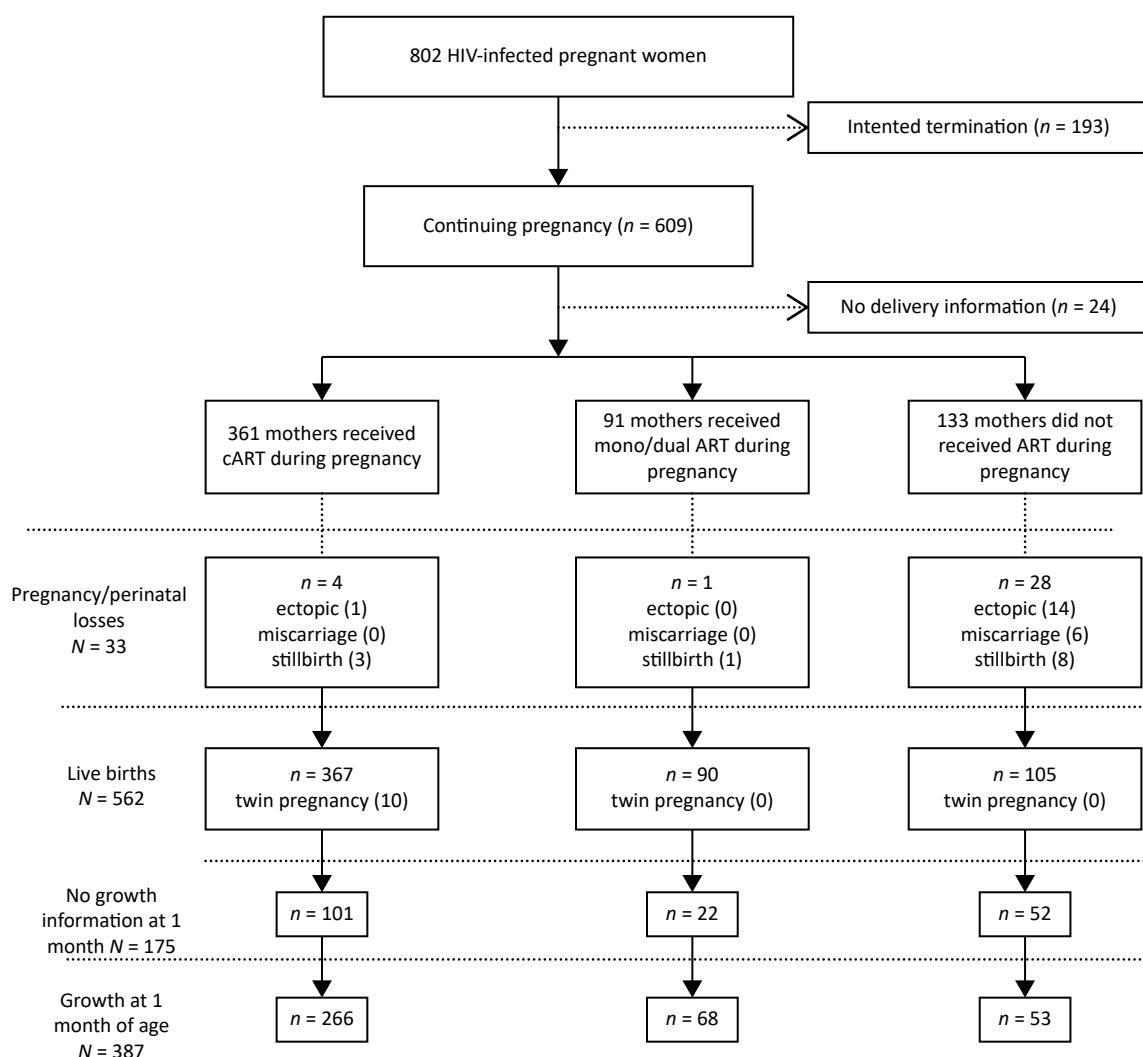


Figure 1. Flow chart indicating the patients excluded from and included in the final analysis.

Table 2. Maternal, pregnancy and delivery characteristics stratified by antiretroviral regimen during pregnancy

Characteristics	cART (N = 361)	Mono/dual ART (N = 91)	No treatment (N = 133)	P-value
Mother's age in years (mean $\pm$ SD)	29.8 $\pm$ 5.0	29.0 $\pm$ 5.1	28.6 $\pm$ 6.0	0.07
Ethnicity, n (%)				< 0.01
Han	329 (91.1)	84 (92.3)	103 (77.4)	
Others	32 (8.9)	7 (7.7)	30 (22.6)	
Mother's education, n (%)				< 0.01
Primary or no education	36 (10.0)	14 (15.4)	27 (20.3)	
Junior high school	179 (49.6)	42 (46.2)	57 (42.9)	
High school and higher	121 (33.5)	26 (28.6)	30 (22.6)	
Missing or unknown	25 (6.9)	9 (9.9)	19 (14.3)	
Mother's occupation, n (%)				0.03
Housewife or none	190 (52.6)	48 (52.7)	66 (49.6)	
Physical work	106 (29.4)	33 (36.3)	36 (27.1)	
Office work	20 (5.5)	6 (6.6)	4 (3.0)	
Missing or unknown	45 (12.5)	4 (4.4)	27 (20.3)	
Marital status, n (%)				0.10
Single	57 (15.8)	15 (16.5)	32 (24.1)	
Married	304 (84.2)	76 (83.5)	101 (75.9)	
Household registration, n (%)				0.02
Guangdong Province	191 (52.9)	44 (48.4)	52 (39.1)	
Other province/country	170 (47.1)	47 (51.6)	81 (60.9)	
Parity, n (%)				< 0.01
Primiparous	283 (78.4)	74 (81.3)	84 (63.2)	
Parous	78 (21.6)	17 (18.7)	49 (36.8)	
Gestational week at the first antenatal care in weeks (mean $\pm$ SD)	19.0 $\pm$ 9.1	21.3 $\pm$ 10.2	26.6 $\pm$ 12.8	< 0.01*
Gestational age starting ART in weeks (mean $\pm$ SD)	20.7 $\pm$ 9.7	21.6 $\pm$ 10.9	–	0.45
Duration of ART during pregnancy in weeks (mean $\pm$ SD)	16.7 $\pm$ 9.9	15.9 $\pm$ 10.4	–	0.48
Number of antenatal care visits (mean $\pm$ SD)	4.7 $\pm$ 2.7	3.8 $\pm$ 3.0	0.5 $\pm$ 1.2	< 0.01*
Last CD4 count (cells/ μ L) during pregnancy, n (%)				< 0.01
< 350	84 (23.3)	19 (20.9)	11 (8.3)	
$\geq$ 350	135 (37.4)	30 (33.0)	5 (3.8)	
Missing or unknown	142 (39.3)	42 (46.2)	117 (88.0)	
Mode of delivery, n (%)				< 0.01
Spontaneous labor	39 (10.8)	11 (12.1)	63 (56.8)	
Elective Caesarean section	265 (73.6)	64 (70.3)	13 (11.7)	
Emergency Caesarean section	56 (15.6)	16 (17.6)	35 (31.5)	
Gestational age at delivery in days (mean $\pm$ SD)	265.3 $\pm$ 10.4	265.3 $\pm$ 14.0	269.2 $\pm$ 20.8	< 0.01*
Birth weight in grams (mean $\pm$ SD)	2777.3 $\pm$ 449.0	2737.4 $\pm$ 432.5	3027.2 $\pm$ 521.6	< 0.01
Newborn's sex, n (%)				0.29
Male	83 (56.1)	41 (45.6)	54 (51.4)	
Female	65 (43.9)	49 (54.4)	51 (48.6)	
Infant antiretroviral prophylaxis, n (%)				< 0.01
Nevirapine	113 (76.9)	62 (68.9)	18 (17.1)	
Zidovudine	33 (22.4)	21 (23.3)	26 (24.8)	
Unmedicated	1 (0.7)	7 (7.8)	61 (58.1)	

Note. Mean $\pm$ SD = mean $\pm$ standard deviation; * Non-parametric test was used.

Overall, 202 (35.1%) of all HIV-infected women experienced an adverse pregnancy outcome, and 121 (31.3%) of all infants included in this analysis exhibited adverse effects on early growth at 4 weeks of age. The rates of adverse pregnancy outcomes, spontaneous abortion, ectopic pregnancy, stillbirth, infant death and perinatal HIV infection were higher among women not receiving ART, compared to those receiving cART or mono/dual ART ($P < 0.05$). However, the rate of SGA was higher among women receiving cART, compared to those not receiving treatment ($P < 0.05$) (Table 3). Meanwhile, no significant differences in congenital anomalies, preterm birth, adverse early growth, stunting, underweight and wasting at 1 month of age were observed among the three treatment groups.

The relationships among ART initiation timing of HIV-infected pregnant women and adverse outcomes suggested that 1-month-old infants of participants who started ART in the second or third trimester were more likely to be wasting than those of participants starting ART in the first trimester or delivery/postpartum ($P < 0.05$) (Table 4). No significant differences were observed in adverse pregnancy outcomes, infant death, HIV infection via MTCT, stunting and underweight at 1 month of age among the four groups of ART initiating timings.

In the unadjusted analyses and model 1, women who received cART had a significantly lower risk of any adverse pregnancy outcome [odds ratio (OR) =

0.59, 95% confidence interval (CI): 0.39-0.89; adjusted OR (aOR) = 0.53, 95% CI: 0.35-0.81] and higher risk of SGA (OR = 1.92, 95% CI: 1.04-3.56; aOR = 1.87, 95% CI: 1.00-3.51), compared to women not receiving treatment. After adjustment for pregnancy covariates, however, no differences in any adverse pregnancy outcomes or SGA were observed among women receiving different antiviral regimens Table 5). Neither the unadjusted nor adjusted analyses indicated differences in any adverse early growth outcomes of 4-week-old infants born to women receiving different antiviral regimens.

DISCUSSION

This study contributes to the limited body of evidence regarding the effects of ART regimens on mother-infant pairs in China and the safety and effectiveness of ART regimens during pregnancy. Our findings suggest that the rates of spontaneous abortion, ectopic pregnancy, stillbirth, infant death and HIV infection of infants via MTCT were higher among women who did not receive ART, suggesting that a failure to provide ART to HIV-infected pregnant women may have more serious consequences. In addition, although we observed no significant effect of the treatment regimen type on adverse early infant growth, the rate of SGA was higher among women receiving cART, compared

Table 3. Comparison of adverse pregnancy outcomes and adverse early growth effects stratified by antiretroviral regimen during pregnancy

Outcomes	cART ($n = 361$)	Mono/dual AR ($n = 91$)	No treatment ($n = 133$)	<i>P</i> -value
Adverse pregnancy outcomes, n (%)	112 (31.9)	31 (34.1)	59 (44.4)	0.04
Spontaneous abortion	0	0	6 (4.5)	–
Ectopic pregnancy	1 (0.3)	0	14 (10.5)	–
Stillbirth	3 (0.9)	1 (1.1)	8 (7.1)	< 0.01
Congenital anomaly	2 (0.6)	2 (2.2)	2 (1.8)	0.33
Preterm birth	44 (12.5)	15 (16.5)	23 (20.5)	0.33
SGA	77 (21.9)	17 (18.7)	14 (10.5)	0.02
Adverse early growth outcomes, n (%)	87 (32.7)	17 (25.0)	17 (32.1)	0.47
Infant death	1 (0.3)	0	3 (2.7)	< 0.01
HIV infection via MTCT	1 (0.3)	0	5 (4.4)	–
Stunting	41 (15.4)	12 (17.1)	2 (3.9)	0.07
Underweight	34 (12.7)	6 (8.6)	5 (9.8)	0.57
Wasting	35 (13.1)	4 (5.7)	6 (11.8)	0.23

Note. SGA, small for gestational age; MTCT, mother-to-child transmission.

with other regimens.

The correlation between preterm birth and ART

is often debated. Our study found a low rate of prematurity and no statistically significant

Table 4. Comparison of adverse pregnancy outcomes and adverse early growth effects stratified by ART initiation timing

Outcomes	1st Trimester (n = 89)	2nd Trimester (n = 247)	3rd Trimester (n = 84)	Delivery/postpartum (n = 39)	P-value
Adverse pregnancy outcomes, n (%)	37 (41.6)	86 (34.8)	26 (31.0)	12 (30.8)	0.46
Ectopic pregnancy	1 (1.1)	0	0	0	0.28
Stillbirth	0	1 (0.4)	0	3 (7.7)	0.24
Congenital anomaly	1 (1.1)	2 (0.8)	0	1 (2.6)	0.47
Preterm birth	12 (13.6)	45 (18.2)	8 (9.5)	6 (16.2)	0.27
SGA	26 (29.5)	52 (21.1)	20 (23.8)	5 (13.5)	0.21
Adverse early growth outcomes, n (%)	17 (23.3)	67 (36.6)	16 (28.6)	3 (14.3)	0.05
Infant death	0	0	0	1 (2.6)	0.28
HIV infection via MTCT	0	0	0	1 (2.6)	0.28
Stunting	13 (17.8)	32 (17.1)	7 (12.5)	1 (5.0)	0.49
Underweight	10 (13.7)	22 (11.8)	7 (12.5)	1 (5.0)	0.82
Wasting	2 (2.7)	29 (15.5)	8 (14.3)	0	0.01

Note. SGA, small for gestational age; MTCT, mother-to-child transmission.

Table 5. Adverse pregnancy outcomes and adverse early infant growth effects at 4 weeks of age stratified by antiretroviral regimens during pregnancy

Items	cART	Mono/dual ART	No treatment
Any adverse pregnancy outcome			
Number of women, n (%)	112/351 (31.9%)	31/91 (34.1%)	59/133 (44.4%)
Crude Model, OR (95% CI)	0.59 (0.39, 0.89)	0.65 (0.37, 1.13)	1 (ref)
Model 1 ^a , OR (95% CI)	0.53 (0.35, 0.81)	0.60 (0.34, 1.05)	1 (ref)
Model 2 ^b , OR (95% CI)	1.16 (0.64, 2.08)	1.28 (0.65, 2.51)	1 (ref)
SGA			
Number of women, n (%)	77/351 (21.9)	17/91 (18.7)	14/133 (10.5)
Crude Model, OR (95% CI)	1.92 (1.04, 3.56)	1.51 (0.70, 3.27)	1 (ref)
Model 1 ^a , OR (95% CI)	1.87 (1.00, 3.51)	1.47 (0.67, 3.22)	1 (ref)
Model 2 ^b , OR (95% CI)	2.10 (0.99, 4.44)	1.53 (0.64, 3.66)	1 (ref)
Any adverse early growth			
Number of children, n (%)	87/266 (32.7%)	17/68 (25.0%)	17/53 (32.1%)
Crude Model, OR (95% CI)	1.03 (0.55, 1.94)	0.71 (0.32, 1.57)	1 (ref)
Model 1 ^a , OR (95% CI)	1.07 (0.56, 2.03)	0.75 (0.33, 1.69)	1 (ref)
Model 2 ^b , OR (95% CI)	1.18 (0.55, 2.57)	0.81 (0.33, 2.00)	1 (ref)
Model 3 ^c , OR (95% CI)	1.10 (0.39, 3.11)	0.71 (0.23, 2.23)	1 (ref)

Note. SGA, small for gestational age. ^aModel 1: covariates mother's education, ethnicity, household registration, parity; ^bModel 2: covariates in model 1, and gestational week at the first antenatal care, number of antenatal care; ^cModel 3: covariates in model 2, and Mode of delivery, gestational age at delivery, birthweight and infant antiretroviral prophylaxis.

relationship between preterm birth and the use of different ART regimens, consistent with previously published findings^[29-31]. Although recent studies suggested that a protease inhibitor (PI)-based ART regimen may increase the risk of preterm birth^[17,32], our further analysis did not confirm this association (The rates of preterm birth were 15.4%, 15.5%, 16.7%, and 16.2% for HIV-infected women receiving NNRTI-based cART, receiving PI-based cART, receiving mono/dual ART and receiving no treatment, respectively. Data was shown in Table 6. Some studies demonstrated fetal exposure to antiretroviral drugs increased the risks of preterm delivery and other adverse pregnancy outcomes^[15,21]. Differences in the types of antiviral drugs, timing of ART initiation and maternal HIV disease stage prior to conception may have a stronger influence on the risk of preterm birth than the ART regimen type. In addition, the causes of preterm birth are multifactorial, and associated risk factors include the socioeconomic status, maternal body-mass index, maternal smoking, under-nutrition, environmental exposure and maternal infection^[33].

Few studies that investigated the effects of in utero exposure to ART and the occurrence of SGA births have yielded inconclusive results. Our study suggested that exposure to cART during pregnancy was associated with a higher risk of SGA when compared with no treatment. Erika Aaron found that women who received a non-nucleoside reverse-transcriptase inhibitors-based regimen (NNRTI-based cART) were less likely to have a SGA neonate, compared to women receiving a PI-based regimen^[34]. However, after adjusting for socio-demographic factors, medication and HIV disease severity, no association of ART regimen type was associated with SGA. Still, one study conducted in Botswana found an association of SGA with cART during pregnancy^[30]. The ATHENA cohort suggested that the use of triple-drug ART, particularly a PI-based regimen, prior to conception was associated

with SGA^[35]. Other studies reported no evidence of an association between ART during pregnancy and SGA at delivery^[31,36,37].

A systematic review reported inconclusive findings regarding the effects of in utero HIV and ART exposure on postnatal weight gain in HIV-exposed infants^[38]. A smaller study conducted in China found no effect of maternal cART use during pregnancy on infant growth at 18 months of age^[39], consistent with our findings. Still, other studies demonstrated that HIV-exposed infants exhibited poorer growth than their HIV-unexposed counterparts^[40,41]. One study conducted in Botswana suggested that children exposed to cART in utero had significantly lower length-for-age and weight-for-age Z scores, compared to those exposed to zidovudine monotherapy^[29]. Another study conducted in South Africa found no association between the duration of Tenofovir exposure in utero and the early linear growth of infants^[42]. These inconsistent findings may be attributed to the use of different antiviral drugs by the mothers, the evaluation of infants in different age groups and differences in the feeding modes and nutritional statuses during early infancy.

Our study had several strengths, including the reported effects of in utero HIV and ART exposure on pregnancy outcomes and early infant growth at 4 weeks-age. Such research is rare in China, where a huge number of HIV-infected women have yet to receive ART in compliance with the implemented PMTCT. We comprehensively discussed the effects of three groups of mothers—those receiving no treatment, mono/dual ART or cART—to inform target populations and policy makers for advance the universal access.

However, our study also had some limitations. First, the study used an observational design, rather than a randomized controlled clinical trial design, to address whether the uses of different ART regimens would be associated with adverse pregnancy outcomes and adverse early infant growth. Some unmeasured confounders may have biased our results. We could not compare other outcomes such as the maternal viral load at the time of labor, maternal nutrition, maternal BMI and the induced or spontaneous status of preterm birth. However, several studies of pregnant HIV-infected women documented associations between poor nutrition, a low maternal BMI and advanced maternal HIV disease^[43,44]. Second, few women with HIV underwent CD4 count analyses during the third trimester, as the new ART treatment guidelines do

Table 6. Association of preterm birth with NNRTI-based cART, PI-based cART, Mono/dual ART and no treatment

Item	Preterm birth	Term birth	P-value
NNRTI-based cART	23	126	0.99
PI-based cART	34	186	
mono/dual ART	15	75	
No treatment	17	88	

not require this test prior to ART initiation. However, this deficiency would randomly appear among the three groups. Third, growth information was not available for 175 of 562 newborns (31.1%), which may have biased the research results. Although 90% of infants received early HIV testing in recent years, the body length, weight and other indicators were not measured in many children because their guardians considered the physical growth of infants to be unimportant. Finally, this study focused only on the short-term effects of pregnancy outcomes and infant growth at 4 weeks' postpartum and could not address the long-term effects of intrauterine exposure to ART.

In conclusion, the administration of ART to HIV-infected pregnant women will remain a global high-priority issue, as even mono/dual ART can improve pregnancy outcomes and infant survival in resource-limited countries. The reduction of serious adverse fetal and infant outcomes and the risk of MTCT are critical issues. Further studies are needed to monitor the short- and long-term health effects of HIV and ART exposure and thus optimize antiretroviral therapy during pregnancy.

ACKNOWLEDGMENTS

We thank all pregnant women and their children for their participation in the study. We are grateful to the obstetric and pediatric care providers who have assisted the implementation of the IPMTCT program.

CONTRIBUTORS' CONTRIBUTION

LIN Sui Fang and MA Ying Hua conceptualized and designed the study; HU Fang carried out the whole program, performed the initial analyses, drafted the initial manuscript; LIANG Jing Jing interpreted the data, critically reviewed the manuscript; LU Jian Jun coordinated and supervised data collection; HU Yi Fei critically reviewed the manuscript; HU Yan coordinated and supervised data collection; YU Jia coordinated and supervised data collection; ZOU Xing Wen coordinated and supervised data collection.

Received: February 26, 2019;

Accepted: July 12, 2019

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