Pregnancy and Infant Outcomes Among Women Using the Dapivirine Vaginal Ring in Early Pregnancy

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Background: Monthly use of the dapivirine vaginal ring has been shown to be safe and effective for HIV-1 prevention in nonpregnant reproductive-aged women. The impact of dapivirine on pregnancy outcomes and infant is not known. We compared pregnancy incidence and outcomes by study arm among HIV-1–uninfected women who became pregnant while participating in MTN-020/ASPIRE.

Methods: ASPIRE was a randomized, double-blind, placebo-controlled phase III safety and effectiveness study of the dapivirine ring for HIV-1 prevention. Sexually active women aged 18–45 years from Malawi, South Africa, Uganda, and Zimbabwe were enrolled. Urine pregnancy tests were performed monthly, and, if positive, study product was withheld during pregnancy and breastfeeding. Pregnancy-related outcomes included the following: pregnancy incidence, pregnancy outcomes (live birth, preterm birth, pregnancy loss, and congenital anomalies), and infant growth.

Results: Of 2629 women enrolled in ASPIRE, 169 became pregnant during follow-up, resulting in 179 incident pregnancies and 181 pregnancy outcomes. No difference in pregnancy incidence by study arm was observed (hazard ratio = 0.93; 95% confidence interval: 0.68 to 1.26). The distribution of pregnancy outcomes was similar by study arm, and no difference was noted in the frequency or pattern of congenital anomalies or infant growth parameters by study arm.

Conclusions: Dapivirine use in the periconception period does not seem to be associated with adverse effects on pregnancy or infant outcomes. Our findings provide support for additional safety studies of the dapivirine ring throughout pregnancy.

Key Words: dapivirine, pregnancy, HIV prevention, women, Africa

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INTRODUCTION

Reproductive-aged women are disproportionately affected by HIV-1, accounting for 56% of adults living with HIV-1 in sub-Saharan Africa.[1] In addition, pregnancy is a time of heightened HIV-1 risk, and women in sub-Saharan Africa have some of the highest fertility rates in the world.[2,3] As a result, reproductive-aged women living in this region represent a key target population for HIV-1 prevention interventions. As new biomedical HIV-1 prevention interventions prove efficacious, it is critical to evaluate the safety of these tools in pregnancy, in part so that country regulatory authorities have data to inform conditions of licensure, including for pregnant women.

A vaginal ring containing dapivirine, a novel non-nucleoside reverse transcriptase inhibitor, was well-tolerated and reduced HIV-1 incidence in 2 phase III randomized trials[4,5] and represents a promising new HIV-1 prevention technology for reproductive-aged women. Data from animal toxicity studies

that evaluated different concentrations of dapivirine vaginal gel, including concentrations substantially higher than the available concentration in the vaginal ring, did not identify any adverse effects on the maternal animals or the developing embryo/fetus.[6] However, the effects of dapivirine exposure in humans during pregnancy are unknown. Despite contraceptive counseling and provision of highly effective contraceptive methods during the conduct of the dapivirine ring trials, pregnancies occurred, resulting in inadvertent exposure to dapivirine during the periconception period. Study product use was stopped once a pregnancy was diagnosed; therefore, investigational product exposure was limited to early pregnancy. The objective of this analysis was to compare pregnancy incidence, pregnancy outcomes, and infant growth among HIV-1–uninfected women randomized to receive the dapivirine ring versus matching placebo in MTN-020/ASPIRE.

METHODS

Study Population and Procedures

ASPIRE was a phase III, double-blinded, placebo-controlled randomized trial that assessed the safety and effectiveness of the dapivirine vaginal ring for HIV-1 prevention (Clinicaltrials.gov NCT01617096). Detailed study procedures have been described elsewhere.[4] Briefly, 2629 women from Malawi, South Africa, Uganda, and Zimbabwe were enrolled between 2012 and 2014. Participants were HIV-1–uninfected, between 18 and 45 years of age, not pregnant or breastfeeding, sexually active, and in good health. The use of a highly effective method of contraception at enrollment was a requirement to enroll in the trial. Eligible women were randomly assigned in equal proportions to receive either the dapivirine vaginal ring or placebo ring. Participants provided written informed consent, and applicable local and national ethical and regulatory authorities approved the study protocol.

At enrollment and monthly follow-up visits, standardized face-to-face interviews were conducted to collect data on demographic, clinical, and behavioral characteristics, such as study product use, contraceptive method, reported condom use, and sexual behaviors. Contraceptive methods were provided on-site or could be obtained from local health providers. Women were permitted to change contraceptive method during follow-up. HIV-1 antibody tests were performed monthly, and study product was permanently discontinued in the event of HIV-1 seroconversion. Urine β-human chorionic gonadotropin (β-hCG) tests were performed monthly or when clinically indicated. To monitor adherence to study product during the trial, plasma samples were collected quarterly and were tested for dapivirine using a validated liquid chromatography–mass spectrometry assay.[4,7]

All participants were counseled at enrollment regarding that the effect of exposure to the study drugs in pregnancy, including the effect of the study drug on the fetuses of women who use the vaginal ring when pregnant, is unknown. Participants who became pregnant during follow-up were referred to local health services for further care depending on her pregnancy intentions. Study product was withheld for the duration of pregnancy and breastfeeding, and participants whose pregnancies resulted in a live birth were counseled on the benefits of infant breastfeeding in accordance with World Health Organization (WHO) recommendations and local guidelines.[8] All pregnancies were followed until an outcome could be ascertained. Pregnancy outcomes and infant congenital anomalies identified at the time of delivery were determined by participant report and medical record review, when available, and recorded on case report forms. Product use was resumed after the pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff, and after complete cessation of breastfeeding, as reported by the participant.

Participants who became pregnant in ASPIRE were invited to enroll in MTN-016, a prospective open cohort study designed to assess whether exposure to investigational antiretroviral-based HIV prevention agents impacts pregnancy and infant outcomes during the first year of life.[9] Separate written informed consent was provided for participation in MTN-016. Infants were first assessed within 10 days of birth and followed for 1 year with follow-up visits at months 1, 6, and 12. Growth was assessed by study staff using serial measurements of length, weight, head/abdominal circumference, and the WHO growth charts at all[10] scheduled study visits.

Statistical Analysis

Women who reported a bilateral tubal ligation at enrollment, were found to be HIV-1–infected at enrollment, or did not return for follow-up were excluded from the present analysis. In this analysis, pregnancy was defined by a single positive urine pregnancy test. Pregnancy incidence by arm was calculated per 100 person-years of follow-up using Poisson modeling and compared using an Andersen–Gill proportional-hazards model with censoring at HIV-1 infection (date of first positive HIV-1 rapid test). Gestational age and estimated date of delivery were assigned using several methods, which may have been used in combination, including date of last menstrual period, ultrasound, or physical examination. The prevalence of each pregnancy outcome and congenital anomalies were summarized by arm using descriptive statistics and compared using Fisher's exact test.[10] Infant growth parameters were standardized using the WHO Z-score. Two-sample t tests and linear mixed-effects models with fixed effects for time (age in years, modeled as a flexible restricted cubic spline), and infant gender, were constructed to compare sex-adjusted Z-scores for each growth parameter by study arm of the mother.

A sensitivity analysis was performed categorizing participants in the dapivirine arm based on plasma concentrations of dapivirine in plasma, collected at quarterly visits. Participants with plasma dapivirine levels >95 pg/mL were considered to have had recently used the ring (a level that corresponds to approximately 8 hours of continuous ring use).[4,7] Pregnancy and infant outcomes were compared between participants with recent ring use based on the plasma sample at pregnancy detection (or within 6 months before pregnancy detection) compared to participants with no recent ring use (≤95 pg/mL dapivirine detected in plasma) and participants in the placebo arm using the same methods described above. All analyses were performed using R, version 3.2 (Vienna, Austria).

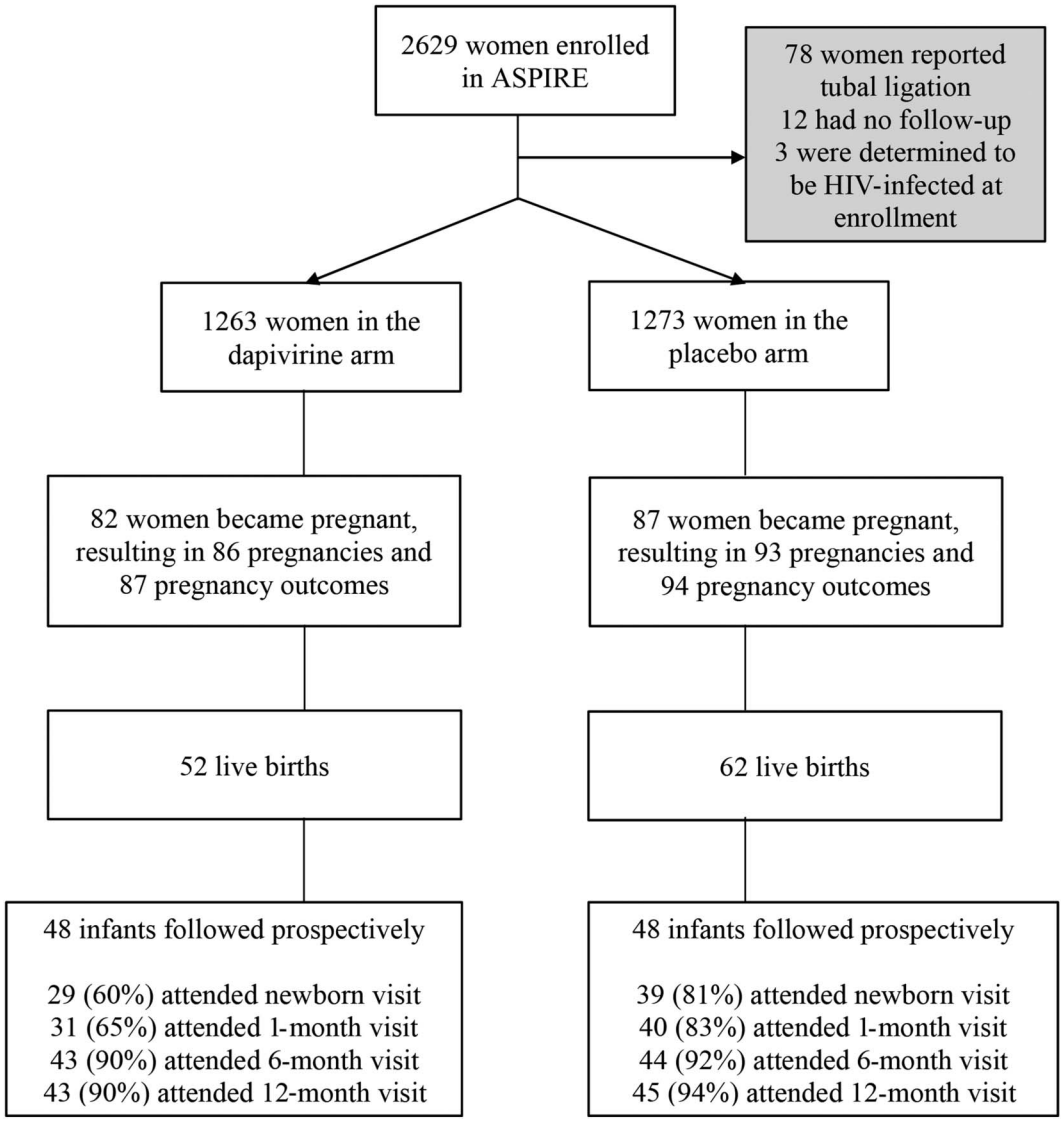

FIGURE 1. Analysis population.

RESULTS

Population Characteristics

Of 2629 women enrolled in ASPIRE, 78 reported tubal ligation at enrollment, 3 were determined to be HIV-1–infected at enrollment, and 12 had no follow-up. Therefore, our analysis population included 2536 women, of whom 1263 (50%) were assigned to the dapivirine arm and 1273 (50%) assigned to the placebo arm (Fig. 1). There were 179 incident pregnancies among 169 women. Among the 179 pregnancies, 175 pregnancies resulted in a single outcome, 3 pregnancies resulted in 2 outcomes (twins), and 1 pregnancy had no outcome available, resulting in a total of 181 pregnancy outcomes. Of the 169 women who became pregnant, the median age at enrollment in ASPIRE was 23 years [interquartile range (IQR) 21–27], median number of live births was 2 (IQR 1–2), 65 (38%) were married, and 94 (56%) had secondary education or greater (Table 1).

Pregnancy Incidence and Outcomes

Overall, we observed 179 pregnancies during 4334 person-years of follow-up [incidence = 4.1 per 100 person-years; 95% confidence interval (CI) 3.5 to 4.9]. There were 86 pregnancies during 2162 person-years of follow-up in the dapivirine arm (incidence = 4.0 per 100 person-years; 95% CI: 3.1 to 5.1) and 93 pregnancies during 2172 person-years of follow-up in the placebo arm (incidence = 4.3 per 100 person-years; 95% CI: 3.4 to 5.5), with no difference in pregnancy incidence by study arm (Table 2). Median gestational age at pregnancy detection was 5.4 weeks (IQR 4.3–6.8), which also did not differ by arm (dapivirine arm = 5.4 weeks; placebo arm = 5.6 weeks). The proportion of pregnancies by country generally mirrored the proportion of participants enrolled in ASPIRE from the participating countries, with 53% of pregnancies occurring among participants from South Africa, 27% from Zimbabwe, 15% from Uganda, and 5% from Malawi.

TABLE 1. Baseline Characteristics of Women Who Became Pregnant in ASPIRE*

	Became Pregnant During Follow-up			Did Not Become Pregnant During Follow-up, N = 2367
	Placebo, n = 87	Dapivirine, n = 82	Overall, N = 169	
Age	24 (21, 27)	23 (20, 27)	23 (21, 27)	26 (22, 31)
Married	36 (41%)	29 (35%)	65 (38%)	962 (40%)
Secondary education or greater	50 (57%)	44 (54%)	94 (56%)	1093 (46%)
No. of live births	2 (1, 2)	1 (1, 2)	2 (1, 2)	2 (1, 3)
Country:				
Malawi	6 (7%)	3 (4%)	9 (5%)	238 (10%)
South Africa	43 (49%)	47 (57%)	90 (53%)	1293 (54%)
Uganda	12 (14%)	13 (16%)	25 (15%)	221 (9%)
Zimbabwe	26 (30%)	19 (23%)	45 (27%)	630 (26%)
Condom used at last sex act	56 (64%)	51 (62%)	107 (64%)	1366 (57%)
Any curable STI at enrollment†	11 (13%)	24 (29%)	35 (21%)	501 (21%)

*Data presented as N (%) or median (IQR).
†STI, sexually transmitted infection; this included *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, or syphilis. STIs were treated per local guidelines.

The distribution of pregnancy outcomes by arm is presented in Table 2. Of 181 pregnancy outcomes, there were 105 (58%) full-term live births, 9 (5%) preterm births, 39 (22%) spontaneous abortions, and 22 (12%) elective/therapeutic abortions. There were 4 stillbirth/intrauterine fetal deaths, 2 in each arm (2%). The distribution of pregnancy outcomes did not differ by study arm. Of 114 deliveries resulting in a live birth, the majority of deliveries (93%) occurred at a hospital or clinic, with spontaneous vaginal delivery being the most common method of delivery (77%). Caesarean birth occurred in 24 (21%) of deliveries and did not differ by study arm. In sensitivity analyses, no differences were noted by dapivirine drug detection in plasma around the time that pregnancy was detected (Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B230).

Infant Outcomes and Development

Data on congenital anomalies identified around the time of delivery were available for 107 of 114 live births. The frequency and type of reported anomalies by maternal study arm are presented in Table 2. The overall prevalence of anomalies (all structural) was 7% and did not differ by study arm ($P > 0.99$, Table 3). Ninety-six infants were enrolled into MTN-016 and underwent regular assessments of growth through the first year of life. Overall infant retention was high, with 92% completing the 12-month follow-up visit (Fig. 1). Summaries of Z-scores at each study visit and by study arm are presented in Table 4 and Figures 2A–C. Across all visits, we observed no differences in infant weight (mean difference −0.04; 95% CI −0.36 to 0.28), length (mean difference −0.20; 95% CI −0.63 to 0.28), or head circumference (mean difference 0.15; 95% CI −0.27 to 0.57) by study arm, indicating no reductions in infant growth among women with inadvertent exposure to dapivirine in early pregnancy compared with women in the placebo arm. Similar to the pregnancy outcomes analysis, no differences were noted in infant outcomes by dapivirine drug detection in plasma around the time that pregnancy was detected (Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B230).

DISCUSSION

Among women participating in a randomized trial of the dapivirine vaginal ring for HIV-1 prevention, we observed no differences in the incidence of pregnancy between the dapivirine ring and placebo arms, and no adverse effects on pregnancy outcomes, infant congenital anomalies, or infant growth through the first year of life. Although contraception use was a requirement for study eligibility, pregnancies did occur, affording an important opportunity to assess the effect of dapivirine exposure in early pregnancy. To the best of our knowledge, this is the first study to report on pregnancy and infant outcomes among women exposed to the dapivirine vaginal ring during the periconception period. Our findings add to the body of evidence demonstrating the safety of the dapivirine vaginal ring for HIV-1 prevention in reproductive-aged women.

The high fertility rate in sub-Saharan Africa contributes to 25% of pregnancies globally.[3] These pregnancies represent a mix of intended and unintended pregnancies. Pregnancy is a particularly vulnerable time for women in many respects, including a time of increased risk for HIV-1 acquisition.[2] Furthermore, women who acquire HIV-1 during pregnancy are more likely to pass the infection on to their infant during pregnancy or breastfeeding.[11,12] It is imperative that pregnant women have access to safe and effective methods for HIV-1 prevention. Antiretroviral-based strategies represent a promising approach for HIV-1 prevention. For the majority of antiretroviral medications, most of which are used solely for HIV-1 treatment, data on teratogenicity related to in utero exposure are available through the Antiretroviral Pregnancy Registry.[13] Data collected to date are generally reassuring, showing no association between antiretroviral medications used for HIV-1 treatment and teratogenicity.[14] However, some evidence suggests that adverse pregnancy outcomes, such as small for gestational age and preterm birth, may be more common among HIV-infected women using certain antiretroviral regimens.[15–17] In addition, recent observational data regarding a potential association between dolutegravir and risk of neural tube defect underscore the need for continued safety assessments of antiretroviral medications used during pregnancy among both HIV-uninfected and HIV-infected women.[18]

At present, oral combination of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) is the only antiretroviral medication approved by national regulatory authorities as prophylaxis for the prevention of HIV-1.[19,20] Before being evaluated as an HIV-1 prevention intervention, these medications were widely used in HIV-1 treatment, including among HIV-1–infected pregnant women. As a result, robust data support the safety of TDF and FTC/TDF use during pregnancy

TABLE 2. Pregnancy Incidence and Outcomes by Study Arm

	Placebo	Dapivirine	Overall
Pregnancy incidence			
No. of pregnancies	93	86	179
Pregnancy incidence (95% CI)*	4.3 (3.4–5.5)	4.0 (3.1–5.1)	4.1 (3.5–4.9)
Pregnancy outcomes	N = 94†	N = 87	N = 181†
Full-term birth	53 (56%)	52 (60%)	105 (58%)
Preterm birth	9 (10%)	0 (0%)	9 (5%)
Stillbirth/intrauterine fetal demise	2 (2%)	2 (2%)	4 (2%)
Spontaneous abortion	21 (22%)	18 (21%)	39 (22%)
Therapeutic/elective abortion	8 (9%)	14 (16%)	22 (12%)
Ectopic pregnancy	1 (1%)	1 (1%)	2 (1%)
Congenital anomalies	N = 59	N = 48	N = 107
Any congenital anomaly	4 (7%)	4 (8%)	8 (7%)

*Per 100 person-years.

†One hundred seventy-five pregnancies resulted in a single outcome, 3 pregnancies resulted in 2 outcomes (twins), and 1 pregnancy had no outcome available, resulting in a total of 181 pregnancy outcomes.

TABLE 3. Additional Details on Reported Congenital Anomalies

Participant	Study Arm	Pregnancy Outcome	Anomaly
1	Dapivirine	Full-term live birth	Umbilical hernia that was reducible
2	Dapivirine	Full-term live birth	Micrognathia and epicanthic folds
3	Dapivirine	Full-term live birth	Inguinal hernia that was repaired
4	Dapivirine	Full-term live birth	Craniofacial (structural) right frontal skull depression positional plagiocephaly
5	Placebo	Full-term live birth	Reducible umbilical hernia, approximately 4 cm in diameter
6	Placebo	Full-term live birth	Umbilical hernia, uncomplicated
7	Placebo	Full-term live birth	Umbilical hernia noted, 1.8 by 2 cm, reducible and nontender
8	Placebo	Full-term live birth	Polydactyly both hands (bilateral)

among HIV-1–infected women.[21] In addition, findings from the Partners PrEP trial showed no difference in pregnancy incidence, pregnancy outcomes, congenital anomalies, or infant growth among Kenyan and Ugandan women exposed to TDF or FTC/TDF during the periconception period compared with placebo.[22] These data combined with existing evidence from HIV-1 treatment studies led the WHO to recommend that oral PrEP should be offered as an additional prevention choice for pregnant women at substantial risk of HIV infection as part of combination prevention approaches,[23] including as part of routine antenatal care.[24]

By contrast, dapivirine is a novel non-nucleoside reverse transcriptase inhibitor that is not used for treatment and has limited safety data on use in pregnancy. In addition, the vaginal ring is a new method of antiretroviral delivery. Reassuringly, we observed no impact of dapivirine exposure during the periconception period on any pregnancy or infant outcomes. Data on pregnancy and infant outcomes among women at risk for HIV-1 acquisition in resource-limited settings are sparse. The overall frequency of pregnancy outcomes and congenital anomalies observed in ASPIRE was similar to those reported in the Partners PrEP trial (ASPIRE preterm births = 5.0% versus Partners PrEP = 5.7%; ASPIRE pregnancy loss = 36.8% versus Partners PrEP = 33.3%; ASPIRE congenital anomalies = 7.4% versus Partners PrEP = 6.7%). Participants in both ASPIRE and Partners PrEP underwent monthly pregnancy testing using highly sensitive urine β-hCG assays to detect pregnancies before clinical signs or symptoms to limit fetal exposure to study product. As a result of such frequent testing, we identified pregnancies that terminated spontaneously before clinical recognition (chemical pregnancies), thus increasing the number of pregnancy losses. However, our results are consistent with previous studies that conducted frequent and sensitive pregnancy monitoring, which reported a pregnancy loss rate of 31%.[25]

Of note, our pregnancy incidence was substantially lower than what has been reported in other HIV prevention trials with similar contraceptive requirements for enrollment.[26] Efforts to increase uptake of long-acting reversible contraceptive methods contributed to the overall lower pregnancy incidence,[27] which did not differ by study arm. As new antiretroviral-based HIV-1 prevention interventions are evaluated, such as injectable cabotegravir,[28] it is critical that rigorous and expeditious safety assessments be conducted to ensure that novel antiretroviral-based prevention interventions are safe and effective for use during pregnancy.

Our study includes a number of strengths, including leveraging the randomized controlled trial design to assess outcomes by study arm, infant follow-up through 12 months of life, and high retention in the parent study as well as the prospective cohort for mothers and infants. However, several limitations should be considered when interpreting the results. Dapivirine exposure was limited to the periconception period with a short duration of in utero exposure after conception. Future studies should evaluate the use of the dapivirine vaginal ring at different points during gestation to evaluate whether ring use is safe throughout pregnancy. In ASPIRE, we enrolled over 2000 women; however, the number of pregnancies and live births that occurred was relatively small. As a consequence, there were few congenital anomalies; therefore, results should be interpreted with caution given the small numbers and potential for misclassification based on maternal self-report in cases where medical records were not available. Reassuringly, there were no patterns of anomalies that indicated a potential association with dapivirine ring use.

Safe and effective HIV-1 prevention interventions are urgently needed for women during the full course of their reproductive life, including during pregnancy, when HIV incidence is higher than in nonpregnant women of the same age. The dapivirine vaginal ring represents an exciting new HIV-1 prevention technology, and assessing its safety for

TABLE 4. Standardized Infant Z-Scores for Growth Measures by Study Arm and Visit

		Placebo		Dapivirine		
Measurement	**Visit**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	***P***
Head circumference-for-age	Newborn	39	0.29 (1.39)	29	0.83 (1.33)	0.11
	Month 1	40	0.94 (2.08)	31	0.77 (1.39)	0.68
	Month 6	44	0.73 (1.47)	43	0.95 (1.56)	0.51
	Month 12	45	0.99 (1.12)	43	1.34 (1.86)	0.30
Length-for-age	Newborn	39	−0.12 (1.58)	29	0.09 (1.47)	0.56
	Month 1	40	−0.14 (1.38)	31	−0.30 (1.45)	0.64
	Month 6	44	−0.25 (1.68)	43	−0.37 (1.74)	0.95
	Month 12	45	−0.16 (1.64)	43	−0.23 (1.43)	0.83
Weight-for-age	Newborn	39	−0.39 (0.92)	29	−0.20 (0.84)	0.37
	Month 1	40	−0.11 (0.85)	31	−0.47 (1.15)	0.16
	Month 6	44	0.24 (1.52)	43	0.11 (1.01)	0.66
	Month 12	45	−0.00 (1.28)	43	0.14 (1.03)	0.51

use in pregnancy is of critical importance. Our findings provide important evidence supporting the safety of dapivirine use in early pregnancy and provide support for additional studies of the dapivirine ring at different gestational ages to confirm the safety of dapivirine ring use throughout pregnancy.

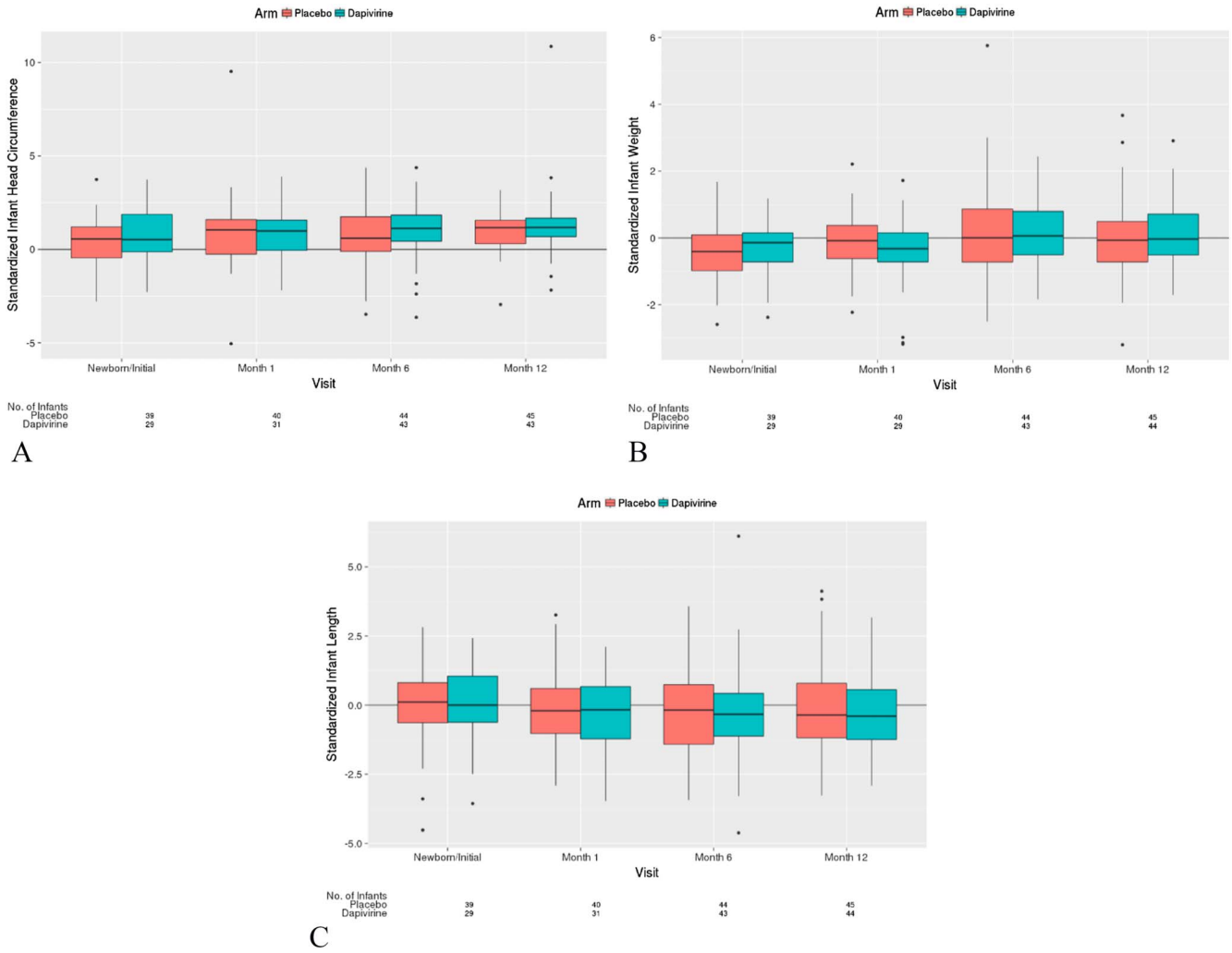

FIGURE 2. Box plots of standardized infant growth measures by study arm and visit.

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