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clinical practice

Surveillance of pregnant women with potential exposure to Zika virus following travel

D. SPILIOPOULOS, M. PANCHAL, D.L. ECONOMIDES

SUMMARY: **Surveillance of pregnant women with potential exposure to Zika virus following travel.**

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Aim. *To describe the experience of a single fetal medicine unit in evaluating pregnant women with potential exposure to Zika virus (ZIKV) following travel.*

Method. *Between February 2016 and June 2017, a multidisciplinary team evaluated pregnant women by developing a local pathway based on Public Health England guidance. All pregnant women were offered serial fetal ultrasound scans (USS). If they presented with a history of clinical symptoms consistent with ZIKV infection during or within two weeks of travel or fetal USS was suggestive of microcephaly, reverse transcriptase polymerase chain reaction (RT PCR) and/or serology was used.*

Results. *69 women were referred. Eight patients reported symptoms consistent with ZIKV infection (11.6%) and six (8.7%) patients reported mosquito bites. Maternal exposure was mainly during the preconception period and the first trimester in 35 (50.8%) and 19 (27.5%) women, respectively. Prenatally, there was no evidence of microcephaly in any of the 69 referrals. Sixty-two live births and seven miscarriages were reported. One patient had serology confirming ZIKV infection during pregnancy. At birth, 57 babies had normal head circumference (HC) measurements, including the baby born to the Zika positive mother. Two babies had small HC measurements but were not infected and were small for gestational age.*

Conclusions. *One case of maternal ZIKV infection was detected but without any fetal congenital abnormalities postnatally. The number of potentially infected patients referred to our unit is a demonstration of the concern regarding perinatal ZIKV infection in the pregnant population.*

KEY WORDS: Pregnancy - Zika virus (ZIKV) - Microcephaly - Head circumference.

Introduction

Zika virus (ZIKV) is an arthropod-borne flavivirus transmitted by Aedes mosquitoes (most commonly Aedes aegypti) (1-4). The World Health Organisation (WHO) declared ZIKV and its associated complications a public health emergency of international concern (PHEIC) between February and November 2016. Zika virus and its associated consequences remain a significant and enduring public health challenge (5, 6).

Zika-specific RNA has been found in saliva, urine, blood, semen, amniotic fluid and breast milk, raising issues of global public health prevention and control of ZIKV infection (7-17). Approximately 20% of patients presents clinical manifestations of infection including symptoms such as maculopapular pruritic rash, arthralgia and conjunctivitis.

Vertical transmission of ZIKV from mother to fetus during pregnancy has been associated with serious sequelae. The greatest risk is with first trimester infection, but serious sequelae can be observed in offspring after infection in any trimester (18-21). In utero ZIKV infection can result in fetal growth restriction and central nervous system abnormalities such as ventriculomegaly (33%), microcephaly (24%) and intracranial calcifications (27%) (22). The major clinical features associated with congenital Zika syndrome include microcephaly, facial disproportion, hypertonia/spasticity, hyperreflexia, seizures, irritability, arthrogryposis, ocular abnormalities and sensorineural hearing loss.

Fetal Medicine Unit, Royal Free London NHS Foundation Trust, London, UK

Corresponding author: Dimitrios Spiliopoulos, e-mail: dimspiliop@yahoo.com; spiliodimi@gmail.com

Microcephaly is an important clinical finding in infants with congenital Zika syndrome. However, a normal head circumference does not exclude ZIKV infection (23, 24). Both proportionate and disproportionate microcephaly has been reported in infants with congenital ZIKV infection. "Proportionate microcephaly" refers to infants who are born small for gestational age (SGA), have a small head circumference and also have small weight and height for gestational age (GA). However, "Disproportionate microcephaly" refers to infants who have a small head circumference but have adequate weight and height parameters for GA. Microcephaly appears to be a consequence of ZIKV infection early in pregnancy but proportionate microcephaly has been observed in the offspring of women infected as late as the third trimester of pregnancy (21). The WHO has defined "Zika virus-related microcephaly" as occipitofrontal circumference (head circumference) greater than two standard deviations below the mean or less than the 3rd percentile based on standard growth charts for sex, age and gestational age at birth.

As soon as the outbreak has been described, the Centers for Disease Control and Prevention (CDC) and the Public Health England have issued developing guidelines for obstetricians, neonatologists, midwives and fetal medicine specialists. These are used for counselling and testing of pregnant women or during the preconceptual period with potential exposure to ZIKV in affected areas.

We present the experience of a single fetal medicine unit in evaluating pregnant women with positive history of travel to Zika affected areas that have been managed using a national testing algorithm. We also describe the importance of the setup of a dedicated multidisciplinary Zika clinic to ensure that these women have access to a standardised pathway of care.

Patients and methods

From February 2016 to June 2017, a population of pregnant women living in North London was evaluated in a single fetal medicine unit. The patients were referred to our unit if there was travel history to Zika affected areas or sexual contact with a person who has travelled to these areas. Guidelines published by Public Health England in February 2016 were followed. Testing criteria based on symptoms and exposures in pregnant women were modified based on updated guidelines in August 2016.

Upon referral by the GP or midwife, all pregnant women with relevant symptomatology and/or a significant travel history to ZIKV affected areas and/or partners with similar history were referred to a dedicated fetal medicine 'Zika' clinic composed from a team of obstetricians, midwives, paediatricians and infection specialists. We offered a fetal ultrasound scan (USS) at 20, 28 and 34 weeks by a fetal medicine specialist (Figure 1) and screened for ZIKV infection using reverse transcriptase polymerase chain reaction (RT PCR) and/or serology if they presented with a history of clinical symptoms consistent with Zika during or within two weeks of travel. They were also screened for ZIKV infection using RT PCR and/or serology if fetal USS was suggestive of microcephaly.

According to the national UK Algorithm published in February 2016, we offered ZIKV RT PCR test on blood and urine only to those women who reported clinical illness consistent with ZIKV disease during or within two weeks of travel. After the guidelines were revised in August 2016, RT PCR was offered to all pregnant women reporting clinical illness even if the symptoms have resolved. The urine of these women was also tested if within 21 days of symptoms' onset.

If the patient had a positive or inconclusive ZIKV RT PCR and/or antibody test result, we submitted further samples, as advised by the Rare and Imported Pathogens Laboratory (RIPL), and would have further evaluation and follow-up. When the patient had negative ZIKV antibody and PCR test results, we confirmed the results on a further serum sample if appropriate, and would be returned to normal pregnancy care.

We also offered a baseline fetal ultrasound screening in all women with history of travel during pregnancy to an area with active ZIKV transmission in the last nine months. If the screening ultrasound at or before 20 weeks was normal, we considered repeating it at 28 and 34 weeks. Descriptive statistics and one way ANOVA tests for non-parametric data were used to evaluate the results. Stata 14.0 (StataCorp, USA) was used for descriptive statistics and analysis of confidence intervals.

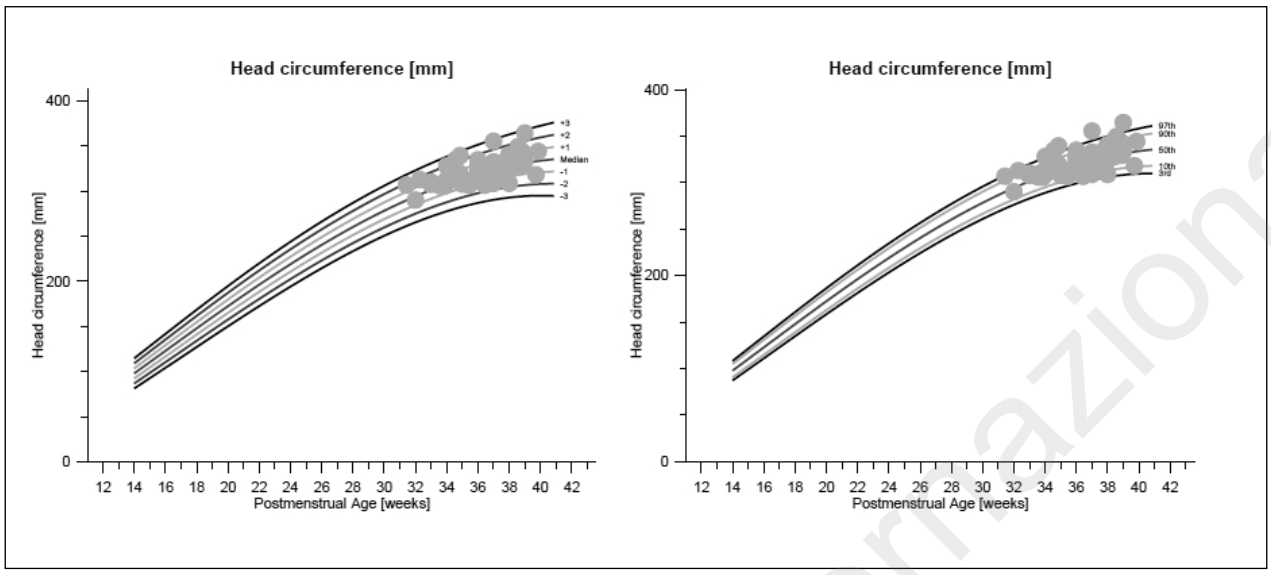

Figure 1 - Prenatal HC measurements (in mm) at the last fetal growth USS before delivery (measurements based on INTERGROWTH-21st reference charts).

Results

During the evaluation period, we identified 69 pregnant women who were potentially exposed to ZIKV by travel to affected areas or sexual contact with partner that had travelled to these areas (Table 1). Our cohort ranged in age from 20 to 46 years (mean age 31.7 years). Geographic exposure data showed Central/South America (49.2%) and the Caribbean (27.5%) to be the most common areas of travel. Women travelled also to the USA (5.8%), South-East Asia (8.7%) and Africa (1.5%) (Table 1). Two women (2.9%) had partners who had travelled to Zika endemic areas and detailed travel history was missing in four cases (5.8%).

Within our population, eight patients reported symptoms consistent with ZIKV infection (11.6%) and six (8.7%) patients reported mosquito bites. Skin rash and headache were the commonest symptoms. Four of the symptomatic patients had travelled to Central/South America. The time of exposure was mainly during the preconception period in 35 women (50.8%) and during the first trimester in 19 women (27.5%). We assessed the necessity of performing a test to submit at RIPL after reviewing the guidelines at the time of the patient's visit in our fetal medicine unit. We submitted virus specific serological tests for the eight symptomatic women and kept a serum sample for the rest of the cases referred to us. IgM, IgG assays were done in the eight symptomatic patients and Zika maternal RT PCR was ordered in one case.

One patient with travel history to Jamaica during both the first and third trimesters, presented with small fetal HC measurement (30.8cm, 4th percentile) at 37 weeks of gestational age and concomitant positive maternal serology for Zika IgM and IgG. The fetal medicine USS did not reveal any intracranial abnormalities. The mother and the female baby were followed up postpartum. The mother was IgM and IgG positive with no evidence of Zika RNA in the blood, urine, placenta or umbilical cord. Her baby's serology tested IgM negative and IgG positive but Zika RNA was not detected in the blood or urine. The HC measurement at birth (38 weeks) was 31.9 cm (on the 11th percentile) (Figure 3). These results most probably represent a passive transfer of maternal antibodies to the baby.

Another two cases with maternal travel history to the Philippines and Brazil, presented as SGA babies at 30 and 34 weeks of pregnancy, respectively. The HC measurements were lying on the 5th and 3rd centile for the relative gestational ages antenatally. We obtained negative maternal serology and PCR results for both cases. We did not identify any fetal brain or limb abnormalities in these babies and the HC measurements at birth were 33 cm (13th centile, at 41 weeks) and 34.5 cm (80th centile, at 40 weeks), respectively (Figures 2, 3).

Fifty-nine women had delivered at term, three preterm (less than 37 weeks) and seven had

TABLE 1 - PATIENT CHARACTERISTICS.

Characteristics	**n (%)**	**Value (mean)**	**Std. Err., 95%CI**
Age (years)	69	31.73	0.53 30.68 - 32.79
Index traveler			
Patient	67 (97.1)		
Patient's partner	2 (2.9)		
Region of travel			
Central/South America	34 (49.2)		
Caribbean	19 (27.5)		
SE Asia	6 (8.7)		
USA	4 (5.8)		
Pacific Islands	1 (1.5)		
Africa	1 (1.5)		
Other	4 (5.8)		
Timing of exposure			
Preconception/conception	35 (50.8)		
T1	19 (27.5)		
T2	8 (11.6)		
T3	3 (4.3)		
Unknown	4 (5.8)		
Symptomatic (consistent with Zika)			
Yes	8 (11.6)		
No	58 (84)		
Not reported	3 (4.4)		
Gestational Age at delivery (weeks)			
<37	3 (4.4)	39.4	0.19
>37	59 (85.4)		39.06 - 39.86
Miscarriages	7 (10.2)		
Birth weight (g)			
<2500	3 (4.3)	Female: 3167	80.57
2500-4000	49 (71)	Male: 3539	3193.1-3517.9
>4000	7 (10.1)		
HC (cm)			
Female	26 babies	32.1	
Male	33 babies	32.4	
IgM, IgG requested	8 (11.6)		
RT PCR requested	1 (1.4)		
Serum Save only	60 (87)		

miscarried. In three cases, women transferred care and we did not have data on HC measurements and birth weight at birth. The mean gestational age at birth was 39.4 weeks. The mean birthweight of male and female babies was 3539 g and 3167 g, respectively. The mean HC measurement at birth for

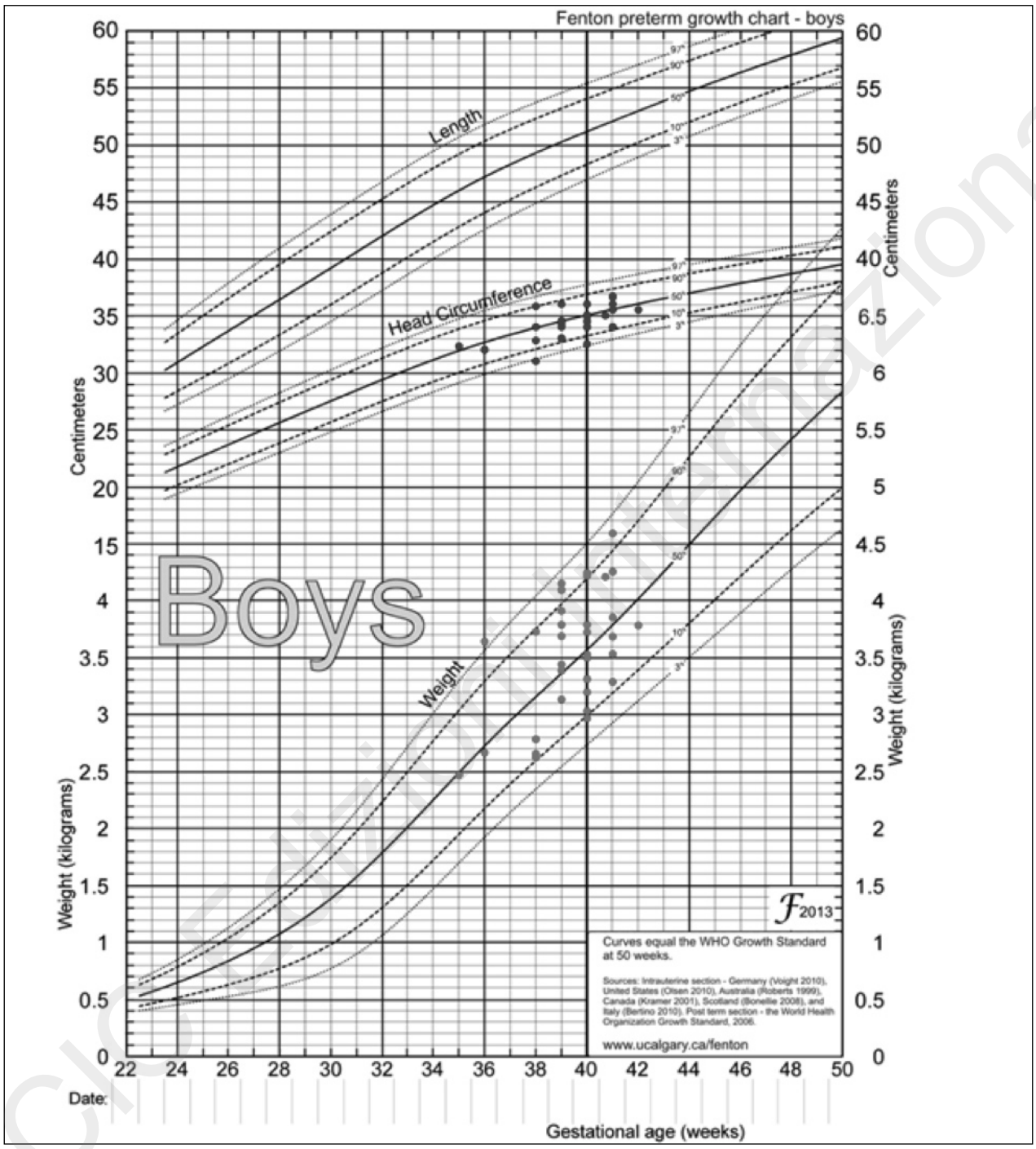

Figure 2 - HC measurements (in cm) and weight (in kilograms) at birth for boys (WHO Growth standards).

male and female babies was 32.4 cm and 32.1 cm, respectively. No congenital sequelae were detected in any of the babies delivered. The infant with positive IgG at birth appeared to be healthy at three months of follow-up and has shown no signs of ZIKV congenital syndrome on serial pediatric examinations.

Discussion

Due to the geographical location of our fetal medicine unit in London (United Kingdom), the majority of patients referred to us were primarily exposed to a potential infection by ZIKV through travel to affected countries during the critical

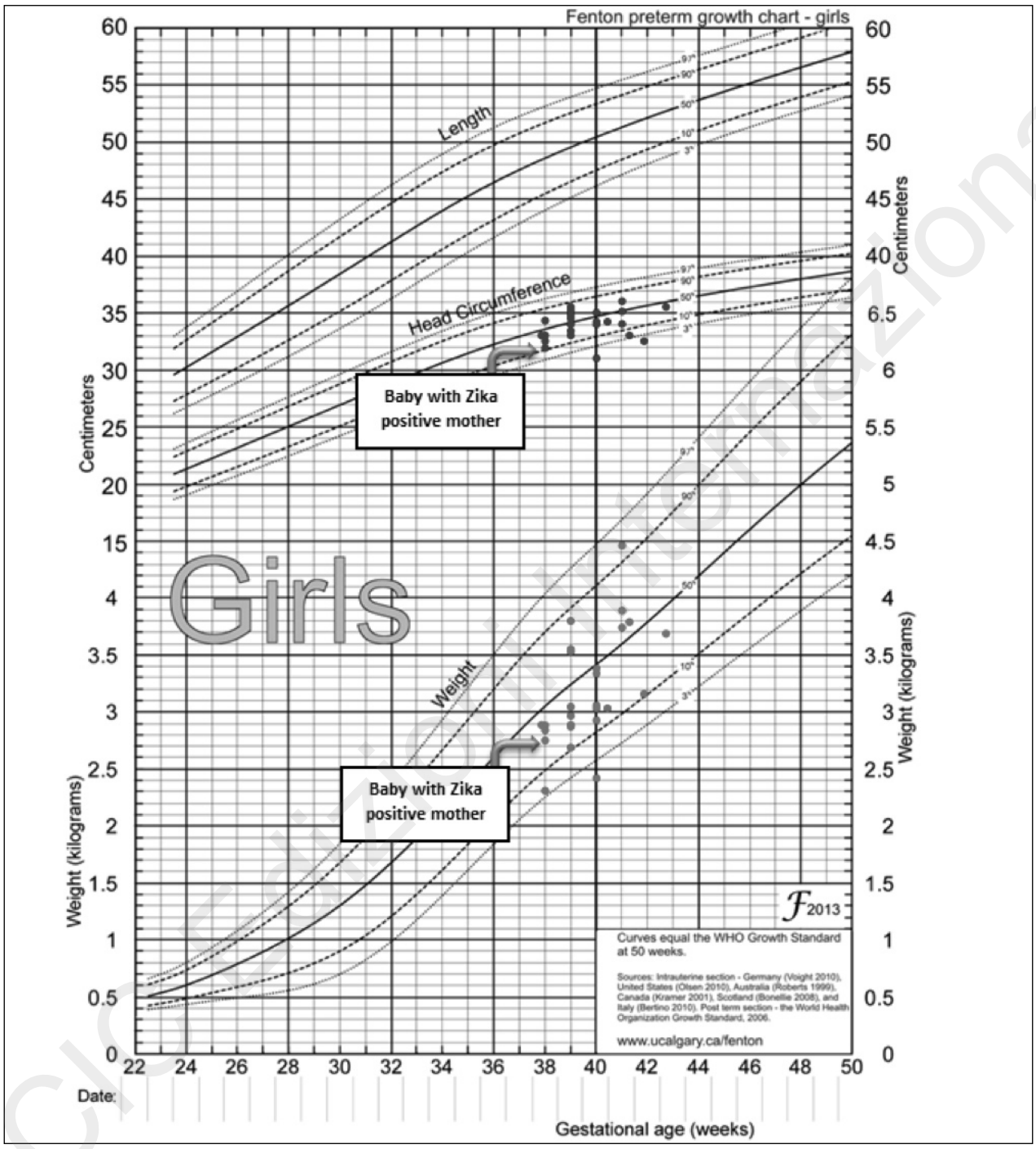

Figure 3 - HC measurements (in cm) and weight (in kilograms) at birth for girls (WHO Growth standards). The arrows represent the baby born to the Zika positive mother.

preconceptional period or the first trimester of pregnancy. The multicultural character of the city of London, together with the high rate of air passenger's movement between London and destinations outside Europe (especially travel to an American location), were reflected on the travel history of the referred patients with the majority of them travelling to Mexico and Brazil.

In our population, only one maternal Zika virus infection was confirmed with no fetal or neonatal infections or sequelae attributed to ZIKV. Despite the low rates of maternal infection and the absence

of neonatal infection in our cohort, health care providers should be fully aware of the importance of this evolving crisis in terms of the potential fetal congenital sequelae (congenital ZIKV syndrome). They need to be able to apply in everyday clinical practice the national recommendations and guidelines regarding management of potential ZIKV infected pregnant women. The national algorithms are becoming more important considering maternal symptomatology is often subtle, if not absent, and the need to screen every case through accurate history taking in an attempt to keep costs from screening as low as possible. Rao et al. (25) in a recent study, evaluated 185 women with potential ZIKV exposure and identified low rates of confirmed maternal ZIKV infection (one of 153 of those tested) (0.7%). They had also concluded that the magnitude of concern among patients and physicians regarding ZIKV infection is high, despite low rates of confirmed maternal infection in their cohort, and emphasized the need for health care providers to be able to counsel patients appropriately.

The communication between different specialties (e.g. during multidisciplinary meetings) is extremely important. Midwives and general practitioners (GPs) are usually the first to listen to a relevant history of travel and exposure to the virus. They are the professionals who will refer and escalate these cases to obstetricians or fetal medicine specialists in the hospital setting. The role of the virologists and paediatricians cannot be underestimated as very often their clinical input will determine the follow-up of these cases after delivery of the baby.

Health professionals providing care to pregnant women should follow recommendations published by Public Health England, WHO and CDC. Since this is still an evolving crisis affecting a sensitive part of the population with no vaccine available, it is important to be vigilant using the most up-to-date information available. However, it appears that the risk of infection to pregnant women travelling to Zika affected areas is actually small.

Conflict of interest

The Authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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