MONOCHORIONIC TWINS ACCOUNT FOR MOST OF THE EXCESS MORTALITY OBSERVED IN TWINS

At all stages of pregnancy, twins, and particularly monochorionic (MC) twins, are at increased risk for fetal death. Miscarriage rates are approximately 6% for MC and 1.9% for dichorionic (DC) twins in the second trimester of pregnancy, and the rates of stillbirth range from 4–6% for MC, about 1% for DC twins. Most research to date, however, has sought to understand the mechanisms for this increased mortality by analyzing viable twin pregnancies or live-born twin cohorts. In addition, previous studies of stillborn infants have frequently excluded twins, and/or not made them the primary focus in stillbirth analysis.

In order to extend the current research on the incidence of miscarriage, stillbirth, and lethal anomalies among twins, Korelsky and McPherson (p. 350, 10.1002/ajmg.a.61014) conducted a systematic analysis of all twin pregnancies recorded in a state database of stillbirths and miscarriages. Using the Wisconsin Stillbirth Service Program cohort of 3137 stillbirths and second-trimester miscarriages, 175 twin pregnancies were identified. The excess of twins observed among miscarriages/stillbirths was largely attributed to MC pairs, and the leading causes of fetal demise among twins were twin–twin transfusion, acardia, and twin–twin disruption. As compared with single births, maternal causes of death, primarily premature rupture of membranes, were moderately increased for twin births. Deceased twins were smaller than viable twins at comparable gestational ages, but placenta weights of the deceased MC twins were large compared to combined fetal weight, indicating that placental inefficiency was probably caused by vascular shunting.

IDENTIFICATION OF NEW PATIENTS ALLOWS FURTHER REFINEMENT OF PRIMROSE SYNDROME PHENOTYPE

Primrose syndrome, a rare autosomal dominant condition caused by heterozygous missense variants within ZBTB20, has been previously associated with a moderate to severe intellectual disability, a recognizable facial appearance, and macrocephaly with or without tall stature. Of the 15 reported Primrose syndrome ZBTB20 pathogenic variants, 14 are missense variants that cluster within the first (3 variants), second (6 variants), and third (2 variants) zinc finger domains and the linker region between the first 2 motifs (3 variants). As part of the Deciphering Developmental Disorders study, Cleaver et al (p. 344, 10.1002/ajmg.a.61024) used exome sequencing to identify 5 unrelated individuals with previously unreported de novo ZBTB20 pathogenic missense variants. These 5 missense variants all target the C2H2 zinc finger domains. “This genotype-up approach has replicated the previous finding that ZBTB20 missense variants target the zinc finger domains and has allowed a nonbiased refinement of the Primrose syndrome phenotype,” note the authors.

The new findings replicate data from previous studies that showed Primrose syndrome missense variants cluster within the zinc finger domains, and the clustering also expands to include the third zinc finger domain. In the third zinc finger, only 2 pathogenic variants had previously been detected. The identification of these 5 additional patients with pathogenic ZBTB20 missense variants has now increased the total number of patients with de novo ZBTB20 missense variants to 19 and will allow further refinements to be made to the Primrose syndrome phenotype.

MANY RISK FACTORS IDENTIFIED FOR DOWN SYNDROME IN WESTERN MEXICO

Down syndrome, or trisomy 21, is the most commonly identified genetic form of intellectual disability and is caused by the presence of all or part of a third copy of chromosome 21. In the United States, it occurs in 13.6 per 10,000 live births or 1 in 732 infants and is more or less uniform across different racial and ethnic groups. However, higher prevalence has been observed in certain populations. Hispanics of Mexican origin residing in the United States have been identified as a having a particularly higher rate of Down syndrome, but data are limited concerning Down syndrome in Mexico itself.

Corona-Rivera et al (p. 435, 10/1002/ajmg.a.61044) conducted a prospective case-control study of infants born with Down syndrome between 2007 and 2017 at a tertiary academic center in Guadalajara, and examined the associations between Down syndrome and potential risk factors. A total of 230 cases from a total of 89,332 live births were included in their final analysis.

The overall prevalence of Down syndrome was 25.7 per 10,000 or about 1 in 388 live births, but much lower in mothers aged 20–24 years (1 in 907 live births). This rate gradually increased until it reached 1 in 64 live births for mothers 40 years of age and older. Other risk factors included a family history of Down syndrome, relatives with thyroid disease, maternal and/or paternal age ≤ 19 years, pre-pregnancy BMI ≥ 25 kg/m2, and pre-pregnancy alcohol consumption.