Topiramate, zonisamide and small for gestational age: maternal factors, timing of exposure and baby fat

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Small for gestational age (SGA) is commonly defined as weight below the 10th percentile for gestational age (1). The concern regarding SGA is its implications for development; it is associated with an increased risk for neonatal distress, permanent deficits in growth and neurocognitive development, and mortality. However, SGA babies are a heterogeneous group, and approximately 50% are constitutionally small, due to maternal ethnicity, body habitus, and body mass index (BMI) and these infants will develop normally (2). In 2005, 10% of births to Hispanic, American Indian/Alaska Native, and non-Hispanic white women in the United States met the criteria for SGA, and the occurrence in non-Hispanic Black births was 17% (1).

Topiramate is associated with an increased risk of major congenital malformations (MCMs), with 1.4% of births showing facial clefts, recently described by this group (3, 4) and others (5). These rare cases were excluded from the analysis herein. Within the North American Antiepileptic Drug Pregnancy Registry (NAAEDPR), a structurally related drug, zonisamide has been associated with a low risk of MCMs, with none occurring in 90 monotherapy exposures, therefore the upper limit of the 95% confidence interval (CI) is 3.3% (3).

The authors adjusted for many factors that could contribute to small for gestational age, including smoking, maternal illness, and socioeconomic indicators. The overwhelming majority of mothers were Caucasian (> 85%) which minimizes the ethnic variability that could result in some SGA babies. This was also very highly educated cohort. Having at least 2 years of college education was reported in 45% of the topiramate-treated mothers, and this was the least educated group.

Topiramate's mechanism of action in producing weight loss may be primarily through the hypothalamus, affecting both the sense of satiety mediated in the ventromedial hypothalamus and hunger recognition mediated in the lateral hypothalamus. Decreased gastric motility has also been proposed as a contributing mechanism, controlled in the dorsomedial hypothalamus.
hypothalamic nucleus. One recent report (10) supports this hypothesis; in a study of 40 migraine patients treated with topiramate 100 mg/day for three months, a significant reduction in body fat occurred, without a change in the resting metabolic rate (RMR), pointing toward a hypothalamic mechanism.

There was no dose effect found, but there was a profound timing effect. The proportion of SGA in offspring whose mothers stopped topiramate monotherapy before the third trimester was quite low at 7.3%, while for those who continued it throughout the third trimester, the rate was highest at 19.6%. This difference was not significant, likely due to small numbers (not given), but the trend is interesting, as is the trend polytherapy on increasing the rates of SGA especially with topiramate use.

The third trimester is the period of gestation when most fetal body fat is deposited. At 20-weeks gestation, fat comprises 0.5% of the fetal body, after which the amount increases, reaching 7.8% at the 34-weeks gestation, and 16% before birth. Nearly 500 g of fetal body fat are acquired in the last trimester of pregnancy and during the last month of intrauterine life the fetus gains as much as 14 g of fat per day (11). Does topiramate minimize fetal body fat deposition, as suggested by timing of an adverse effect in correlation with fetal growth patterns?

This information, while incomplete and difficult to explain since fetuses don’t eat and we do not have information on maternal weight gain, deserves consideration when counseling women with epilepsy and migraine who take these medications. These mothers may need to consciously override their hypothalamically-mediated behavior and eat more!

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References
2. Royal College of Obstetricians and Gynaecologists. The Investigation and Management of the Small-For-Gestational-Age Fetus Guideline No. 31. 2002