

## Correspondence

# Statin Drugs and Congenital Anomalies

### To the Editor:

In their article on mechanistic and epidemiologic considerations of adverse birth outcomes following gestational exposure to statins, Edison and Muenke [2004] indicate that causal inferences are not possible from the case reports they describe. We agree. The authors go on to indicate, however, that even small numbers of reports describing *highly similar rare anomalies* following an *apparently small number of gestational exposures* (emphases added) to specific lipophilic statins are a signal that deserves further attention. Furthermore, they suggest that the reported cases display patterns consistent with dysfunction of cholesterol biosynthesis, diminished Sonic Hedgehog activity, and Smith-Lemli-Opitz syndrome.

We do not believe Edison and Muenke have made their case. Smith-Lemli-Opitz syndrome, a well-characterized abnormality of cholesterol biosynthesis, features microcephaly, mental retardation, hypotonia, incomplete development of the male genitalia, and short nose with anteverted nostrils. Two of the three probands in the original description [Smith et al., 1964] also had pyloric stenosis. Holoprosencephaly and agenesis of the corpus callosum, a minor form of holoprosencephaly, have been described in Smith-Lemli-Opitz patients. The collection of cases gathered by Edison and Muenke does not show this syndrome after statin exposure during pregnancy.

Edison and Muenke put forward five cases of central nervous system (CNS) anomalies including: (1) holoprosencephaly, (2) a case of “apparent holoprosencephaly,” (3) unspecified neural tube defect, (4) spina bifida, and (5) microtia. The case of “apparent holoprosencephaly” was reported to FDA by a statin manufacturer. From discussions with the manufacturer, we learned that the case involved a cardiac ventricular septal defect and not a cerebral ventricular defect. The mother of the case of spina bifida had diabetes mellitus, a known risk factor for spina bifida. The unspecified neural tube defect is more likely related to disorders of folate metabolism than to disorders of cholesterol metabolism. Microtia, an anomaly of the ear, is an abnormality of the pharyngeal arches, not the central nervous system. These putative cases of CNS anomalies can hardly be said to demonstrate a pattern, let alone a pattern suggesting Smith-Lemli-Opitz syndrome.

Edison and Muenke indicate that there were five cases of limb deficiency that demonstrated a consistent pattern. These cases included: (1) aplasia of all structures distal to the left forearm, (2) VACTERL syndrome with shortened left femur and aplasia of left metatarsals and phalanges, (3) limb deficiency consisting of 9% shortening of one tibia and fibula,

agenesis of one tarsal bone, and 16% shortening of one foot, (4) clubbed foot, and (5) VATER syndrome with aplasia of the left radius and thumb and shortened left ulna. We fail to see a pattern emerging from these reports, let alone a pattern suggesting Smith-Lemli-Opitz syndrome, in which the characteristic limb defect is syndactyly or adactyly.

For each of the anomalies described above, there is a background prevalence in the general population. The question of importance is whether the anomalies are more prevalent in the exposed than the general population. Muenke and Edison make an estimate of what they believe the exposed population to be and indicate general population prevalence rates of some of the anomalies they have described, suggesting to the reader that the appearance of such rare anomalies in the “small” exposed population is a “meaningful signal.”

To make an estimate of the exposed population through May 2001, the authors put forward a series of assumptions by which they estimate that the maximum number of cumulative global exposed births from the beginning of statin use in the late 1980s through May 2001 is 104,775. With additional assumptions about unplanned pregnancy, abortion, and prescription adherence, a smaller “adjusted” estimate of the number of globally exposed births is said to be 15,716. Whether these are reliable estimates of the number of gestational exposures to statins is anyone’s guess, but giving Edison and Muenke the benefit of the doubt, we remain unconvinced that they have identified a problem.

To make the presumed incidence of anomalies among statin case reports appear high, Edison and Muenke cite prevalence rates such as 1 in 500,000 for one of the cases of VATER and 1 in 100,000 for “mixed” lower limb defect. They have taken liberties with the citing of background prevalences. For the case of VACTERL, Edison and Muenke cite Kim et al. [2001]. Kim et al. do not estimate a prevalence rate for VACTERL; they cite another study [Rittler et al., 1996], which estimated the prevalence rate for VACTERL as 1 in 5000. Kim et al. cite a second study [Khoury et al., 1983] in which the authors indicate that fewer than 1% of VACTERL cases have co-occurrence of five or more of the VACTERL anomalies. Kim et al. do not report a prevalence rate for having five of the VATER anomalies. Edison and Muenke do their own multiplication ( $1\% \times 1/5000$ ) to arrive at 1 in 500,000, a rate based on eight cases of the population surveyed by Khoury et al. The variability about that rate must be extreme. Furthermore, whether a prevalence rate should even be reported by the number of VATER elements is questionable. VATER is most commonly reported using the general convention of three or more associated elements.

On the subject of limb deficiencies, the Edison and Muenke cite McGuirk et al. [2001]. McGuirk et al. use a malformations surveillance program at the Brigham and Women’s Hospital in Boston and some additional data from eight physicians’ offices and Boston Children’s Hospital to estimate a prevalence rate for limb deficiency of 0.69/1000, a rate they indicate as consistent with other reported rates for limb deficiency. McGuirk et al. also report prevalence rates for various limb deficiency classifications (e.g., amelia, intercalary, meromelia, etc.) but do not indicate whether the prevalence rates for their various limb deficiency classifications are consistent with other reports or if other prevalence rates even exist for these

Dr. H. Gibb and Dr. A.R. Scialli report receiving consulting fees from Merck.

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Received 4 February 2005; Accepted 24 February 2005

DOI 10.1002/ajmg.a.30685

classifications. Within the category “mixed meromelia” (estimated prevalence = 0.07/1000), McGuirk et al. indicate that 1 of their 12 cases of meromelia was a mixed meromelia of the legs. McGuirk et al. do not define what a mixed meromelia of the legs or arms is, but Edison and Muenke apparently interpret two of the cases in their case series (the case of the limb deficiency of the leg and foot and the VACTERL case) as being mixed meromelia of the legs because the two cases involved the legs and feet. It appears that Edison and Muenke then multiply the estimated prevalence of mixed meromelia (0.07/1000) from McGuirk et al. by 1/12 and arrive at a prevalence rate of approximately 1/100,000. Such a rate, based on one case, is extremely unstable. It is also interesting to note that the McGuirk et al. database includes children only up to 5 days of age; the case of the limb deficiency of the leg and foot reported by Edison and Muenke was diagnosed at 4 years of age. Furthermore, it is interesting that Edison and Muenke use the case of VACTERL to compare with both the prevalence rate for VACTERL and the prevalence rate for limb deficiencies (i.e., a double counting).

Edison and Muenke have attempted to link a theory of diminished Sonic Hedgehog signaling to the case reports, particularly holoprosencephaly. There is no evidence that statins affect Sonic Hedgehog signaling. There was only one case of holoprosencephaly among the case reports, as indicated above. The prevalence of holoprosencephaly has been reported as 1 in 10,000 [Forrester and Merz, 2000] and 1 in 11,000 to 20,000 [Moog et al., 2001]. Even given Edison and Muenke’s “adjusted” exposed population of 15,716, one case would be expected. With regard to limb deficiencies, the prevalence in the general population is about 1 in 1000 [McGuirk et al., 2001]; the five limb deficiency cases (including the two cases of VATER) in Edison and Muenke’s case series is considerably fewer than the 16 expected based on their estimated exposed population. The two cases of VATER would also be less than the three expected given the background prevalence of VATER of 1 in 5,000 [Kim et al., 2001].

Holoprosencephaly as a marker of Sonic Hedgehog dysfunction due to impaired cholesterol biosynthesis has been supported by the rat studies of Charles Roux and his colleagues [reviewed by Roux et al., 2000]. They used distal cholesterol synthesis pathway inhibitors (not statins) during gestation to produce offspring primarily with abnormalities of the

holoprosencephaly type. They also identified a critical level of maternal blood cholesterol (<50% of normal) above which abnormalities did not occur, suggesting that it was hypocholesterolemia rather than other effects of the administered agents that caused the abnormal embryogenesis. To our knowledge, no statin at any dose has been shown to produce holoprosencephaly in rats, and it appears reasonable to postulate that maternal cholesterolemia is not reduced by statins to the extent necessary to interfere with embryo development. We find the experimental animal studies plus the lack of a pattern of abnormalities in the case reports of Edison and Muenke to be reassuring.

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