the protein content of the diets at 6 months differed by only about 5 percentage points. After 2 years, no significant difference in body weight was found among the groups, although among subjects who completed the study, those who consumed higher-protein diets weighed about 1 kg less than those who consumed lower-protein diets (P=0.11).[10] Together, these two studies suggest that the ratio of carbohydrate to fat has relatively little importance for weight control among persons consuming a low-glycemic-index diet, and higher protein intake may have additional benefits.

The Diogenes study provides reassurance regarding three long-standing concerns about glycemic index: that measured values apply to individual foods only and have no relevance to mixed meals, that effects observed in clinical trials arise from confounding by macronutrients or fiber, and that the concepts are confusing and impractical for the general public. Indeed, the higher study-completion rate in the low-glycemic-index groups provides compelling evidence of the practicality of low-glycemic-index diets.

Several recent clinical trials have shown no significant difference in weight loss among various popular diets, leading to the notion that dietary composition is less important than adherence to a diet, whatever it might be. However, this conclusion does not consider the fundamental relationship between psychology and physiology. A person's ability to maintain adherence over time may be influenced by the way in which a diet affects hunger and metabolism. Additional research is needed to clarify the mechanisms by which dietary composition regulates body weight and to devise novel strategies to effect behavioral changes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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# Proton-Pump Inhibitors and Birth Defects — Some Reassurance, but More Needed

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Limited data on safety are usually available when new medications are first marketed, but for appropriate ethical reasons, safety studies of the use of medications during pregnancy are rarely conducted before marketing. Because we must await postmarketing studies to resolve questions of fetal safety,[1] it becomes critical to identify medications that are commonly used during pregnancy and to study them quickly. The report on proton-pump inhibitors (PPIs) in this issue of the *Journal*[2] is therefore both timely and important.

Taking advantage of a series of linked databases covering every live-born infant in Denmark, Pasternak and Hviid identified increasingly high rates of prescriptions for PPIs filled in the weeks before conception and throughout pregnancy. They estimated that antenatal exposure to a PPI among infants born between 2005 and 2008 peaked at about 2%; exposure during the first trimester, when teratogenic risk is greatest, was about 0.7%. This pattern is not unique to Denmark; in our Slone Birth Defects Study, the fre-

quency of the use of PPIs (prescribed or over-the-counter) during the first trimester reached about 2% between 2006 and 2008 (unpublished data), and the rates in other Western countries are likely to be similarly high. Given the prevalence of these exposures, Pasternak and Hviid investigated whether the use of PPIs might be associated with an increased risk of major birth defects. On the basis of data from more than 840,000 live births, and taking into consideration a wide range of potential confounding variables, the authors found no evidence to suggest that the use of the most common PPIs (omeprazole, lansoprazole, and esomeprazole) anytime during pregnancy increased the risk of birth defects overall, and in the case of omeprazole, the PPI used most commonly during pregnancy, they found no evidence of a risk among selected subgroups of major birth defects. These findings, together with earlier reports that were based on smaller numbers of pregnant women exposed to PPIs,[3,4] are important in providing some reassurance about the safety of these drugs when they are taken during pregnancy.

As the authors acknowledge, however, these data provide only a broad — and incomplete — overview. First, teratogens tend to increase the risks of specific birth defects, not birth defects overall or even defects classified according to organ system (e.g., "heart defects" include a wide variety of defects that are susceptible to different developmental insults). Second, although members of a given drug class (e.g., PPIs) share pharmacologic effects, they may have very different effects in terms of teratogenicity.[1] Unfortunately, despite the large size of this cohort, the study had insufficient power to consider the risks of specific birth defects in relation to specific PPIs. Third, despite the richness of these databases, they lack information on important potential confounding variables, including the indications for the use of PPIs, as well as exposures to over-the-counter medications, in particular folic-acid supplements taken during the periods immediately before and after conception — an exposure that is critical to the study of birth defects. As the authors themselves note, case–control studies are needed to provide the power to consider specific defects in relation to individual PPIs, and future analyses must also include information on critical potential confounders; until such studies are available, the current findings, although reassuring, must be considered far from definitive.

A strength of the study was the researchers' separate assessments of risks associated with exposures during the first trimester and those associated with exposures in the 4 to 12 weeks preceding conception. Unexpectedly, exposures to PPIs exclusively in the preconception period were associated with an increased risk of birth defects overall, an observation that the authors consider to be biologically implausible and likely to be due to chance or unrecognized confounding. However, it is not clear that this concern can be dismissed so simply. Roughly half of the pregnancies in the United States are unplanned,[5] and any teratogenic effect that might result from exposure before conception would have important clinical and public health implications. Biologic plausibility cannot be dismissed purely on the basis of a medication's half-life but should also consider the medication's longer-term pharmacologic effects, such as a reduction in acid or a rebound increase in acid after discontinuation of the drug; it is conceivable, for example, that exposure to PPIs before conception might lead to a depletion of micronutrients during organogenesis, whereas depletion as a result of exposure in the first trimester might occur too late to be teratogenic.

Apart from chance or a true causal effect, the most likely explanation for the increased risk associated with exposure to PPIs before conception is unmeasured confounding. In this exposure period, the increased risk associated with PPIs overall varied among the specific PPIs, and despite overlapping confidence intervals, differences between the two most commonly used agents were noteworthy: The risk of major birth defects associated with lansoprazole was increased by a factor of approximately 2, whereas there was no apparent risk associated with omeprazole. Furthermore, while prescriptions for omeprazole increased markedly throughout pregnancy, prescriptions for the newer PPIs declined markedly in the last two trimesters. The absence of risk associated with omeprazole in the period before conception and the marked differences in prescribing trends for omeprazole and the newer PPIs before and during pregnancy suggest that the increased risk associated with the use of PPIs before conception may reflect varying indications for prescribing particular PPIs

before, rather than during, pregnancy. For example, the indication for a PPI prescribed before pregnancy is more likely to reflect an underlying gastrointestinal condition, such as symptoms associated with *Helicobacter pylori* infection, whereas the same symptoms occurring during pregnancy are more likely to reflect pregnancy-associated dyspepsia. It is possible, then, that the underlying condition itself, other treatments prescribed for that underlying condition (such as concomitant antibiotic therapy for *H. pylori*), or the effects of one or the other on nutrient absorption[6,7] — rather than the use of a PPI itself — might confer a predisposition to birth defects.

Until additional studies answer these and other important points, the report by Pasternak and Hviid represents the best available data on the possible risk of birth defects associated with the use of PPIs during pregnancy, and it supports two conclusions. First, the PPIs most commonly represented in the study do not appear to carry major teratogenic risks when they are taken during the first trimester or later in pregnancy. Second, the modestly increased risk during the period before conception that was observed with PPIs as a group was not seen with omeprazole. Until we have a better understanding of what might explain this latter finding, it may be prudent to consider omeprazole to be the PPI of choice when PPI treatment is clearly needed for women of childbearing potential and particularly for those who are planning to become pregnant.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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