

Folate forever- all methyl group donations welcome!

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As “scientific” as weather forecasting has become, thanks in large measure to the satellite data bounced back into the news studios on a 24/7 schedule, our predictive powers in medicine remain a contentiously contested topic. Take, for example, the stream of papers that continue to populate journals in the field of reproductive medicine that set contingency clauses for treatment of infertility. This issue of *JARG* plays host to several contributions of the predictive variety on topics as far ranging as live birth outcome from distinct ovarian reserve biomarkers (see papers from the Lin and Mutlu clinics) to the use of a confocal microscope to determine the ovarian lipid content in lean patients undergoing controlled ovarian hyperstimulation (see paper from the Dumesic laboratory). Forecasting for most any health issue now assumes the cloak of “prevention at all costs” when we finally come to accept the fallibility and increasing costs of our most sensitive tests in this day and age of super resolution microscopy or whole genome sequencing. What the technology of today will bring of predictive powers in the future is a story waiting to be told. And yet, a look back into the not too distant past will remind us that even the simplest of lifestyle adjustments—low tech for sure—can reap significant health benefits for future generations.

It is along these lines I recall an experience shared with my daughter some years ago that has kept the subject of folic acid imprinted deep within some of the few remaining operational synapses I conspire with in serving as your EIC.

Capsule A recent study in *JAMA* reinforces the notion that pre- and peri-conceptual folate supplements may reduce the incidence of autism. This report is discussed in light of two *JARG* papers in previous issues that bring to the forefront the link between oocyte and embryo metabolism and the regulation of genomic imprinting.

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Jenny was newly matriculated MPH student at the Rollins School of Public Health at Emory University when we had the occasion to share a coffee outdoors on what was a brisk and brilliant fall day in Atlanta. As an “academic” father, the conversation not surprisingly turned to courses she was taking and her first impressions of her professors and class mates. In one class, the professor had asked how many of the students were taking folic acid supplements, noting that the majority were young women and that, as aspiring public health aficionados, some fraction must have already been sensitized to the importance of prenatal supplements. But why now and why at the beginning of class? The conversation never left this topic because of an unusual coincidence: Was there to be a link between the professor’s suggestion that pre-conceptual folate might benefit the health of children, and one of the first public debates on the impact of ARTs on embryonic imprinting, staged just a few weeks ago at the ASRM meeting in Montreal? Seemed like too many dots to connect at the time but, given that Jenny and I next transitioned to the annual Atlanta Beer Festival, the likelihood that any cerebral etching would have mattered over the long haul was remote at best. Not so fast!

As it turns out, said professor was one of the leading proponents and advocates for the use of folic acid in the prevention of neural tube defects. Mind you, this was well before our sensitivity to lifestyle, diet, and the like would be fully appreciated in terms of specific neurological risks imposed upon offspring health and antedated even the pronouncement of the cardinal rules for genomic imprinting that were just being solved at a mechanistic level. And what about the issues of offspring health raised in the context of human ARTs? Many studies have come and gone and will remain the subject of much debate, but we all share what will be far more than a passing concern: Are the conditions in which embryos are produced, maintained, and stored impacting the remarkable pre- and post-natal development that affects the brain? While the connections in the literature

between ARTs in general and ICSI in particular with conditions like autism still resonate within the basic science and clinical research laboratories pursuing this and related questions, it has remained an intellectual challenge to understand how or why something like not having enough dietary folic acid might be predisposing children to complex neurological disorders. As food for thought, we offer our readership insights into this dilemma based on a recent study out of Norway and salient contributions from one of our distinguished editorial board members that have appeared in the pages of *JARG*.

As reported in *JAMA* this past February, Pal Suren and colleagues investigated the impact of pre- and periconceptional use of folic acid supplements on the prevalence of autism spectrum disorders in a cohort of Norwegian children (*Association between maternal use of folic acid supplements and the risk of autism spectrum disorders in children*. 2013, *JAMA* 309: 570–577). Drawing on a study sample comprised of 85,176 children derived from the Norwegian Mother and Child Cohort Study (MoBa), an incidence of 0.1 % was found for autistic disorder in children whose mothers used folic acid supplements. It is important to note that this group of patients used folic acid from 4 weeks prior to conception through to 8 weeks after conception. In contrast, children born of mothers not using folic acid had an autism disorder incidence of 0.21 % within an appropriately age matched group of study participants with the analyses being adjusted for parity, maternal education and year of birth. While studies of this kind imply an association between autism disorders and folic acid supplements prior to and just after conception, the authors are quick to point out the lack of causality in their findings and the need for “further investigating genetic factors and other biological mechanisms...” that may underlie the intriguing inverse relationship revealed by their studies.

Importantly, these “other biological mechanisms” are tractable targets for discovery as a result of previous concerns discussed in the context of ART offspring health. One of the leaders in the field of embryo metabolism and the impact of culture conditions on gestational and postgestational events has been Professor Yves Menezo.

Menezo and colleagues first suggested a link between autism and folate in a commentary published in *JARG* in 2011 (28:1143–1145; DOI [10.1007/s10815-011-9645-2](https://doi.org/10.1007/s10815-011-9645-2)). Here the foundation was laid for two key principles. First, the identification of hypomethylated imprinted genes in ART cases provided a plausible liason between methyl donor availability and homocysteine metabolism. Second, from examining patterns of gene expression and metabolism in ART embryos, the case was made that recycling of key intermediates in the homocysteine scavenger pathway responsible for the generation of methyl donors might be rate limited by the need for folate within the follicle. Thus, folate supplementation before conception might provide an advantageous supply of methyl donors as methylation alterations of the zygotic genome take place following fertilization.

More recently, the meat of the matter for folate and other “supplementable items” was presciently outlined in a review article entitled “New insights into human pre-implantation metabolism in vivo and in vitro” (Menezo et. al. *J Assist Reprod Genet* (2013) 30:293–303; DOI [10.1007/s10815-013-9953-9](https://doi.org/10.1007/s10815-013-9953-9)). I urge anyone interested in the relationship between oocyte and embryo quality and offspring health to take a close look at not simply the substance (it will displace many a reader back into the crypts of biochemistry), but at the critical perspective this kind of thinking brings to the heart of human ARTs. Perhaps a good dose of preventive medicine will go a long way to assure the health and well being of our children, whether they be conceived the natural way or as a result of ART.