Methods | This short commentary is the result of the authors’ work on methylation, imprinting, and metabolism in gametes and embryos integrated with the current literature on brain disease and gamete quality.

Results | Disturbances in DNA methylation can originate in the spermatozoon, linked to the age of the male progenitor, and this is expressed as deficiencies in epigenetic mechanisms. Sperm of older men have a higher level of DNA damage, due to a lower resistance to oxidative stress: offspring conceived by older men carrying a high level of sperm DNA fragmentation may escape miscarriage but may instead carry disorders originating from DNA damage that may lead to neuropsychiatric disturbance.

The oocyte expresses folic acid transporters to a high level, whereas cystathionine β-synthase is not expressed, while betaine homocysteine methyltransferase is only weakly expressed. In the absence of an adequate endogenous pool of folic acid in the oocyte, the early embryo’s ability to recycle homocysteine is handicapped (Figure). Intrafollicular homocysteine levels increase in assisted reproductive technologies; therefore, any deficiency in maternal folic acid supplies will affect methylation during very early preimplantation stages of embryo development. Prenatal folic acid supplements have been shown to partially protect against neurodevelopmental disorders in the offspring, as well as have a positive effect on the risk of neural tube defects. A wide range of disorders, including neuropsychiatric disorders, autism, and cognitive impairment, are associated with increased homocysteine levels in biological fluids. Bisphenol A and other plastic-derived endocrine disruptors have the capacity to inhibit methylation and affect imprinting, inducing epigenetic transgenerational inheritance of metabolic and reproductive disorders, including sperm epimutations. Bisphenol A is a well-known inducer of oxidative stress, as is a high level of circulating glucose. It has been shown that maternal diabetes significantly increases the prevalence of autism in offspring.

Comment | There is therefore a link between methylation and oxidative stress in gametes and the first stages of embryonic development, which potentially affects epigenetic transgenerational transmission. The increase in autism spectrum diseases may also be linked to an increase in environmental endocrine disruptors, which increase oxidative stress and perturb methylation. This effect may manifest in the first 3 days postfertilization up to the blastocyst stage, the period when maintenance of methylation has a significant effect on the imprinting processes, or in the fetus, when imprinting is reset in the germ cells. The sex ratios observed in some disorders may be explained by the higher resistance of female embryos, linked to the XIAP gene expression. However, DNA methylation by definition differs between male and female genomes, whether or not it is linked to imprinting; a difference in the sex ratio with respect to autism might therefore be expected. These observations advocate treatment with nutritional supplements that support the 1-carbon cycle for older male and female patients, as well as for female diabetic patients who seek to achieve a pregnancy. The supplementation should include all of the cofactors that contribute to the 1-carbon cycle because, for example, vitamin B12 deficiency can induce adverse neurological problems.

Yves J. R. Menezó, PhD, DSc
Kay Elder, PhD, MD
Brian Dale, PhD, DSc

Author Affiliations: London Fertility Associates, London, England (Menezó); Bourn Hall Clinic, Cambridge, England (Elder); Centre for Assisted Fertilization, Naples, Italy (Dale).

Corresponding Author: Brian Dale, PhD, DSc, Centre for Assisted Fertilization, Via Tasso 480, Naples 80123, Italy (brian.dale@virgilio.it).


Author Contributions: Dr Menezó had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: Menezó.

Drafting of the manuscript: Menezó and Elder.

Critical revision of the manuscript for important intellectual content: Menezó and Dale.

Administrative, technical, or material support: Menezó.

Study supervision: Menezó and Dale.

Conflict of Interest Disclosures: None reported.


Potential Utility of a Smart Thermometer to Predict and Avert Epidemics

Recent epidemics and fear of epidemicshave increased the importance of passive surveillance of fever and symptoms at a population level. The Kinsa Smart Thermometer combines an interactive app and a US Food and Drug Administration-approved digital thermometer that connects to a user’s mobile device. Together, the hardware and software measure the user’s temperature as well as collect attendant symptoms. Data are uploaded to the cloud, and via geocoding, users will be able to see what other symptoms and fevers are present in their local area. Widespread uptake of such a technology would not only give individuals access to local data but, at a population level, could provide a way of tracking, predicting, and potentially preventing the spread of contagious illnesses, thereby mitigating epidemics. The purpose of this study was to describe usage and trends in fever and symptoms based on early data from Kinsa thermometer usage nationally.

Methods | This is a descriptive study intended as a proof of concept.
Results | Two thousand nine hundred eighty thermometers have been used at least once since September 2014. The average thermometer has been used approximately 7 times and 50% of these users also recorded symptoms with the app. Notably, there was a discernible spike in usage in the Dallas, Texas, area after the first patient was diagnosed with Ebola on September 30, 2014. Between September 1 and September 27, 2014, there were 5.6 readings per user and between November 1 and November 28, 2014, there were 10.6 readings per user ($P < .01$). Data on overall usage by month and symptoms reported are summarized in Figure 1 and Figure 2.

Conclusions | “Smart” thermometers have the potential to passively gather signs and symptoms of infection at a population level. Initial data suggest ecological sensitivity to contagion concerns. These data could help predict and prevent epidemics; however, greater market penetration will be needed to assess their utility.

Dimitri A. Christakis, MD, MPH

Author Affiliations: Seattle Children's Hospital Research Institute, Center for Child Health, Behavior, and Development, Seattle, Washington; Associate Editor, JAMA Pediatrics.