Epigenetics of gestational diabetes mellitus and offspring health: the time for action is in early stages of life

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ABSTRACT: The epidemic increase of type 2 diabetes and obesity in developed countries cannot be explained by overnutrition, physical inactivity and/or genetic factors alone. Epidemiologic evidence suggests that an adverse intrauterine environment, in particular a shortage or excess of nutrients is associated with increased risks for many complex diseases later in life. An impressive example for the ‘fetal origins of adult disease’ is gestational diabetes mellitus which usually presents in 1% to >10% of third trimester pregnancies. Intrauterine hyperglycemia is not only associated with increased perinatal morbidity and mortality, but also with increased lifelong risks of the exposed offspring for obesity, metabolic, cardiovascular and malignant diseases. Accumulating evidence suggests that fetal overnutrition (and similarly undernutrition) lead to persistent epigenetic changes in developmentally important genes, influencing neuroendocrine functions, energy homeostasis and metabolism. The concept of fetal programming has important implications for reproductive medicine. Because during early development the epigenome is much more vulnerable to environmental cues than later in life, avoiding adverse environmental factors in the periconceptional and intrauterine period may be much more important for the prevention of adult disease than any (i.e. dietetic) measures in infants and adults. A successful pregnancy should not primarily be defined by the outcome at birth but also by the health status in later life.

Key words: developmental origins hypothesis / fetal overnutrition / fetal programming / gestational diabetes mellitus / metabolic disease

Introduction

The number of pregnancies complicated by gestational diabetes mellitus (GDM) is increasing worldwide. Depending on the diagnostic criteria and ethnic populations, the incidences range from ~1 to over 10% (Ben-Haroush et al., 2004). In industrialized countries, approximately every 10th pregnancy is affected and without universal screening programs, many of them may remain unrecognized and untreated (Plagemann, 2011). GDM and type 2 diabetes share a common etiology. The increasing food supply to the fetus during late pregnancy creates a diabetogenic situation (moderate peripheral insulin resistance) for the mother. GDM presents in women without pregestational diabetes, when the maternal β-cell function cannot adapt to the increased insulin demand of late pregnancy; usually it disappears again after delivery (Gilmartin et al., 2008). GDM is diagnosed by an elevated fasting plasma glucose and/or a pathological oral glucose tolerance test (American Diabetes Association, 2006; Coustan et al., 2010). Many pregnant women with GDM can control their glucose levels with a diet, consisting of ~45% carbohydrate, 30–35% fat and up to 20% protein, although some women require insulin therapy. Common risk factors for GDM are maternal obesity and a family history of diabetes (Kim et al., 2007; Gilmartin et al., 2008; Torloni et al., 2009). Several genetic variants, including genes for β-cell function have been associated with GDM (Rabotaille and Grant, 2008; Riddervall and Groop, 2009). However, in addition to genetics, overnutrition and physical inactivity, other factors, in particular epigenetic programming of the metabolism early in life appear to play a predominant role (Fernández-Morera et al., 2010; Hanson et al., 2011; Nolan et al., 2011; Pinney and Simmons, 2012).

Children born to mothers with GDM have an increased risk for stillbirth, perinatal complications and notably high birthweight (Schwartz, 1990; Hawdon, 2011). In contrast to the well-known teratogenic effects of periconceptional hyperglycemia in mothers with type 1 or 2 diabetes (Greene, 1999; Corrigan et al., 2009), hyperglycemia in mothers with GDM usually develops during the third trimester when organogenesis is largely completed. Therefore, congenital malformations are not significantly increased. Fetal visceromegaly and macrosomia in neonates exposed to GDM may be largely due to the growth-promoting effects of fetal insulin which is produced in response to the high levels of maternal glucose (overstimulation of fetal
glucose levels can interfere with the epigenetic programming machinery. Tissue culture experiments demonstrated that elevated insulin and metabolic disorders in childhood (Boney et al., 2013), type 2 diabetes (Clausen et al., 2009), metabolic and cardiovascular complications (Wright et al., 2009; Moore, 2010), and even cancer (Wu et al., 2012). Discordant human siblings born before and after the development of maternal diabetes (Dabelea et al., 2000) and embryo transfer experiments in rats (Gill-Randall et al., 2004) provided compelling evidence that these later life phenotypic consequences are caused by the diabetic environment in utero. Maternal obesity (with and without GDM) also leads to fetal overnutrition and appears to be a separate (confounding) risk factor for fetal macrosomia and metabolic disorders in childhood (Boney et al., 2005; Armitage et al., 2008; Drake and Reynolds, 2010).

The phenomenon of adverse environmental exposures during early life, especially with regard to nutrition, increase the lifelong risk of many chronic diseases is now referred to as developmental programming or the ‘Barker hypothesis’ (Barker et al., 2002; Gillman, 2005; Gluckman et al., 2009). Interestingly, there is a U-shaped relationship between birthweight, which reflects the uteroplacental supply of nutrients and hormones to the fetus, and disease risk (Harder et al., 2007; Baker et al., 2008; Caughley and Michels, 2009). Transient overnutrition and undernutrition in early stages of life appear to have the same negative and long-lasting impact on setting (and fine-tuning) of the neuroendocrine control systems of the metabolism, leading to a lifelong increased morbidity. The mechanisms underlying this developmental programming of metabolic and cardiovascular diseases are still largely unclear. Epigenetic modifications are generally assumed to mediate gene–environment interactions, leading to persistent changes of gene regulation and metabolic pathways (Fernández-Morera et al., 2010; Hanson et al., 2011). Tissue culture experiments demonstrated that elevated insulin and glucose levels can interfere with the epigenetic programming machinery (Chiang et al., 2009; Wellen et al., 2009).

Epigenetics studies the inheritance of information beyond the DNA sequence. Biochemical changes, i.e. in forms of DNA methylation and histone modifications, control the spatial, temporal and parent-specific highly coordinated gene expression patterns. Each of the >200 cell types of the body is endowed with a specific combination of silenced and expressed genes, which is established during development and differentiation and then stably inherited during cell divisions. The epigone is the sum of the epigenetic modifications which bring a cellular phenotype into being. The most thoroughly studied epigenetic modification is the methylation of cytosine-phosphatidyl-guanine (CpG) sites. In contrast to non-coding regions of the genome where most CpGs are methylated to prevent retrotransposition activity (Yoder et al., 1997), CpG islands in 5′ cis-regulatory regions of genes are usually unmethylated. Methylation of these CpG islands during development or disease processes is associated with post-translational histone modifications that lead to a locally condensed inactive chromatin structure and gene silencing (Jaenisch and Bird, 2003; Weber et al., 2007). One important hallmark of the epigenome is its enormous plasticity in response to internal (i.e. during differentiation) and environmental factors (Faulk and Dolinoy, 2011; Feil and Fraga, 2012). In this light, epigenetics is by far the most likely mechanism by which the intrauterine environment affects health and disease of the offspring.

### Epigenetic effects of maternal nutritional environment on the offspring: evidence from animal models

A number of elegant animal studies have shown that nutritional factors can modify the epigenome of the developing offspring. One of the most impressive examples is the Agouti viable yellow (A<sup>vy</sup>) mouse model, in which insertion of a transposable IAP element has created a metastable epiallele that can be turned on or off during early development. Depending on the degree of methylation at this IAP element, which is increased and decreased by methyl donor supplements (Waterland and Jirtle, 2003) and endocrine disruptors (Anderson et al., 2012) in the maternal diet, respectively, A<sup>vy</sup>/a offspring show a pseudoagouti (comparable to wild-type), a mottled (mosaic) or a viable yellow phenotype. The latter is characterized by the yellow coat color and susceptibility to metabolic diseases and cancer.

Neonatal overfeeding in rats was associated with epigenetic changes in the hypothalamic proopiomelanocortin (Pomc) and insulin receptor (Insr) genes that are important for the neurovegetative control of body weight and metabolism. The degree of hypermethylation was directly dependent on the glucose level (Plagemann et al., 2009, 2010). Feeding pregnant rats a protein-restricted diet altered the DNA methylation and expression patterns of the glucocorticoid receptor (Nr3c1) and peroxisome proliferator-activated receptor alpha (Ppara) genes in the liver and heart of the offspring (Lillycrop et al., 2005, 2007; Slater-Jefferies et al., 2011). In a rat model for fetal programming of hypertension, exposure to a low-protein diet and/or maternal glucocorticoid in early pregnancy led to reduced methylation and increased expression of the adrenal angiotensin receptor (At1b) gene (Bogdinar et al., 2010). Treatment of pregnant guinea pigs with glucocorticoids in late gestation induced changes in global DNA methylation and expression of several genes involved in epigenetic regulation in the offspring and subsequent generations (Crudo et al., 2012). However, in general, even when statistical significance was reached, the absolute methylation differences in the above-mentioned studies were low. The offspring of mouse dams experiencing dietary protein restriction showed robust expression changes in several imprinted (i.e. Gnos and Grb10) and non-imprinted (Ppara) genes in the liver, whereas the DNA methylation patterns remained largely unaltered, suggesting that epigenetic mechanisms other than DNA methylation contribute to developmental programming (Ivanova et al., 2012).

Indeed, in a genome-wide chromatin immunoprecipitation survey, it was shown that streptozotocin-induced maternal diabetes and, independently, maternal consumption of a high-fat diet affected the histone H3 and H4 acetylation in chromatin of the mouse embryo. Increased H3K27 acetylation marks were enriched near neural tube defect genes, suggesting that epigenetic changes contribute to the teratogenic effects of maternal diabetes (Salbaum and Kappen, 2012). In cultured cells, hyperglycemia increased histone acetylation via the citrate lyase pathway (Wellen et al., 2009). A conceptually
related study in primates (Aagaard-Tillery et al., 2008) also revealed that in utero exposure to a caloric-dense high-fat maternal diet alters fetal chromatin structure (increased hepatic H3 acetylation).

Effects of maternal malnutrition in humans

In humans strong evidence for the long-lasting effects of an adverse early nutritional environment on health and disease comes from a well-studied cohort of men and women who were exposed in utero to the Dutch famine of 1944–1945. Comparison of individuals who had been exposed during early gestation and their unexposed siblings showed subtle blood methylation changes in several imprinted, i.e. the insulin-like growth factor 2 (IGF2), and non-imprinted, i.e. the leptin (LEP), genes (Heijmans et al., 2008; Tobi et al., 2009). The peptide hormone leptin plays an essential role in the regulation of body weight. The prenatally exposed individuals suffered from increased risks for metabolic and cardiovascular diseases, accelerated cognitive ageing and schizophrenia (Susser et al., 1996; Painter et al., 2006; Stein et al., 2007; De Rooij et al., 2010). At least some of the observed epigenetic and phenotypic effects depended on the timing of exposure during gestation (with early gestation being the most vulnerable period) and sex of the exposed individual (Roseboom et al., 2006; Tobi et al., 2009). The observation of an increased neonatal adiposity in the offspring of exposed women suggests possible transgenerational effects of maternal undernutrition (Painter et al., 2008).

During the rainy season in rural Gambia, pregnant women experience deficiencies in several micronutrients and the resultant offspring display a high incidence of low birthweight, and childhood morbidity and mortality. Maternal micronutrient supplementation (with vitamins and minerals) around the time of conception had widespread and sex-specific effects on the epigenome of the offspring. Some of the observed DNA methylation changes were shown to persist into early infancy (Cooper et al., 2012; Khulan et al., 2012). Similar to fetal adaption to maternal malnutrition, neonates with intrauterine growth restriction exhibited specific changes in DNA methylation, in particular the hepatocyte factor 4 alpha (HNF4A) gene (Einstein et al., 2010). Consistent with evidence from animal models, these studies in humans suggest that the nutritional environment in which the human embryo and fetus develops can influence the epigenetic programming of gene activity in later life.

Epigenetic effects of gestational diabetes

Using bisulfite pyrosequencing, we have analyzed the methylation levels of seven imprinted genes involved in pre- and post-natal growth, four genes involved in energy metabolism, one anti-inflammatory gene, one tumor suppressor gene, one pluripotency gene and two repetitive DNA families in umbilical cord blood and placenta of neonates of mothers with dietetically treated or insulin-dependent GDM and controls without GDM (El Hajj et al., 2013). The maternally imprinted mesoderm-specific transcript (MEST) and the non-imprinted glucocorticoid receptor NR3C1 genes showed subtly (in the order of several percentage points) but significantly decreased methylation levels in both GDM groups, compared with controls, in both analyzed tissues. In a conceptually related study, a lower DNA methylation level of the adiponectin (ADIPOQ) gene in fetal placenta tissue was correlated with maternal hyperglycemia (Bouchard et al., 2012).

Mouse knockout experiments have shown that the paternally expressed Mest gene plays a role in growth of the embryo and placenta as well as in development of a ‘social brain’ after birth (Lefebvre et al., 1998). Transgenic Mest overexpression led to an enlargement of adipocytes and fat mass expansion (Kamei et al., 2007). The endogenous Mest gene can be up-regulated by early overnutritional environment (Kozak et al., 2010). Variations of Mest expression in genetically identical mice (before overnutrition) correlated with the development of diet-induced adiposity (Koza et al., 2006). The glucocorticoid receptor NR3C1, which was also susceptible to metabolic programming, is a transcription factor involved in many cellular processes, including proliferation and differentiation. In the rat model, environmentally (i.e. by maternal diet or early care) induced epigenetic changes in Nr3c1 have been associated with long-term effects on metabolism, stress response and behavior (Weaver et al., 2004; Lillycrop et al., 2007). Similarly in humans, prenatal (Oberlander et al., 2008) and childhood experiences (McGowan et al., 2009; Tyrik et al., 2012) of adverse parental behavior were associated with blood and brain NR3C1 methylation changes, increased stress reactivity and risk for adult psychopathology. The circulating hormone ADIPOQ is secreted abundantly by adipocytes and has anti-inflammatory, anti-atherogenic and anti-diabetic (insulin-sensitizing) effects (Pryzak et al., 2010).

In addition to single copy genes, interspersed ALU repeats also showed a slightly (1% point) lower methylation level in cord blood and placenta of neonates who were exposed to GDM in utero (El Hajj et al., 2013). Transposable ALU elements comprise ~10% of the human genome and, when inserted into promoters/first exons, can affect the regulation of gene expression (International Human Genome Sequencing Consortium, 2004). This suggests that hyperglycemia during pregnancy affects multiple loci in the fetal epigenome, which is not unexpected considering the manifold long-term phenotypic effects of an adverse fetal environment.

In humans, it is difficult to study the long-term consequences of altered methylation patterns in blood and/or placenta of neonates. We found significantly decreased blood MEST methylation levels in adults with morbid obesity, compared with normal-weight controls (El Hajj et al., 2013). The observation that MEST is specifically up-regulated in fat tissue of obese individuals (Kosaki et al., 2000) supports the view that intrauterine malprogramming of MEST contributes to obesity predisposition throughout life. Godfrey et al. (2011) analyzed the methylation levels of five candidate genes (selected on the basis of animal studies and methylation array data) in umbilical cord tissue of healthy newborns and found an association of perinatal promoter methylation of the retinoid receptor α (NRXRA) and endothelial nitric oxide synthetase (NOS3) genes with childhood adiposity at 9 years of age.

Limitations

In general, epigenetic changes due to maternal nutritional exposure are relatively small at the single gene level but appear to be widespread (Tobi et al., 2009; Khulan et al., 2012; Salbaum and Kappen, 2012; El Hajj et al., 2013). Similar to the genetic variants that have
been identified by genome-wide association studies (GWASs), the effect sizes of epigenetic markers that have been associated with an adverse periconceptional and prenatal environment may be small. Thus, consistent with the multifactorial threshold model for complex diseases, stochastic and environmentally induced epigenetic variations in many genes and pathways may determine the disease risk later in life. Highly penetrant disease-causing epimutations, i.e. in imprinted genes are very rare (Ivanova et al., 2012; El Haj and Haaf, 2013) and, evidently, cannot explain the fetal programming of adult disease.

An additional shortcoming is that DNA methylation patterns are cell type and tissue-specific. At least in humans, it is not possible to study the target tissues for metabolic disease, i.e. the hypothalamo-pituitary—adrenal axis, fat, liver, skeletal muscle and/or pancreatic islets. It is generally assumed that the observed epigenetic changes in accessible tissues such as blood or placenta can identify genes susceptible to fetal programming in the target tissues. Even animal studies so far largely ignored that the cell composition of a tissue may vary between groups, i.e. exposed and unexposed individuals.

Because intrauterine exposures are nearly impossible to quantify in time and space and each exposure has the potential to induce numerous changes with small effect sizes, most likely interacting with each other, it is difficult to prove that the epigenetic changes that have been associated with different developmental experiences are directly involved in the pathogenesis of chronic disease later in life and not just a consequence of the pathology. One of the most impressive examples of the phenotypic consequences of aberrant methylation patterns is epigenetic silencing of tumor suppressor genes such as BRCA1 that plays an important role in breast and ovarian cancer development (Esteller et al., 2000; Hansmann et al., 2012). In vitro methylation and transfection assays showed that repression of the BRCA1 promoter directly depends on the number of methylated CpGs (Magdiniuer et al., 2000). It is usually the density of methylated CpGs rather than individual CpGs that turns a promoter or an imprinting control region off (Weber et al., 2007). Similarly, inactivation of the somatostatin gene in gastric cancers is characterized by an inverse correlation between promoter methylation level and mRNA expression (Jackson et al., 2011). It is plausible to assume that the methylation changes that have been linked to different nutritional exposures also alter gene expression and, thus, phenotypic information.

Conclusions

So far, the main focus of reproductive medicine has been on pregnancy rates and the outcome at birth. The long-term consequences of environmental factors around the time of conception and during pregnancy are largely neglected. The epigenome is most plastic in early stages of embryo development when parent-specific genome reprogramming occurs (Mayer et al., 2000; Reik et al., 2001). This plasticity is then steadily decreasing during prenatal and post-natal life (Gluckman et al., 2009). If gestational hyperglycemia can permanently increase an individual’s risk of chronic disorders in later stages of life, we should be more concerned about the possible adverse effects of assisted reproductive technologies (ART), in particular embryo culture on adult health and disease (El Haj and Haaf, 2013). In vitro produced lambs and calves, suboptimal embryo culture has been linked to aberrant expression of imprinted genes, causing large offspring syndrome (Young et al., 1998, 2001). Similarly, mouse studies provided clear evidence that embryo culture conditions can affect epigenetic gene regulation and cause adverse phenotypic changes, including organomegaly, glucose intolerance, as well as neurodevelopmental and behavioral alterations (Khosla et al., 2001; Ecker et al., 2004; Fernández-Gonzalez et al., 2004; Mann et al., 2004; Calle et al., 2012).

A systematic comparison of mouse embryo responses to different human ART culture protocols showed significant differences in blastocyst and fetal developmental rates, demonstrating the dramatic impact of the culture system on somatic differentiation (Market-Velker et al., 2010; Schwarzer et al., 2012). Because gametogenesis and embryonic development differ considerably in rodents and humans, mouse oocyte and embryo assays do not necessarily allow one to extrapolate to the human situation. Owing to the striking similarities with human development, bovine oocytes and embryos are increasingly used as models for human ART (Menez and Herubel, 2002; Wrenzycki et al., 2005; Heinzmann et al., 2011). For legal and ethical reasons, it is not possible to use large numbers of human ART and non-ART embryos to systematically study the epigenetic and phenotypic effects of early human life conditions. Because it is problematic to assess the epigenetic safety of human ART protocols using rodent or large animal models, manipulation of oocyte and embryo should be restricted to a minimum or to the advantage of a specific technique (i.e. selection during embryo culture and blastocyst transfer) and must outweigh possible negative epigenetic effects (i.e. during extended embryo culture). Therefore, long-term epidemiologic studies on the lifelong risks of different ART protocols for metabolic, cardiovascular, neurodevelopmental, behavioral and other complex diseases are urgently needed. One important prerequisite for such studies is that future medical records of an individual also include information on parental infertility, mode of conception, and in the case of ART, which protocols have been used.

It is now widely accepted that an adverse periconceptional and intrauterine environment is associated with epigenetic malprogramming of the fetal metabolism and predisposition to chronic, in particular, metabolic disorders later in life (Barker et al., 2002; Gillman, 2005; Fernández-Morera et al., 2010; Hanson et al., 2011; Plagemann, 2011). Considering that in highly industrialized Western countries, up to 20% of women are obese at the start of pregnancy and up to 10% develop GDM during late pregnancy (Ben-Haroush et al., 2004; Kim et al., 2007), fetal overnutrition with glucose, free fatty acids and amino acids and the resulting hyperinsulinism may play a major role in the etiopathogenesis and current epidemics of obesity and type 2 diabetes (Fig. 1). The genetic variants that have been identified so far in large GWASs explain only a small fraction of the considerable heritability of type 2 diabetes and obesity (26 and 70%, respectively; Imamura and Maeda, 2011; Manco and Dallapiccola, 2012). In our opinion, modulations of the fetal epigenome by maternal diabetes and/or obesity provide the most reasonable mechanism for non-genetic inter-generational transmission of the phenotype. The missing heritability of complex disorders may be largely attributable to epigenetic inheritance.

To prevent metabolic disease epidemics, it is important to break the vicious cycle (Fig. 1) in which mothers with GDM and/or obesity have babies with epigenetic changes who are prone to develop metabolic disease later in life and, thus, give rise to a new generation of mothers with GDM/obesity. Considering the enormous
plasticity of the epigenome during late stages of oocyte and early stages of embryo development (El Hajj and Haaf, 2013), one could hypothesize that the best time for action is periconceptionally. However, the true challenge resides in finding a solution as to how we can optimize the periconceptional environment with our currently limited knowledge on the underlying mechanisms and the optimum supply of macro- and micronutrients around conception, both in vivo and in vitro. In the sheep model it was shown that micronutrient deficiencies, such as folic acid and vitamin B12 during the periconceptional period cause widespread epigenetic alterations and long-term health implications for the offspring (Sinclair et al., 2007). Dietary restriction of folic acid, methionine, choline, and/or vitamin B12 can perturb transmethylation pathways (i.e. for DNA methylation) by decreasing the availability of methyl groups (Niculescu and Zeisel, 2002). One interesting study on a relatively small number of Gambian women (Khulan et al., 2012) suggests that micronutritional supplementation around the time of conception can affect the epigenome of the offspring (Khulan et al., 2012), possibly reducing fetal maladaptation to inadequate nutrition during gestation. This is consistent with animal studies demonstrating that methyl supplementation of the maternal diet (i.e. with folic acid) can at least to some extent prevent a metabolic phenotype in the offspring (Waterland and Jirtle, 2003; Lillycrop et al., 2005, 2007; Burdge et al., 2008).

From a clinical point of view, it is important to note that effective treatment of maternal diabetes (Dörner et al., 2000; Plagemann, 2011) as well as large weight loss of obese women before pregnancy (Kral et al., 2006; Smith et al., 2009) appears to reduce the metabolic disease risk in the offspring. To prevent materno-fetal hyperglycemia and fetal hyperinsulinism, it is important to screen all pregnant women for disturbed glucose tolerance and to normalize a diabetic intrauterine environment by dietetic measures or insulin therapy. At the same time, we need biomarkers that help to assess adverse intrauterine exposures and lasting disease predispositions. This requires a more systematic comparison of fetal epigenomes using genome-wide methylation arrays or reduced representation bisulfite sequencing. Since the effect size of a single methylation change, i.e. in the MEST gene is low, we have to develop fetal and perinatal methylation profiles with more predictive power.

In contrast to genetic mutations/variants, epimutations are in principle reversible. This offers the exciting possibility to eventually compensate the epigenetic effects of an adverse intrauterine environment by pharmacological, dietary or behavioral interventions after birth. In the rat model of maternal undernutrition, neonatal leptin treatment and pre-weaning growth hormone treatment could compensate the epigenetic effects of an adverse intrauterine environment by pharmacological, dietary or behavioral interventions after birth. In the rat model of maternal undernutrition, neonatal leptin treatment and pre-weaning growth hormone treatment could prevent fetal programming of adult obesity, hypertension and vascular dysfunction (Vickers et al., 2005; Gray et al., 2013). Similarly, increasing folic acid intake during the juvenile-pubertal period was shown to reverse the negative phenotypic effects of prenatal undernutrition (Burdge et al., 2009). So far, in humans conclusive studies on the reversibility of fetal programming by specific post-natal treatments are missing. Breast feeding is generally recommended to avoid post-natal overfeeding (Plagemann, 2011). However, much more research is needed toward an optimal post-natal environment/management to correct adverse prenatal experiences.

**Authors’ roles**

All authors provided substantial contributions to the review conception and data interpretation. T.H. wrote and H.L. and U.Z. critically revised the manuscript. All authors approved the submitted manuscript.

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**Conflict of interest**

None declared.

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