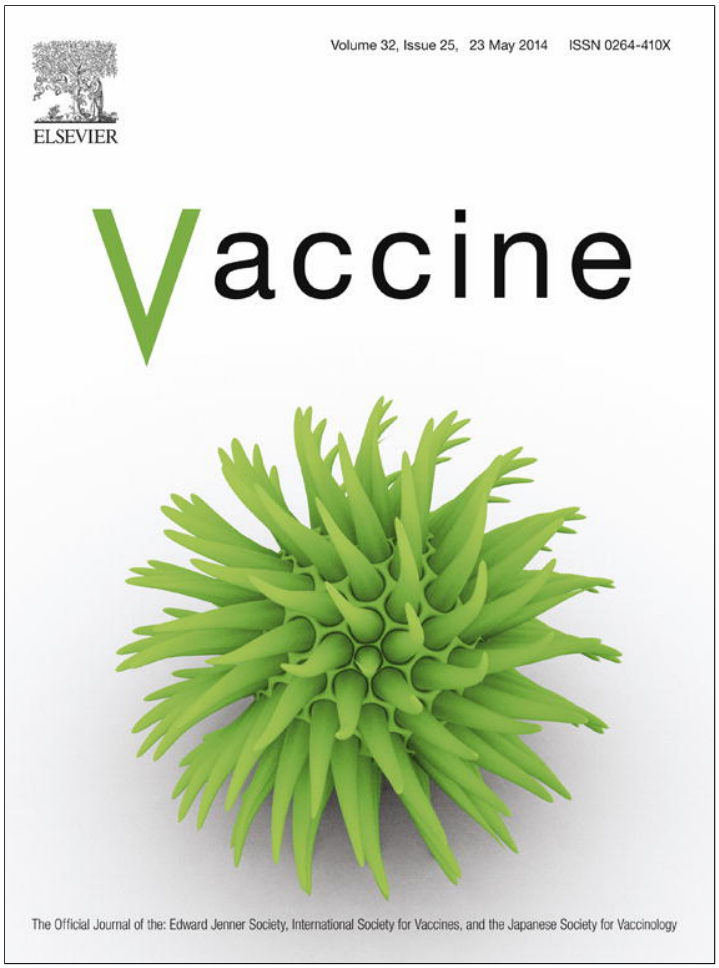

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Review

Optimizing benefits of influenza virus vaccination during pregnancy: Potential behavioral risk factors and interventions

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ABSTRACT

Pregnant women and infants are at high risk for complications, hospitalization, and death due to influenza. It is well-established that influenza vaccination during pregnancy reduces rates and severity of illness in women overall. Maternal vaccination also confers antibody protection to infants via both transplacental transfer and breast milk. However, as in the general population, a relatively high proportion of pregnant women and their infants do not achieve protective antibody levels against influenza virus following maternal vaccination. Behavioral factors, particularly maternal weight and stress exposure, may affect initial maternal antibody responses, maintenance of antibody levels over time (i.e., across pregnancy), as well as the efficiency of transplacental antibody transfer to the fetus. Conversely, behavioral interventions including acute exercise and stress reduction can enhance immune protection following vaccination. Such behavioral interventions are particularly appealing in pregnancy because they are safe and non-invasive. The identification of individual risk factors for poor responses to vaccines and the application of appropriate interventions represent important steps towards personalized health care.

1. Introduction

1.1. Influenza virus vaccination recommendations for pregnant women

Pregnant women are at high risk for complications, hospitalization, and death due to influenza [1–5]. It is now established that influenza virus vaccination during pregnancy reduces risk of influenza in women and provides antibody protection to infants via both transplacental transfer and breast milk [6]. Studies show no adverse effects of vaccination for risk of preterm labor, C-section, or fetal malformation [7–10]. Serious problems from influenza vaccine, such as severe allergic reaction, are rare. Primary risks are mild and include soreness where the shot was given, aches, fever, and fatigue. Thus, vaccination is recommended by the Centers for Disease Control (CDC) and American College of Obstetricians and Gynecologists (ACOG) to all women without contraindications who are pregnant or will be pregnant during flu season [11,12]. The US Department of Health and Human Services *Healthy People 2020* goal is to achieve 80% influenza vaccination coverage among pregnant women.

Pregnant women have historically received trivalent inactivated influenza vaccine (IIV3), which targets the A/H1N1, A/H3N2, and B strains expected to be predominant in the approaching season. However as of the 2013-2014 flu season, quadrivalent inactivated influenza vaccine (IIV4) is available which includes a second B strain. Inactivated influenza vaccine is now available in intradermal as well as intramuscular forms.

Although benefits for pregnant women and infants are well-documented, influenza vaccines are only 50–70% effective in preventing clinically proven influenza [13,14]. There is great variability in the degree to which individual women mount an adequate antibody response, maintain antibody levels over time (i.e., over the course of pregnancy), and transfer antibody to the fetus/infant. Thus, a next logical step in this clinical effort is to identify factors which may hinder and optimize the effectiveness of vaccination across women and infants. This paper reviews knowledge to-date

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with a focus on behavioral risk factors for poor immune protection following vaccination and behavioral interventions which may promote optimal responses.

1.2. Responses to influenza virus vaccine in pregnant women

Influenza virus vaccine is effective in pregnant women and benefits for their infants. In 2008, the first landmark randomized clinical trial of IIV3 in pregnancy showed a 29–36% reduction in all febrile respiratory illness in women and their infants up to 6 month of age and 63% reduction in clinically proven influenza in the infants during the same time period [14]. Protection from influenza during pregnancy may provide unique health benefits during the perinatal period. Among infants born during influenza season, maternal vaccination has been associated with reduced risk of preterm delivery, small-for-gestational age at birth, and fetal death [15,16]. Further, maternal influenza infection has been linked to increased risk of schizophrenia in adult offspring [17–19], a risk that vaccination could mitigate.

In addition, infants from 0 to 6 months of age have among the highest rates of influenza-associated complications with >1000 hospitalizations per 100,000 infants [20]. Influenza virus vaccine is not approved for infants <6 months. However, maternal vaccination in pregnancy is an effective strategy for protecting infants prior to 6 months. Prospective studies of laboratory-confirmed influenza, including the trial cited above, show that maternal vaccination significantly reduces risk of influenza infection in infants and reduces flu severity in infants who do become infected [14,21–26].

Although beneficial, the protection afforded by flu vaccines is far from 100%. For flu vaccines, it is generally accepted that anti-influenza antibody titers are a good marker of clinical efficacy [27]. Serological studies show that pregnant women in any trimester mount antibody responses to flu vaccines similar to nonpregnant adults [26,28–31]. A protective response is commonly considered to be a 4-fold increase in antibody levels to a specific strain or a titer $\geq$40 in adults, with peak titers achieved at 2–4 weeks after vaccination. The level of IgG antibody to the viral hemagglutinin correlates directly with resistance to influenza infection [27,32,33]. Thus, the ability of women to mount and sustain an adequate antibody response is key to clinical protection.

As in adults, antibody levels predict flu risk in infants. For example, among 573 infants of women vaccinated during pregnancy, risk of flu was directly correlated with cord blood antibody levels for all eight viral antigens assessed across three influenza seasons [23]. As expected, cord blood antibody levels were associated with the magnitude of maternal antibody response [23]. However, despite active transplacental transfer of IgG, an adequate maternal response does not guarantee sufficient antibody in the newborn [31]. Protection in infants depends on both adequate maternal response and sufficient antibody transfer. Notably, recent evidence indicates that in children a titer of 1:110 is required to achieve 50% clinical protection against infection, while the conventional adult cut-off of 1:40 is associated with only 22% protection in children [35]. Thus, it is of clinical value to identify factors which promote sufficient transplacental antibody transfer to the fetus/infant.

Importantly, vaccination during pregnancy can also confer benefits via breastfeeding. In a study of 340 pregnant Bangladeshi women who received either IIV3 or pneumococcal polysaccharide vaccine (control group) during the third trimester of pregnancy, influenza-specific IgG A antibody levels in breast milk were significantly higher for at least 6 months postpartum in women who had received influenza vaccine [34]. Moreover, greater exclusivity of breastfeeding in the first 6 months of life was associated with fewer respiratory illnesses in the infants of the influenza-vaccinated mothers, but not the infants of mothers who received the pneumococcal vaccine.

2. Potential behavioral risk factors for poor antibody responses to vaccination

There are limited data on factors which may negatively affect flu vaccine immunogenicity in pregnant women. Given the recommendation for universal vaccination in pregnancy and ongoing public health efforts to increase vaccination uptake in this population, such research is highly justified. Detailed below, research in non-pregnant populations suggests that two factors that may be of particular importance are weight and psychosocial stress. However, the extent to which these findings translate to pregnancy is not known. Given the considerable neuroendocrine and immune changes observed, effects of stress and obesity on immune parameters may differ in pregnancy versus non-pregnancy. Moreover, in pregnancy, not only the initial antibody response, but also antibody maintenance over time and antibody transfer to the neonate are of particular importance. Thus replication and extension of findings in non-pregnant adults to the context of pregnancy is needed.

2.1. Maternal body mass index: Obesity and underweight

In the U.S., 34.0% of women 20–39 years are clinically obese (BMI $\geq$ 30) [36]. Obesity predicts greater risk of secondary infections among hospitalized patients and respiratory-tract infections in community-dwelling adults [37,38]. Following the 2009 H1N1 pandemic, the CDC for the first time cited obesity as an independent risk factor for influenza severity, hospitalization, and mortality [39–41]. For example, in California, one half of adult hospitalizations for influenza were among obese patients, 2.2 times the prevalence of obesity in the state indicating that the obese were over-represented among those with influenza-related complications [41].

Animal studies support the CDC recognition of obesity as a risk factor for influenza-related complications. Obese mice infected with seasonal flu virus had 6-fold higher mortality rates [42]. In addition, as compared to lean mice, obese mice exposed to a weak strain of influenza showed poorer memory T-cell responses upon secondary exposure to a stronger strain [43,44]. This model parallels memory T-cell responses in the context of vaccination. In addition, in a mouse model, genetically and diet-induced obese mice infected with influenza virus showed greater lung pathology associated with impaired wound repair, suggesting a mechanism by which obesity may result in greater influenza-related complications [45].

Notably, clinical trials of vaccine efficacy often fail to report information on demographics and health behaviors which may affect vaccine immunogenicity. In an analysis of 83 vaccine trials, *none* reported information about obesity [46]. One study in non-pregnant adults reported that obese and non-obese adults exhibited similar peak antibody responses at one month post-vaccination, but obese adults showed steeper drops in antibody levels over the subsequent 11 months, indicating poorer maintenance of protective antibody levels over time [47]. Data also show that, compared to healthy weight controls, peripheral blood mononuclear cells (PBMCs) from overweight and obese adults showed deficiencies in activation and function when stimulated ex vivo with live influenza A virus [48]. These effects have not been replicated in pregnancy. In addition, potential effects of maternal obesity on transplacental anti-influenza antibody transfer are unknown.

Underweight is also a risk factor for poor antibody responses to vaccination. Due to the risks of flu in older adults, studies have

examined underweight and frailty in relation to vaccine immunogenicity in this population [49,50]. In elderly adults, frailty (defined by five indicators including poor endurance, weakness, and shrinking) has been associated with impairment in antibody response to IIV3, as well as increased rates of influenza-like illness and laboratory confirmed influenza infection despite vaccination [49,50]. Moreover, in the general adult population, underweight has been associated with increased rates of influenza-associated pneumonia [51]. An estimated 2.1–4.6% of US women 20–44 years are underweight (i.e., BMI < 18.5) [52]. Maternal underweight is recognized as a risk factor for preterm birth and low birth weight [53]. Thus, although obesity represents a much more prevalent public health risk, potential effects of underweight on vaccine immunogenicity in pregnancy also warrant attention.

2.2. Psychological stress

In non-pregnant adults, psychological stress predicts poorer antibody responses to vaccinations including influenza, hepatitis B, and meningococcal C [54–65]. A meta-analysis of 13 studies of stress and influenza vaccine concluded that stress consistently impairs antibody responses (Cohen's $d = 0.37$, medium effect size) [64]. This effect was similar among older and younger adults. This corresponds to adequate responses in 41% of stressed versus 59% of those less stressed for strains responsive to stress (A/H1N1 & B) [64]. Psychosocial stress has also been associated with impaired maintenance of antibody levels over time [58].

Psychological stress and distress are common in pregnancy, particularly among women from economically disadvantaged backgrounds and those lacking stable social support. For example, it is estimated that 14–23% of pregnant women will experience a depressive disorder while pregnant [66,67]. Among women of low socioeconomic status, rates of clinically significant depressive symptoms may be as high as 47–52% [68,69]. Due to substantial pregnancy-related immune changes, pregnant women may be more susceptible than non-pregnant adults to stress-induced immune dysregulation [70,71]. However, despite their high risk status for influenza complications, the literature lacks information on effects of psychological factors on antibody responses following influenza vaccination in pregnant women.

With regard to offspring, prenatal stress alters antibody transfer from mothers to offspring in rats, pigs, and non-human primates [72–74]. For example, in squirrel monkeys, exposure to repeated stress (changes in social group), showed lower IgG antibody levels as well as altered antibody transfer to the offspring. The direction of this effect differed based on the sex of the infant; compared to undisturbed controls, mothers exposed to chronic stress showed poorer transfer of antibodies to males offspring, but *enhanced* transfer to female offspring. The mechanism for this sex difference is unknown, although the authors speculate that the IgG receptor may have been selectively up-regulated on the placentas of the female fetuses to compensate for reduced antibody in the mothers [72]. Sex differences have also been reported in relation to cognitive and behavioral development following exposure to prenatal stress or stress hormones [75]. Thus, effects of maternal stress on the neonate may not be simple or direct, but rather may be affected by moderating factors and/or compensatory mechanisms. Examination of such effects in human pregnancy is needed.

Transplacental antibody transfer occurs primarily in the final weeks of pregnancy. Thus, preterm infants have significantly lower IgG antibody levels against various infections (measles, mumps, rubella) [76]. Though not found in all studies, maternal stress has repeatedly been linked to spontaneous and medically-indicated preterm birth [77–81]. Thus, shorter gestation is also a key pathway by which stress may adversely affect newborn antibody levels.

Of note, the deleterious effects of stress described apply to chronic stress. Data from both human and animal models indicate that exposure to acute stressors, such as those lasting minutes in duration, can *improve* antibody responses to vaccination [82–84]. It has been hypothesized that acute stress occurring in close temporal relation to the immune challenge may enhance the immune response by induction of endogenous adjuvants [85,86]. In comparison to potential interventions such as exercise or stress reduction detailed below, eliciting acute stress responses may be a less acceptable approach in a public health context. In addition, beneficial effects of acute stress may only be observed in individuals with a healthy fight-or-flight response; those who are chronically stressed or depressed show dysregulation in immune and neuroendocrine responses to acute stress [87]. However, studies in this area highlight that the distinction between acute and chronic stress is an important consideration [88].

3. Interventions to improve antibody responses to vaccines

Numerous studies in non-pregnant adults support the idea that behavioral interventions, particularly focused on exercise or stress reduction, can enhance immune responses to various vaccines. Such approaches are particularly appealing in pregnancy because they are safe and non-invasive. Interventions could be targeted specifically to individuals at risk for poor response.

3.1. Exercise

Exercise is a behavioral adjuvant which can enhance antibody responses to vaccination, particularly among those at risk for poor response [89]. In older adults, those classified as more active show greater antibody responses than their more sedentary counterparts [90,91]. Data from randomized interventional trials support a causal effect in this relationship. In one study, older adults who completed a 10-month cardiovascular training intervention showed greater initial antibody responses following influenza vaccination [92]. Another study using a similar intervention found no effects on initial antibody responses, but reported greater seroprotection at 24 weeks after vaccination in the intervention group, demonstrating better maintenance of antibody levels across the flu season [93].

An extended intervention of this type is clearly burdensome from a clinical standpoint. Thus, it is notable that a single bout of moderate to high intensity exercise immediately prior to vaccination can have adjuvant benefits. Exposure to a 45-min bout of moderate cycling prior to influenza vaccine improved antibody responses in women when measured at 4 weeks and 20 weeks post-vaccination [83]. Similarly, exposure to a 25-min session of eccentric exercise (bicep curls and lateral raises) prior to vaccination enhanced antibody responses to influenza vaccination in women [94].

Acute exercise may require a minimum threshold to exert such effects; a trial utilizing a brisk 45-min walk resulted in no differences in subsequent antibody responses to influenza or pneumococcal pneumonia vaccines [95]. In addition, such benefits may not be observed in flu seasons in which robust responses are observed in the population in general, resulting in a ceiling effect [96]. Greater information is needed to determine the best type and duration of exercise as well as timing in relation to vaccination. However, given its safe and non-invasive nature, exercise is an appealing potential behavioral adjuvant for vaccination during pregnancy.

3.2. Stress reduction

A variety of approaches may effectively reduce the adverse effects of stress on vaccine responses. In a study of caregivers of spouses with dementia, those who participated in an 8-week stress management group showed greater immune protection following influenza vaccination than controls [97]. Similarly, among 48 healthy adults, those who completed an 8-week meditation intervention exhibited better antibody responses to the flu shot as compared to wait-list controls [98]. Similarly, a study utilizing Tai Chi demonstrated that a 16-week intervention improved responses to varicella-zoster virus vaccine in older adults [99].

In addition to learning relaxation skills, such as meditation or tai chi, utilization of social support networks may bolster immune responses to vaccination. College students who reported greater social support showed stronger antibody responses to influenza vaccination [65] as well as better cellular and humoral immune responses to hepatitis B vaccination [60]. Similarly, when exposed to infectious agents in a controlled laboratory environment, participants reporting more social ties were less likely to develop colds than those reporting fewer social ties [100]. It is important to note that while social support may buffer the effects of stress, having a diverse social network may also result in greater exposure to a broader diversity of viruses. In fact, in a naturalistic study, greater social network diversity was associated with fewer upper respiratory infections only under conditions of low stress [101].

A key beneficial component of social support may be that it provides an outlet for emotional disclosure. Therefore, interventions designed to encourage disclosure may benefit immune function. For example, in a study of 40 medical students who were assigned to write about personal traumatic events or control topics during 4 consecutive daily sessions, those in the disclosure group showed stronger antibody responses to a hepatitis B vaccine [102]. In contrast, in a study of 47 Black adults who were assigned to write about either their experiences with racial discrimination or a neutral topic, those in the emotional expression condition showed poorer antibody responses to an influenza vaccine [103]. Because such disclosure paradigms inherently involve the expression of potentially stressful experiences, ultimate effects on health may be moderated by multiple factors.

Although it seems reasonable to assume that benefits of enhanced immune responses to vaccinations observed in non-pregnancy would translate to pregnancy, it would be of value to examine confirm such effects in pregnant women and quantify potential benefits for the infants as well. A variety of stress-reduction interventions have been examined during pregnancy in relation to parameters including subjective stress/mood, neuroendocrine function, physical functioning, and birth outcomes e.g., [104–108]. Inclusion of responses to vaccination in such trials would be of great value. In addition, in general, data regarding the extent to which stress-buffering interventions may be shortened and reasonably packaged to allow for practical implementation to a broad population is needed.

4. Other considerations: Vaccine uptake, breastfeeding, and vaccine type

A discussion of optimizing benefits of influenza virus vaccination would be incomplete without a focus on improving vaccination rates. Vaccination coverage among pregnant women has been low. An estimated 11.3% of pregnant women were vaccinated in the 2008–2009 flu season [109]. Reflecting substantial public health efforts during the 2009–2010 influenza pandemic, 46.6% and 50.7% of pregnant women received seasonal and 2009 H1N1 vaccine, respectively [110]. In subsequent seasons, this increase in coverage has generally been sustained, but has not improved further [111–114]. Thus, each year, approximately half of pregnant women do not receive the seasonal flu shot. These vaccination rates are considerably below the US Department of Health and Human Services *Healthy People 2020* target of 80% coverage for pregnant women.

Covered extensively elsewhere e.g., [115], major factors affecting vaccine uptake among patients include safety concerns, lack of knowledge about influenza risks, fear of needles, mistrust of the medical establishment, and lack of access to routine prenatal care. The most considerable factors affecting likelihood of vaccination was a recommendation from a healthcare provider and the offer of a flu shot. Women who received both a recommendation and an offer were 1.6 times more likely to be vaccinated (73.5%) than women who received only a recommendation (45.1%) and 4.8 times more likely to be vaccinated than women who received neither a recommendation nor an offer (15.4%) [116]. Among those who do receive both a recommendation and an offer and remain unvaccinated, women commonly site concern that the vaccination will give them influenza (25.6%) or pose a safety risk to their baby (13.1%) [112]. Thus, provider recommendation and offer of a flu shot, as well as patient education are key modifiable factors in improving vaccine coverage in pregnant women.

Benefits of maternal vaccination during pregnancy or postpartum would be maximized by improving breastfeeding initiation, duration, and exclusivity. As described earlier, infants can acquire anti-influenza antibody from vaccinated mothers via breast milk [34]. However, breastfeeding rates in the US are low. According to recent estimates, 75% of mothers in the US initiate breastfeeding but only 43% continue for at least 6 months, including those who supplement with formula [117]. An estimated 13% of infants are exclusively breastfed for 6 months or longer. Moreover, persistent racial disparities are seen; breastfeeding rates among Black infants are approximately 50% lower than White infants at birth, 6 months, and 12 months of age [117,118]. Thus, there is great need for improvement in breastfeeding behaviors in the US.

Finally, behavioral interventions are particularly appealing in pregnancy because they are safe and non-invasive. However, high dose influenza virus vaccine or two dose schedules have demonstrated benefits for other high risk groups including adults over 65 years of age [119,120], children upon initial receipt of vaccination [109], as well as dialysis patients and transplant recipients [121]. Thus, examination of alternate dosing recommendations may also be warranted if consistent immune decrements are documented based on specific risk factors.

5. Summary and conclusions

It is well-established that maternal receipt of influenza virus vaccine during pregnancy is beneficial for both women and infants. However, current rates influenza virus vaccination lag far behind the *Healthy People 2020* goal to vaccinate 80% of pregnant women annually. Thus, continued efforts to increase accessibility of vaccination and educate the public with regard to the safety and health benefits are needed. Moreover, breastfeeding rates in the US are low. Increasing breastfeeding initiation, duration and exclusivity following maternal vaccination would benefit infant health.

Even if desired vaccine coverage is achieved, however, protection for all vaccinated women is not assured. It is well-documented in non-pregnant adults that a substantial portion mount insufficient antibody responses to influenza virus vaccines. Similarly, though the overall benefits versus risks warrant universal vaccination of pregnant women, a relatively high proportion of pregnant women and their infants do not achieve protective antibody levels against influenza virus following maternal vaccination. It is warranted to identify and quantify the impact of factors which

attenuate as well as enhance immune protection following vaccination.

This paper has focused on influenza because of the clear health implications in pregnancy and the relatively longstanding recommendation for universal influenza vaccination in pregnant women. Moreover, behavioral risk factors and interventions have been most thoroughly studies with respect to influenza vaccine. However, the factors reviewed should be considered with regard to other vaccines. Of particular relevance, due to concerning increases in pertussis in the US, as of 2013 the Centers for Disease Control and Prevention recommend administration of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) for pregnant women during each pregnancy regardless of the woman's prior Tdap vaccination history [122]. The optimal timing of administration is 27–36 weeks gestation, to maximize the maternal antibody response and passive antibody transfer to the infant. Behavioral factors have relevance in this context.

The majority of human studies on behavioral risk factors and interventions in relation to antibody responses to vaccines have not included a mechanistic focus [64]. In the context of stress, activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) affects the immune system, particularly in the case of repeated or chronic stress [123]. Glucocorticoid pathways have relevance in the context of both obesity and stress; animal models demonstrate multiple effects of glucocorticoid hormones on cell-trafficking as well as production of pro-inflammatory cytokines and chemokines that affect antibody responses (for review see [123,124]). Greater attention to the specific biological mechanistic pathways in human studies is needed.

In summary, influenza virus vaccination during pregnancy provides clearly documented health benefits to women and infants. However, there is clinically meaningful variability in response to vaccines between individuals. Thus, efforts to optimize the benefits of influenza and other vaccines should focus not only on increasing uptake, but also on identifying risk factors for poor immune responses and intervening to improve immunogenicity. Although pregnancy is a time of unique vulnerability for maternal and fetal/infant health, this individualized approach represents an important step towards personalized healthcare which is broadly relevant to adults and children in general.

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Conflict of interest statement

The author reports no conflicts of interest.

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