Original Research Article

Woman's Body Symmetry and Oxidative Stress in the First Trimester of Pregnancy

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Objectives: High level of oxidative stress (OS) during the first weeks of pregnancy is related to many serious pregnancy complications. Previous studies showed that body fluctuating asymmetry (FA) is related to OS level in men, suggesting that FA is a marker of oxidative balance in an individual. The aim of this study was to analyze if body FA was related to the level of biomarkers of OS in the first trimester of pregnancy.

Methods: The sample included 34 women in the first trimester of pregnancy, not smoking, and not exposed to toxins in their work environment. The composite FA and levels of two biomarkers of OS, 8-iso-ProstaglandinF2α (an indicator of oxidative damage to lipids) and 8-OH-dG (an indicator of oxidative damage to DNA) were measured. Factors that may affect the level of OS (vitamin supplementation, age, smoking, alcohol drinking, physical activity, and health condition) were controlled.

Results: The levels of OS markers in the first trimester of pregnancy correlated positively with women's FA ($r = 0.52$, $P = 0.002$ for 8-OH-dG; $r = 0.50$; $P = 0.003$ for 8-iso-PGF2α level) and positively with body height ($r = 0.37$, $P = 0.03$ for 8-OH-dG level).

Conclusion: The level of OS is likely to be a substantial and important fitness trait, and FA may convey information on the level of OS in women. The result confirms that FA is an indicator of biological condition, as suggested by an evolutionary approach to morphological human traits perceived as attractive. Am. J. Hum. Biol. 27:816–821, 2015.

INTRODUCTION

Oxidative stress (OS) is defined as a lack of balance between the production of reactive oxygen species (ROS) and antioxidant compounds (Finkel and Holbrook, 2000). The greater the production of ROS and the lower the antioxidant defenses, the greater the OS (Ruder et al., 2008). ROS arises both as a by-product of metabolic processes of aerobic cells and during mitochondrial respiration. These small molecules are unstable and contain one or more unpaired electrons (radicals). They are highly reactive and interact with other cellular substances, including lipids, proteins or DNA, causing damage (Gangestad et al., 2010). Oxidative cellular damage results in senescence (Beckman and Ames, 1998) and mutations (Cheng et al., 1992), and is a component of many disorders, ranging from cardiovascular disease and cancer, to chronic inflammation and autoimmune diseases (Orhan et al., 2003). OS also affects female fertility, negatively impacting oocyte maturation and causing their degeneration (Ruder et al., 2009).

Pregnancy is a state that favors OS in women (Casanueva and Viteri, 2003), as the energy demand of various organs (including the feto-placental unit) and oxygen consumption increase during this period. Although ROS and antioxidants remain in balance during a healthy pregnancy, and cellular damage is repaired effectively, this balance can be easily disrupted (Furness et al., 2011). High OS during the first trimester of pregnancy increases the risk of spontaneous abortion (Agarwal et al., 2006; Burton and Jauniaux, 2004), as it causes the premature oxygenation of the early embryonic environment, which should occur later in the pregnancy (Jauniaux et al., 2000). OS is involved in defective embryo development and retardation of embryo growth, preeclampsia, maternal hypertension, and the risk of preterm delivery (reviewed in Ruder et al., 2009). OS also plays a major role in the etiopathogenesis of pregnancy disorders, such as diabetes and obesity, leading to a higher incidence of miscarriages (Poston et al., 2011), vasculopathy and fetal structural defects. This indicates that the conceptus can be irreversibly damaged by OS (Jauniaux et al., 2006), thus the ability to keep the OS low during the first stage of pregnancy might be crucial for successful pregnancy and the newborn's health.

OS may also be involved in increased body fluctuating asymmetry (FA), as ROS-induced damage to DNA or cell membranes may disrupt cell replication, which could cause asymmetrical growth (Gangestad et al., 2010). It is assumed that small random deviations from perfect bilateral symmetry, increased by deleterious mutations (Parsons, 1992), parasite infections (Moller, 1992), and habitat destruction (Manning and Chamberlain, 1994), reflect minor developmental errors, and show the degree to which individuals are adapted to their environment (e.g., Van Dongen, 2006). FA is the most common marker of developmental instability (DI) used in empirical research (Van Dongen and Gangestad, 2011). DI (emerging morphologically as FA) has been linked to some aspects of human health (e.g., Manning et al., 1997a; Shackelford and Larsen, 1997; Waynforth, 1998), such as susceptibility to infectious disease (Thornhill and Gangestad, 2006),

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attractiveness (Brown et al. 2008), and reproductive potential in men (Manning et al., 1998; Soler et al., 2003; Gangestad et al., 2010) and women (Jasienska et al., 2006; Manning et al., 1997b; Moller et al., 1995). Those associations are moderate, but statistically highly robust (Van Dongen and Gangestad, 2011), and there is a relative paucity of research revealing how, and precisely why, FA becomes linked to a wide variety of aspects of an individual's fitness (Gangestad et al., 2010). Recently, Gangestad et al. (2010) suggested that one of the processes underlying increased FA that emerges in early stages of development may be the increased OS level, as it may give rise to both developmental instability and disease proneness. They showed that men's individual differences in susceptibility to OS is related to the level of FA (Gangestad et al., 2010).

A woman's high body symmetry is perceived as an attractive physical trait (Grammer et al., 2003; Grammer and Thornhill, 1994). According to evolutionary theory, attractive morphological traits are signals of good biological condition and high reproductive potential (e.g., Gangestad and Scheyd, 2005; Jasienska et al., 2006; Rhodes et al., 2005). Body symmetry reflects developmental stability and is supposed to be an important biomarker of fitness (Grammer et al., 2003; Grammer and Thornhill, 1994). OS also affects female fertility, negatively impacting oocyte maturation, and causing oocyte degeneration (Ruder et al., 2009). Important information about the level of OS in women may thus be conveyed by FA.

FA across many taxa has been related to various measures of stress and (inversely) fitness, health, or "genetic condition" (Moller, 1999). Many theoretical and empirical analyses showed a robust association between DI and measures of health and quality, but also emphasized a large amount of unexplained variations across studies (Gangestad and Thornhill, 1999; Houle, 2000; Van Dongen, 1998; Van Dongen and Gangestad, 2011; Whitlock, 1998). This is mainly due to the fact that FA itself does not cause measured outcomes, but both FA and health-related outcomes result from DI. Thus, the association between FA and measured outcomes underestimates the true effect of DI (Van Dongen and Gangestad, 2011). OS is a good candidate for a mechanism underlying the relationship between FA and DI (Gangestad et al., 2010).

In this study, we examined the association between maternal FA and biomarkers of OS in the first trimester of pregnancy. More specifically, we tested if symmetrical women, without any pregnancy conditions, have lower levels of urinary 8-iso-ProstaglandinF2α (8-iso-PGF2α) and urinary 8-hydroxydeoxyguanosine (8-OH-dG) (Chen and Scholl, 2005), two markers of OS widely used in research (Stein et al., 2008). Previous studies have shown that elevated levels of maternal 8-OH-dG, a biomarker of oxidative DNA damage, were associated with reduced birth weight and shortened gestation (Kim et al., 2005; Stein et al., 2008). High excretion of 8-iso-PGF2α during pregnancy, a marker of endogenous lipid peroxidation (Chen and Scholl, 2005), results in outcomes primarily related to the mother, and secondarily to the fetus, such as preeclampsia or medically indicated preterm delivery (Chen and Scholl, 2005). Both 8-OH-dG and 8-iso-PGF2α are independent biomarkers for OS early in pregnancy, tracking different aspects of OS (Stein et al., 2008). The hypothesis we put forward in this article is that the level of those two OS markers in early stages of pregnancy negatively correlates with a woman's body symmetry, measured by the level of FA.

MATERIAL AND METHODS

Participants

From among 130 participants who took part in a broader project on women's physiology, morphology, and behavior during pregnancy, we recruited 34 never-smoking women who were in the first trimester of pregnancy (mean week of pregnancy 9.6 ± 1.5 weeks). We excluded those who worked in a setting that regularly exposed them to environmental toxins. There was no relationship between pregnancy week and OS marker levels (for 8-OH-dG: $P = 0.20$; for 8-iso-PGF2α: $P = 0.61$). Participants' mean age was 28.50 (± 3.22). All women reported occupations that did not require physical activity. The research protocol was approved by the ethics committee of the Lower Silesian Doctors Chamber.

Procedures

Participants arrived for a scheduled laboratory session. After providing informed consent, each participant was given a questionnaire to complete, containing a number of variables pertinent to our analyses (e.g., alcohol consumption, cigarette smoking, exposure to toxins, vitamin use, weight before pregnancy, physical activity, type of work [physical vs. mental]). Questions about age, reproductive history, and past use of hormonal medication were also included. During the session, women provided a sample of morning urine, and anthropometric measurements were performed.

Assessment of FA

The reliability and validity of FA as a marker of DI can be bolstered by using a composite asymmetry measurement, aggregating FA of multiple developmentally independent traits (e.g., ear and knee asymmetry) (Van Dongen, 2012; Van Dongen and Gangestad, 2011). In this study, 10 bilateral features were measured: ear width, ear height, wrist width, elbow width, length of the 2nd and 4th finger, ankle width, knee width, foot length, and width. The left and right sides were measured twice with precise calipers. The mean correlation between the first and the second measurements was 0.92 ($P < 0.001$). Inter-observer reliability, estimated using the technical error of measurement (TEM), and relative technical error of measurement (rTEM), were acceptable for each measurement (Table 1). The measures were averaged for each trait for each individual, and the absolute difference between the sides were used in analysis. Each trait's FA was standardized (divided) by average trait size across all women in the sample. We examined signed right-left (R-L) differences for directional asymmetries. The mean R-L differences did not deviate significantly for any of the traits ($P > 0.05$). Because a single trait's FA taps organism-wide developmental instability very weakly (Gangestad and Thornhill, 1999), we aggregated the FA of all 10 features into a composite measure. For ease of interpretation we multiplied the sum by 10. The mean composite FA of 2.44 for the sample means that, on average, across 10 traits, the average woman's FA was 2.44% of the mean trait size. The SD was 0.69, and the range from 0.73 to 3.93. The mean kurtosis was 0.64. Leptokurtosis seems to be a common feature of the distribution of FA (Gangestad and

TABLE 1. TEM and rTEM values for measurements (H-height; EL-Ear Length; EW-Ear Width; WW-Wrist Width; ELW-Elbow Width; 2D-2nd Digit Length; 4D-4th Digit Length; KW-Knee Width; AW-Ankle Width; FL-Foot Length; FW-Foot Width)

		Right side										Left side									
	H	EL	EW	WW	ELW	2D	4D	KW	AW	FL	FW	EL	EW	WW	ELW	2D	4D	KW	AW	FL	FW
TEM (cm)	0.12	0.03	0.04	0.02	0.03	0.05	0.07	0.04	0.05	0.06	0.04	0.03	0.03	0.03	0.04	0.03	0.04	0.07	0.05	0.03	0.05
rTEM (%)	0.07	0.49	1.52	0.39	0.37	0.44	0.99	0.37	0.76	0.25	0.50	0.50	1.13	0.60	0.49	0.73	0.57	0.66	0.76	0.12	0.60

Thornhill, 1999) and is suggested to be the result of early loss of highly asymmetrical individuals (Martin et al., 1999). None of the participants had broken, sprained or injured any feature measured.

Assessment of urinary biomarkers of oxidative stress

During the session, each woman was asked to provide a urine sample. The sample was frozen at −20 °C until analysis. We measured urinary levels of 8-hydroxydeoxyguanosine (8-OH-dG), a biomarker of oxidative DNA damage, and urinary level of 8-iso-ProstaglandinF2α (8-iso-PGF2α), a biomarker of lipid peroxidation. 8-OH-dG, a ROS-induced modification of a purine residue of DNA, is a sensitive index of oxidative DNA damage, and is considered a marker of total systemic OS *in vivo* (Chen and Scholl, 2005). The quantitative determination of the human oxidative markers in urine samples were measured by enzyme-linked immunosorbent assay (ELISA). Detection of the 8-OH-dG were performed using commercial kits (8OHdG-Check, DEMEDITEC and Urinary 8-epi-ProstaglandinF2α, OxisResearch) according to manufacturer instructions. For the calculation of concentration, the standard curve was constructed. The values of the samples were calculated on the calibration curve to obtain the corresponding values of the concentrations expressed in ng/mL.

Assessment of potential confounders and other correlates of oxidative stress

Most ROS are formed as a consequence of the mitochondrial respiratory chain, but can also be formed in response to exogenous exposures such as tobacco smoke, alcohol, and environmental pollutants (Ruder et al., 2009), thus we controlled for potential confounders. None of our participants smoked during pregnancy. We controlled for alcohol use at the beginning of pregnancy, and as dietary antioxidants (e.g., vitamins) may affect OS level (Mayne, 2003), we also controlled for vitamin or herbal supplement use. Some studies show an increase in oxidative level with age (Tarin, 1996), thus we tested if the level of OS correlated with age. As body weight is related to the level of OS (Furukawa et al., 2004), and may also be an indicator of a lifestyle before and during the first trimester of pregnancy (Martinez, 2000), maternal body weight before and at the 1st trimester of pregnancy was controlled for as well. Also, women who planned their pregnancy may differ from women who did not, in terms of lifestyle components that could influence the OS just before and at the beginning of pregnancy (e.g., alcohol drinking, smoking, diet, exercise, and supplement use). Maternal height and sport activity were controlled for as well. Twelve women declared regular sports activity. As there were only two types of physical activity (swimming or gymnastics), and all women declared similar time devoted to these activates per week (2 or 3 times; 60 min each training), we created a YES/NO variable for physical activity.

Statistical analyses

We used *t*-test for tracking the differences in OS marker levels among women who were exposed to potential confounders and women who were not. Spearman correlation was used to test the relationship between maternal height, age, and weight before and during the 1st trimester of pregnancy. To test for the relationship between the level of OS markers and body morphology traits (weight and height) and woman's age we used the Spearman correlation and regression model.

RESULTS

Potential confounders and other correlates of oxidative stress

There was no difference in mean levels of OS markers between women who were taking supplements and those who did not use any supplements, and between women who planned the pregnancy, or practiced sport, and women who did not. There was also no difference in the mean level of OS markers between women who claimed to suffer from allergies or recurrent anemia, and women who claimed to be in perfect health. There was no difference in the mean levels of OS markers between women who reported drinking some alcohol since the beginning of pregnancy and women who did not (Table 2).

We found no relationship between maternal weight before pregnancy and 8-iso-PGF2α ($r = -0.05$, $P = 0.78$), nor with 8-OH-dG ($r = -0.04$, $P = 0.81$). There was also no relationship between maternal weight at the 1st trimester of pregnancy and 8-iso-PGF2α ($r = -0.07$, $P = 0.68$), nor with 8-OH-dG ($r = 0.01$, $P = 0.95$). A woman's age was not related to 8-iso-PGF2α ($r = 0.03$, $P = 0.87$) nor to 8-OH-dG ($r = -0.33$, $P = 0.06$). However, the correlation between 8-OH-dG and a woman's age was marginally significant ($P = 0.06$), thus in further analyses we controlled for age. There was also no correlation between age and FA ($r = 0.03$, $P = 0.87$).

Oxidative stress and composite FA

We examined the correlation of composite body asymmetry with the levels of two markers of OS. As hypothesized, FA significantly positively predicted OS in pregnant women. The Spearman correlation between body asymmetry and each of the markers of OS were: $r = 0.52$ ($P = 0.002$) for 8-OH-dG, and $r = 0.50$ ($P = 0.003$) for 8-iso-PGF2α level (Fig. 1 for the scatterplots).

To control for a potential confounding effect of age, at both OS marker levels, we also ran the regression analysis with FA and age as predictors. The regression model showed: for 8-OH-dG: adjusted $R^2 = 0.42$, $F(2,31) = 11.07$, $P < 0.001$ (Composite asymmetry: $\beta = 0.55$, $t = 4.04$,

TABLE 2. Oxidative stress biomarker levels (means and standard deviations) in groups of women differing in supplements and vitamin use, allergy and recurrent anemia, alcohol use since the beginning of pregnancy, planned vs. unexpected pregnancy, and sport practice

	8-OH-dG [ng/ml] M = 16.49 ng/ml (±10.63)				8-iso-PGF2α [ng/mL] M=1.51 ng/mL (±1.05)			
	YES (M ± SD)	NO (M ± SD)	t	P	Yes (M ± SD)	No (M ± SD)	t	P
Supplements and vitamins	16.02 ± 10.99 (N = 14)	16.83 ± 10.65 (N = 20)	0.21	0.83	1.58 ± 1,25 (N = 14)	1.46 ± 0.92 (N = 20)	−0.31	0.76
Allergy and recurrent anemia	17.90 ± 12.51 (N = 14)	15.51 ± 9.32 (N = 20)	0.64	0.53	1.33 ± 0.99 (N = 14)	1.64 ± 1.10 (N = 20)	−0.85	0.40
Alcohol use since the beginning of pregnancy	16.93 ± 9.14 (N = 6)	16.40 ± 11.07 (N = 28)	−0.11	0.91	1.41 ± 0.26 (N = 6)	1.53 ± 1.16 (N = 28)	0.26	0.79
Planned pregnancy	16.22 ± 11.26 (N = 28)	17.76 ± 7.69 (N = 6)	−0.32	0.75	1.58 ± 1.13 (N = 28)	1.21 ± 0.54 (N = 6)	0.78	0.44
Sport practice	18.53 ± 10.99 (N = 12)	15.38 ± 10.52 (N = 22)	−0.82	0.42	1.18 ± 1.20	1.69 ± 0.94	1.36	0.18

Difference between groups were analyzed by t-test.

$P < 0.001$; Maternal age: $\beta = -0.35$, $t = -2.53$, $P = 0.017$); for 8-iso-PGF2α: adjusted $R^2 = 0.29$, $F(2,31) = 6.46$, $P = 0.004$ (Composite asymmetry: $\beta = 0.53$, $t = 3.50$, $P = 0.001$; Maternal age: $\beta = 0.11$, $t = 0.71$, $P = 0.48$). We also ran the regression analysis controlling for the maternal height. The regression model showed: for 8-OH-dG: adjusted $R^2 = 0.42$, $F(3,30) = 8.57$, $P < 0.001$ (Composite asymmetry: $\beta = 0.51$, $t = 3.67$, $P < 0.001$; Maternal age: $\beta = -0.32$, $t = -2.34$, $P = 0.026$; Maternal height: $\beta = 0.22$, $t = 1.58$, $P = 0.125$); for 8-iso-PGF2α: adjusted $R^2 = 0.29$, $F(2,31) = 6.22$, $P = 0.005$ (Composite asymmetry: $\beta = 0.54$, $t = 3.51$, $P = 0.001$; Maternal height: $\beta = -0.06$, $t = -0.41$, $P = 0.68$).

DISCUSSION

This study showed that the level of OS markers in the first trimester of pregnancy correlated with the level of woman's body FA, irrespective of potential confounders.

Oxidative damage is recognized as one of the proximate costs of reproductive effort (Alonso-Alvarez et al., 2004) and the result of this study may indicate that symmetrical women bear a lower cost of reproduction. Reproduction requires energy from the production of gametes to the raising of offspring, and elevates both basal and field metabolic rate (Ellison, 2003; Jasienska, 2009). Since higher metabolism results in more ROS produced, one might expect that, unless the antioxidant defenses also increase, reproduction should enhance the susceptibility to OS (Alonso-Alvarez et al., 2004). Slightly heightened OS during pregnancy is a physiological phenomenon, but women with lower susceptibility to OS do not need to divert so much energy into one pregnancy, which permits greater investment in future reproductive effort. A major assumption of models for the evolution of life history strategies predicts that limited energy budget forces a trade-off between somatic and reproductive effort. Increased allocation of energy/resources into one function cannot be achieved without diverting energy/resources from another function (Stearns, 1992). High individual susceptibility to OS during pregnancy may not only limit future reproductive success, but also shorten the lifespan (Alonso-Alvarez et al., 2004; Dowling and Simmons, 2009).

Low susceptibility to OS during the first stages of pregnancy may be especially important in humans. In normal pregnancy, the earliest stages of fetal development take place in a low oxygen environment. This is crucial during organogenesis, when the extensive division of embryonic and placental cells occurs, and probability of mutations is high (Jauniaux et al., 2006). In comparison to other primates, humans have earlier (precocious in relation to organogenesis), deeper and more extensive placentation.

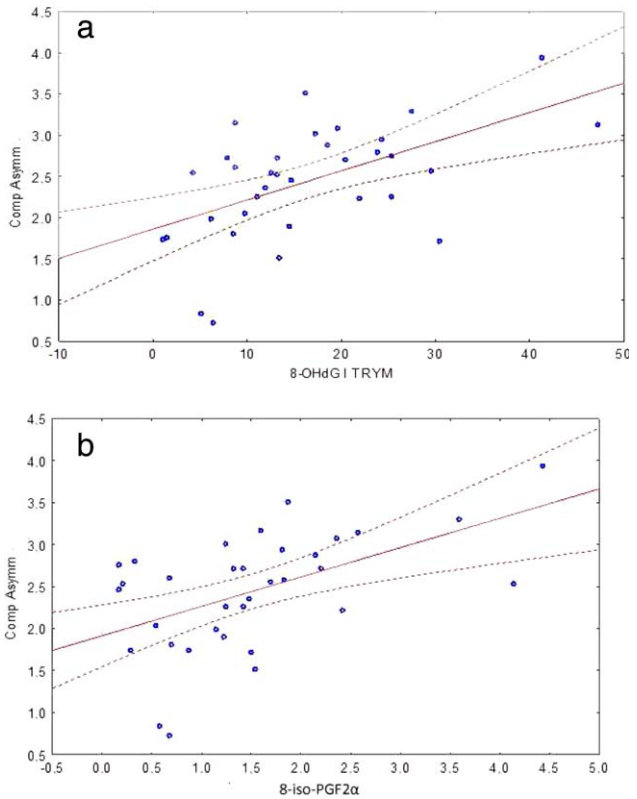

Fig. 1. (a) The correlation between 8-OG-dG and composite FA in the first trimester of pregnancy. (b) The correlation between 8-iso-PGF2α and composite FA in the first trimester of pregnancy.

This permits the oxygen flow to a fetus much earlier than in other mammals, and it is probably the reason why placental-related disorders of pregnancy are almost unique to the human species (Jauniaux et al., 2006). During pregnancy, susceptibility to OS increases, due to a high energy demand for many bodily functions (including placenta functioning). A female's antioxidant defense system should be able to compensate through the induction and increased activity of antioxidant enzymes (Morris et al., 1998; Toescu et al., 2002). If the balance is disturbed, OS arises, and conditions causing pregnancy complications may occur (Chen and Scholl, 2005).

The negative relationship between OS and body symmetry also adds new evidence that helps to explain why symmetrical women are perceived as more attractive, and

supports the hypothesis that the level of body symmetry is related to biological quality (Gangestad et al., 2010; Grammer and Thornhill, 1994; Grammer et al., 2003). Human preference for more symmetrical individuals evolved to facilitate the choice of partners with greater developmental stability and better health (e.g., Grammer et al., 2003). A man who chooses a symmetrical woman benefits, as low FA in a woman is related to lower OS, ensuring a better chance for a healthy, full-term pregnancy, and therefore higher reproductive success.

A woman's height was also a predictor of oxidative damage to DNA, but not to lipids, in the first trimester of pregnancy. The reason for taller women having higher levels of 8-OHdG is not clear, as previous research showed that height, contrary to FA, has little impact on women's reproductive success, and that the relationship is U-shaped with deficits at the extremes. This is due to poor health among very tall and very short women (Nettle, 2002). Regarding the impact of height on pregnancy complications, one could expect a negative correlation between OS and maternal height. Tall women seem to have an advantage, as their children have lower mortality, both in natural fertility (Allal et al., 2004; Pollet and Nettle, 2008; Sear et al., 2004) and western populations (Stulp et al., 2012). Short stature in mothers is also significantly associated with the risk of an emergency Caesarean section (Kirchengast and Hartmann, 2007; Stulp et al., 2011). The relationship between a pregnant woman's height and the level of OS in pregnancy, as shown in this study, should be verified with further research.

Similar to Gangestad et al. (2010), lifestyle did not appear to drive the association between FA and OS in our study. Although there are many factors influencing the level of OS, previous research showed that OS appears to possess substantial temporal stability (Mizoue et al., 2007; Nassi et al., 2009), suggesting that some constant individual differences in OS levels emerge early. It is then very likely that OS is an important factor influencing many aspects of human life history or reproduction and may be a good measure of individual biological differences.

There are some limitations to this study. The sample was relatively small ($N = 34$), thus the outcomes may only be interpreted as preliminary results. However, since the relationship between OS and FA is relatively strong ($P < 0.005$), we do not think that sample size is a serious limitation of our study, but it would be worth testing our hypothesis on a larger sample. Given that the expected relationship between FA and measured fitness outcome is expected to be rather modest (due to an indirect relationship) (Van Dongen and Gangestad, 2011), it is possible that the results of the correlation are somehow overestimated. Another limitation is that OS was assayed at a single time point and some studies show large variability in its level. Many studies, however, show that OS possesses substantial temporal stability (e.g., Mizoue et al., 2007; Nassi et al., 2009). It would also be interesting to study the level of OS before pregnancy in our subjects. There is a possibility that it is only the level of rise in OS during the first trimester that is the most important, and that its change, rather than the relatively life stable level of OS, reflects an individual's antioxidant defense capacity.

This is the first study to show a relationship between a woman's degree of FA and level of OS, which may be helpful in early detection of potential pregnancy problems, and explaining why symmetrical women are perceived as more attractive.

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