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Review

DNA damage and health in pregnancy

D.L.F. Furness [a,*], G.A. Dekker [b], C.T. Roberts [a]

[a] The University of Adelaide, Robinson Institute, Research Centre for Reproductive Health, Adelaide, South Australia 5005, Australia
[b] The University of Adelaide, Women's and Children's Division, Lyell McEwin Hospital, Elizabeth Vale, South Australia 5112, Australia

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ABSTRACT

In healthy pregnancy reactive oxygen species and antioxidants remain in balance and DNA damage is repaired effectively. However, pregnancy is an inflammatory state exhibiting increased susceptibility to oxidative stress such that this balance can be easily disrupted. Increased DNA damage has been shown to be involved in many pathological states including pregnancy complications. Modern lifestyles including exposure to pollutants, poor diet, and lack of exercise cause excess inflammation, oxidative stress, and ultimately DNA damage. There is a growing body of literature providing evidence that these lifestyle changes are increasing our risk of infertility, miscarriage, and late-gestation pregnancy complications. Moreover, baseline DNA damage rises with age and couples in developed societies are delaying childbirth, placing them at further risk. In order to understand the effect of lifestyle and DNA damage on pregnancy health we require large prospective studies, with the collection of samples prior to conception and endpoints of time-to-pregnancy, early pregnancy loss, and late-gestation maternal and fetal health.

1. Introduction

Modern medicine and industrial development have improved the quality of life in developed countries and reduced the incidence of infectious diseases. However, these changes have also exposed the general population to a variety of toxic substances, and lifestyle diseases caused by excess inflammation and oxidative stress are becoming more prevalent. Moreover, these lifestyle changes along with delayed childbirth have increased the global incidence of pregnancy complications (Dietl, 2005; Iborra et al., 2005).

Pregnancy is an inflammatory state exhibiting increased susceptibility to oxidative stress (Kontic-Vucinic et al., 2008). Inflammation-associated reactive oxygen species (ROS) and nitrogen species (NOS) are known to cause DNA damage. DNA damage can affect multiple physiological processes associated with pregnancy health, from early stages such as oocyte maturation and sperm quality through to late-gestation processes involved in placental and fetal development. In addition, DNA repair capacity has been shown to be reduced in pregnant women, making them more susceptible to environmental and endogenous toxins that may lead to disease (Skoner et al., 1995).

This review discusses DNA damage and repair, the techniques used to measure DNA damage, and finally touches on genetic and environmental factors associated with genome and pregnancy health.

1.1. Causes of DNA damage

Every day, the human genome endures approximately one million lesions, including adducts, modifications or fragmentation of the sugar phosphate backbone of DNA (Skoner et al., 1995). Left unrepaired, DNA damage can cause mutations such as base substitutions and chromo-

* Corresponding author at: Robinson Institute, Research Centre for Reproductive Health, University of Adelaide, 6th Floor Medical School North, Frome Road, Adelaide, South Australia 5005, Australia.
Tel.: +61 8 8303 4086; fax: +61 8 8303 4099.
E-mail address: denise.furness@adelaide.edu.au (D.L.F. Furness).

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somal translocations that disrupt normal gene expression or create abnormal proteins that are detrimental to cellular function or viability.

Genetic and epigenetic changes that cause DNA damage are triggered by exposure to endogenous or exogenous substances. Endogenous damage is that caused by agents within the cell itself (i.e., free radicals from normal cellular metabolism). Exogenous damage refers to damage caused by environmental factors (i.e., external chemicals). Both origins can result in similar types of DNA damage and cellular changes (Kulkarni and Wilson, 2008). DNA can be damaged directly from exogenous sources such as radiation or indirectly by exogenous or endogenous agents causing oxidation, alkylation, hydrolysis, bulky adduct formation, and the mismatch of bases (Barzilai and Yamamoto, 2004). Exogenous and endogenous hits can also deregulate epigenetic mechanisms, such as DNA methylation and histone modification. This deregulation can cause silencing of metabolic detoxifying genes, DNA damage repair genes and impairment of multiple cell cycle checkpoints (Sawan et al., 2008; Toyota and Suzuki, 2010). Most of the literature published in relation to health and disease has focused on oxidative stress. Poor lifestyle choices such as smoking, excess alcohol, and fast food consumption contribute to oxidative stress and disease (Cogswell et al., 2003; Ji et al., 1997; Kim et al., 2005; Raimondi et al., 2007).

Oxidative stress occurs when the production of free radicals exceeds the body's natural antioxidant defense mechanisms. Free radicals are unstable and highly reactive. They become stable by acquiring electrons from nucleic acids, lipids, proteins, carbohydrates or any nearby molecule causing a cascade of chain reactions resulting in DNA and/or cellular damage. The two major types of free radical species ROS and NOS are formed continuously as a consequence of endogenous and exogenous factors and oxidize DNA, leading to single- and double-strand breaks (Burcham, 1999; De Bont and van Larebeke, 2004). An example of an ROS, the hydroxyl radical (OH), causes damage to DNA by the addition of double bonds and by abstraction of an H atom from the methyl group of thymine and each C–H bond of 2-deoxyribose (Cooke et al., 2003). Many laboratories have now provided overwhelming evidence that persistent oxidative stress and excess lipid peroxidation are induced by chronic inflammatory processes resulting in the accumulation of massive DNA damage in affected organs (Bartsch and Nair, 2006).

Chronic infections that elicit an inflammatory response are potent generators of lipid peroxidation, ROS and NOS. Nitric oxide and superoxide are produced simultaneously in macrophages and neutrophils produce oxygen bursts of superoxide radical and hydrogen peroxide that can subsequently form the potent hydroxyl radical (Jackson and Loeb, 2001). Thus, chronic inflammatory processes facilitate, through deregulation of cellular homeostasis various types of DNA damage, consequently causing impaired DNA repair pathways, overproduction of proinflammatory cytokines, and reduced apoptotic rates of damaged cells (Bartsch and Nair, 2006). Endogenous DNA damage typically occurs at a higher frequency than exogenous damage; however, epidemiology shows that, in developed societies, exogenous factors from accidental or involuntary exposures contribute to 75–80% of cancer cases (Doll and Pet 1981). No such studies have been performed in relation t pregnancy outcomes. Not surprisingly, research has show in animal models and humans that as we age baselin DNA damage rates increase (Heuser et al., 2008; Redd Thavanati et al., 2008).

1.2. DNA repair

Hundreds of genes are involved in DNA repair and ther is great variation amongst individuals with respect to com mon polymorphisms that impact on protein activity. Th many types of DNA lesions that result from endogenous an exogenous factors are rapidly detected, with subsequen activation of an intricate web of signaling pathways know as the DNA damage response (Barzilai and Yamamot 2004).

The human oocyte is relatively competent at repair ing DNA damage (Menezo et al., 2010); however, matur sperm are not and the majority of embryo DNA damag is thought to originate in the male gamete (Barratt et al 2010). Unfortunately little is known about the quality o DNA in human oocytes presumably due to the lack o material available for study. During spermiogenesis, th maturing sperm gradually loses its ability to repair poss ble DNA damage (Olsen et al., 2005). In the one cell embry the precise replication of the genome is of fundamenta importance (Menezo et al., 2010). There are three option for a somatic or embryonic cell that is facing DNA dam age (Fig. 1). The first is to activate the apoptotic pathway Cell survival will be the result of the balance between pro and anti-apoptotic factors present in the oocyte. The sec ond option is to tolerate the lesion; which may lead t mutations in embryonic and somatic cells and subsequen developmental defects and carcinogenesis in the next gen eration. The third option is to repair the lesion (Menez et al., 2010). Clearly, variations in repair capability woul affect the amount of DNA damage and disease susceptibi ity (Jaiswal et al., 2000).

In the early embryo, several hundred thousand DN repair processes are undertaken employing multiple repa mechanisms for both the maternal and the paterna genome (Menezo et al., 2010). In the oocyte and earl embryo direct reversal of damage (DDR) is used to repa adducts formed by methylating agents such as tobacc nitrosamines and alkylating drugs (Drablos et al., 2004 and anomalies in the methylation of bases; as oocytes hav high methylation activity and imprinting is mainly th result of methylation, this process is of extreme impor tance (Menezo et al., 2007). Single-strand repair (SSR is used when one strand only has been damaged; thi must be carried out rapidly in order to avoid the cre ation of double-strand breaks (DSB) at replication. Onc the damage is detected it is repaired by an incision an then an excision. The complementary strand is used a a pattern to fix the repair. The most dangerous DN lesion is DSB as it induces chromosomal instability an failed rearrangements. A single DSB can cause apoptosi directly inactivate key genes, or lead to serious chromo somal aberrations. DSBs are repaired by two mechanism one based on homologous recombination between sis

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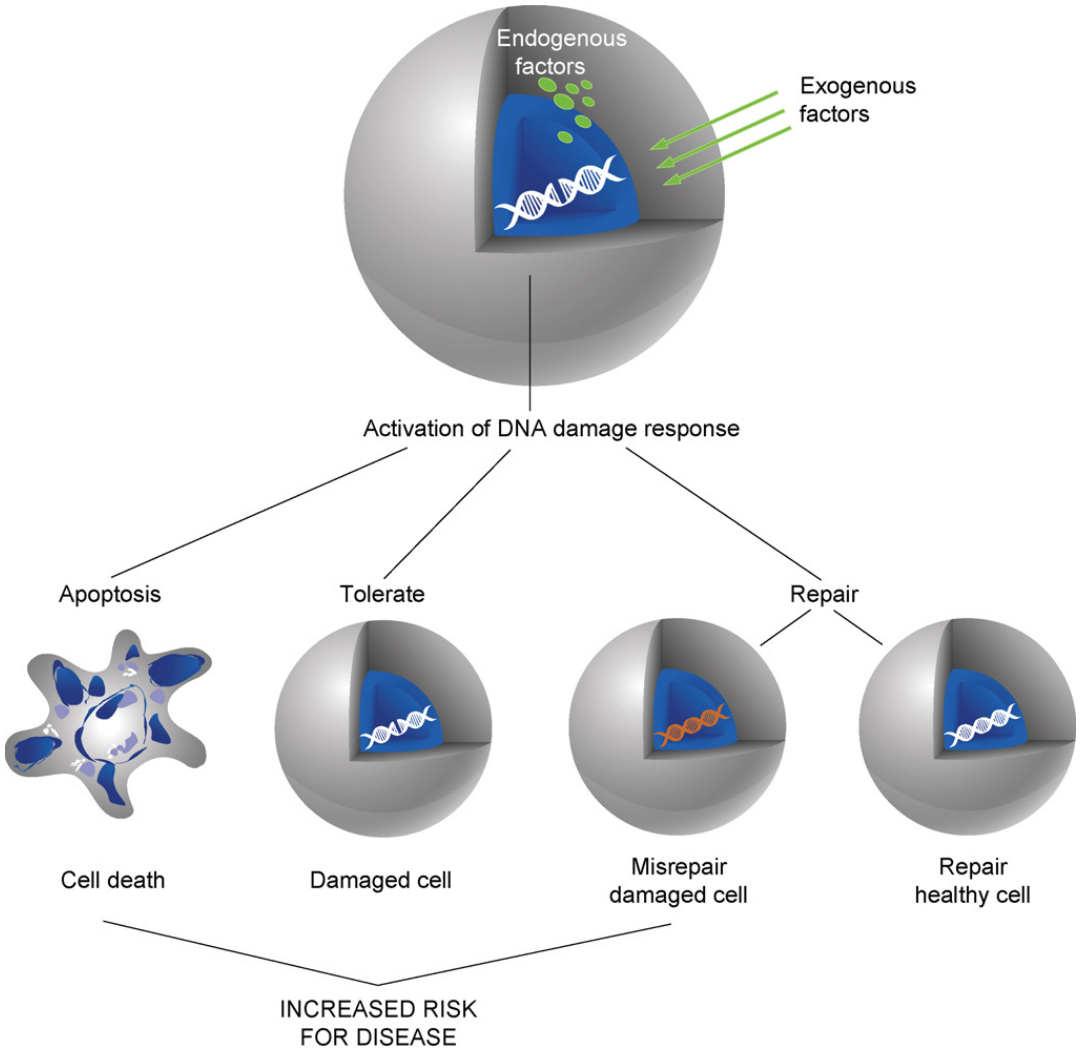

Fig. 1. DNA damage response and cell fate.

ter DNA molecules, and the other on rapid, error-prone, non-homologous end-joining (Barzilai and Yamamoto, 2004).

Oxidative DNA damage is predominantly repaired by base excision repair (BER) enzymes (Jaruga and Dizdaroglu, 1996). After damage identification, endonucleases initiate the repair, in association with XRCC1, a DNA repair protein with the main ligation function after polymerase action. These components are all upregulated in the oocyte (Menezo et al., 2010). It has also been shown that nitrogen oxide, an inflammatory mediator, directly inhibits various DNA repair enzymes including those responsible for BER. The nucleotide excision repair pathway repairs bulky zones of damage that distort the shape of the helix. Mismatch repair fixes errors in DNA replication (mispairing including G/T or A/C pairing) (Menezo et al., 2010). In normal pregnancy, when oxidative stress is increased, antioxidant mechanisms are able to counteract it through enzymatic induction and activity, as well as through non-enzymatic free radical protectors and scavengers. However, pregnancy is a state where this adaptation and equilibrium are easily disrupted (Casanueva and Viteri, 2003).

1.3. Measuring DNA damage

Monitoring DNA damage is most frequently used to assess population exposure to environmental pollutants (mutagens). The measurement of DNA damage is of importance in pregnancy as the human fetus is exposed to a variety of environmental agents and drugs that cross the placenta. DNA damage has been well studied and several classes of products identified such as chromosome loss, single and double strand DNA breaks, DNA fragmentation, and base oxidation.

There are a number of oxidative stress markers that can be measured in blood and urine, but 8-hydroxydeoxyguanosine (8-oxy-G), an oxidized form of guanine, is the most abundant and the most investigated (De Bont and van Larebeke, 2004). 8-Oxy-G is an adduct that has been shown to cause G-to-T transversions and can produce mutations because of its base pairing with adenine as well as cytosine (Burcham, 1999). DNA damage represented by 8-oxy-G has also been shown to be increased in pregnancy complications (Hung et al., 2010; Kim et al., 2005; Matsubasa et al., 2002). This oxidative stress marker can be easily detected by using an ELISA kit; however, this

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technique is not as sensitive as other DNA damage assays, mentioned in the following paragraphs, and is not recommended for diagnostic or medical use.

The terminal deoxynucleotidyl transferase-mediated dUTP-nick end-labeling or "TUNEL" assay is a direct method for the assessment of DNA fragmentation, by quantifying the incorporated dUTP at double-strand DNA breaks catalyzed by terminal deoxynucleotidyl transferase. This assay is frequently used to assess DNA damage in sperm. Sperm DNA damage measured using the TUNEL assay has been associated with infertility and pregnancy loss (Lewis et al., 2008). The single cell gel electrophoresis assay (SCGS), also known as the Comet assay, is another popular technique for detecting DNA damage. The Comet assay is based on the principle that electrophoresis causes DNA fragments and strand breaks to migrate away from the central DNA core, revealing a trailing tail of DNA, i.e., a "comet." The Comet assay has also been used to demonstrate increased DNA damage of pregnancy complications (Babazadeh et al., 2010; Raman et al., 2001; Simon et al., 2010; Wu et al., 2007). The Comet assay is highly reproducible with greater sensitivity than nick translation assays (TUNEL), even without prior chromatin decondensation (Irvine et al., 2000; Leroy et al., 1996). The Comet assay can detect damage equivalent to as few as 50 single-strand breaks per cell and has a broader use in detecting breaks compared with the TUNEL assay. One drawback of the Comet is that it requires trained researchers to perform it optimally and results can vary from laboratory to laboratory. Therefore, the Comet assay would benefit from standardized protocols (Barroso et al., 2009).

The cytokinesis-block micronucleus cytome (CBMN Cyt) assay is one of the most widely used methods employed to evaluate DNA damage and repair, for biomonitoring and genotoxicity testing. A micronucleus (MN) forms whenever a chromosome or a fragment of a chromosome is not incorporated into one of the daughter nuclei during cell division, forming what looks like a smaller nucleus. In newly formed red blood cells in humans, these are known as Howell–Jolly bodies. In this assay chromosome damage is measured in cells that complete nuclear division ex vivo following mitogenic stimulation and are recognized by their binucleated appearance after cytokinesis-block using cytochalasin-B. Restricting scoring of MN in binucleate cells prevents confounding effects caused by altered cell division kinetics, which is a major variable in other MN assay protocols (Fenech, 2007). Studies have shown that CBMN MN frequency is a robust, sensitive, and reproducible method of measuring DNA damage in peripheral and umbilical cord blood lymphocytes and has been employed in many studies (Furness et al., 2010; Govindaiah et al., 2009; Mateuca et al., 2006; Trkova et al., 2000). However, this is a lengthy assay (68–72 h) and must be performed by accurately trained laboratory technicians and researchers.

2. DNA damage and pregnancy

2.1. Correlation between parents and offspring

A myriad of studies have shown a significant correlation between the frequency of DNA damage in mothers and their babies using all of the common techniques mentione previously to evaluate DNA damage (Bocskay et al., 2005 Chen et al., 2010; Grujicic et al., 2008, 2007; Levario-Carrill et al., 2005; Lope et al., 2010; Milosevic-Ethordevic et al 2003; Pedersen et al., 2009; Tian et al., 2000). Most recently Lope et al. (2010) included fathers in their investigation and found that DNA damage (lymphocyte MN frequency was significantly correlated between fathers and mother and between parents and newborns.

During the late 1970s and early 1980s lymphocyt MN frequency was used to determine the toxicologica effects of various compounds and transplacental effect during pregnancy in animal models (Tian et al., 2000 In addition, later studies in humans have shown tha drugs proposed to provide beneficial effects such as gesto gens and betamimetics increase the MN frequency i umbilical cord blood (Grujicic et al., 2008, 2007; Milosevic Ethordevic et al., 2003). More recently, many studies hav indicated that prenatal exposure to environmental po lutants is associated with DNA damage in cord blood. I addition, exposure to traffic-related air pollution has bee associated with many adverse human health effects. Th evaluation of pregnant women who live in polluted area clearly demonstrated increased lymphocyte MN frequenc in mothers and babies compared with those in unpo luted environments (Bocskay et al., 2005; Chen et al., 2010 Pedersen et al., 2009). Furthermore, a Serbian publica tion demonstrated that after air strikes in 1999, causin extensive environmental pollution, a significant increas in cord blood MN frequency was observed in neonate born 12 months after the event. Increased MN frequenc was measured for 7 years after the air strike and ha decreased significantly by 2006, verifying a relationshi between DNA damage and the level of environmental po lution (Milosevic-Djordjevic et al., 2007).

2.2. Infertility and pregnancy loss

Approximately one in six couples suffers from infertil ity (Hull et al., 1985). It is believed that 40% of infertilit cases are due to male factors associated with abnorma sperm, including low sperm count, reduced motility an abnormal morphology, while 40% of cases are due t female factors; the cause of the remaining 20% is unknow (Anderson et al., 2010). Chromosome abnormalities ar the major contributors to the genetic causes of infertilit and recurrent miscarriage (Bobadilla-Morales et al., 2009 Nazmy, 2008). Natural selection prevents the transmis sion of damaged DNA causing infertility, but this protectiv mechanism may be overcome by assisted reproductio techniques (Ferlin et al., 2006). Oxidative stress has bee reported to have an impact on reproductive health, par ticularly in the pathogenesis of infertility (Agarwal et al 2005). Women who fail to achieve pregnancy followin IVF have higher DNA damage in follicular fluid than thos who succeed (Al-Saleh et al., 2010). In addition, sperm DNA damage has been positively correlated with lowe fertilization rates in IVF, impaired implantation rates, a increased incidence of miscarriage and disease in offspring including childhood cancer (Aitken et al., 2004; Lewis et al 2008). The sperm from infertile men have an abnorma

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chromatin structure, microdeletions in chromosomes, aneuploidy, and DNA strand breaks (Aitken and De Iuliis, 2007; Barroso et al., 2000). Oxidative damage has long been implicated as the major etiological factor in sperm DNA damage. In contrast to somatic cells, sperm are very vulnerable to ROS because of their limited antioxidants and protective enzymes (Simon et al., 2010). ROS cause sperm DNA strand breaks and instigate loss of bases or modifications to bases such as 8-oxy-G. There has been less attention paid to female oxidative stress and infertility, but the fertilization ability of oocytes was shown to be negatively correlated with increased cumulus cell DNA damage (Raman et al., 2001).

A study with patients referred for chromosome analysis who had two or more spontaneous miscarriages or who had failed to achieve pregnancy for more than 2 years in which all known causes of miscarriage were excluded in order to classify true idiopathic infertility, demonstrated increased DNA damage (MN frequency) in couples experiencing infertility or miscarriages compared with fertile couples with no history of miscarriage and who had a child younger than 2 years of age (Trkova et al., 2000). Moreover, increased MN frequency has been shown to be associated with recurrent miscarriage (at least three consecutive miscarriages) (Govindaiah et al., 2009).

2.3. DNA damage is associated with late-gestation pregnancy complications

DNA damage, particularly that caused by oxidative stress, has been associated with late-gestation adverse pregnancy outcomes including preeclampsia (PE) and intrauterine growth restriction (IUGR) (Furness et al., 2010; Potdar et al., 2009; Takagi et al., 2004). PE is estimated to affect up to 10% of all pregnancies, being the leading cause of maternal death in developing countries and a major contributor to maternal and perinatal morbidity (Chambers et al., 2001). In Australia, approximately 6.5% of babies are born growth restricted (AIHW National Perinatal Statistics Unit, 2004), but the incidence varies depending on the population under examination and the standard growth curves used as a reference. IUGR is the second leading cause of perinatal morbidity and mortality (Bernstein et al., 2000).

Increased oxidative stress in the placenta of women with PE and IUGR is well documented and numerous studies support notions that inadequate blood supply to the placenta modulates maternal metabolism, inflammation and oxidative stress leading to adverse pregnancy outcomes (Jauniaux et al., 2006; Mandang et al., 2007; Siddiqui et al., 2010; Takagi et al., 2004). Oxidative stress has also been regarded as the major driver of placental apoptosis causing the release of placental debris into the maternal circulation, a key pathogenic process in the progression of PE (Bainbridge et al., 2006). In addition, these changes in circulating markers of ROS precede the development of the clinical symptoms (Jauniaux et al., 2006).

There is an abundance of literature relating ROS to PE and adverse pregnancy outcomes, but measurement of ROS *in vivo* is somewhat controversial. The sensitivity and specificity of various oxidative stress markers is not known. Measurement of biomarkers of ROS is subject to inter-laboratory variation, and inter-observer differences. A more robust and reliable method such as the CBMN cyt assay is needed in multiple studies to determine the relationship between DNA damage and adverse pregnancy outcomes. Only one small study has used this validated technique, indicating that MN frequency is increased in women at 20 weeks' gestation before any clinical symptoms, in women who go on to develop PE and IUGR (Furness et al., 2010).

3. Genetic and environmental factors

3.1. Genetics

The etiology of pregnancy complications is multifactorial and involves genetic, epigenetic, and environmental factors. Couples with genetic polymorphisms and abnormal CpG methylation and histone modification involved in DNA synthesis and repair have reduced activation and detoxification of exogenous chemicals and scavenging of reactive oxygen species (antioxidant enzymes), and they are at increased risk of DNA damage and various diseases, including pregnancy complications (Agarwal et al., 2005; Decordier et al., 2007).

Many of the polymorphisms thought to be associated with DNA damage and adverse pregnancy outcome have not been replicated in other studies and therefore definitive data are not available (Ferlin et al., 2006). Reasons for this include: the size, ethnicity, geographical location, socioeconomic index and lifestyle habits of the study population, the type of polymorphism analyzed, the techniques used, the multifactorial condition, and the inter-individual variability in the phenotypic effect. In addition, the phenotypic effects of gene polymorphisms are modulated by other genetic and environmental factors that may also interact. Furthermore, many of the proteins encoded by these genes depend on micronutrient cofactors for optimal function (Fenech, 2010). With the advent of next-generation sequencing, including genome-wide association studies (GWAS) and whole exome sequencing, single nucleotide polymorphism approaches to gene discovery and clinical testing are likely to be replaced in the near future. However, most of the common genetic variants identified using GWAS appear to confer modest risk and few causal alleles have been identified (Manolio et al., 2009). This has led to the re-examination of the contribution of gene–environment interactions. In addition, a tremendous challenge to enable "next-generation" medical genomic studies is to develop appropriate tools for analysis (De La Vega et al., 2011).

The most widely studied polymorphism in association with pregnancy complications is the 5,10-methylenetetrahydrofolate reductase (MTHFR) cytosine to thymine transition at position 677, which results in reduced enzyme activity and is considered a definite risk factor for the development of neural tube defects (Harisha et al., 2010; Lissak et al., 1999; Sohda et al., 1997). Another polymorphism, MTHFR 1298, does not reduce activity to the same degree, but compound heterozygosity for the 677 and 1298 MTHFR polymorphisms has been associated with a higher risk of pregnancy complications (Khong

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and Hague, 2001; Weisberg et al., 2001). Specifically, the MTHFR 677TT genotype is associated with elevated DNA damage and plasma homocysteine when folate status is low (Bagley and Selhub, 1998; Frosst et al., 1995; Jacques et al., 1996), a clear example of gene–diet interactions (Furness et al., 2008).

3.2. Diet

Dietary and lifestyle habits have a significant impact on health and disease. Over the last decade there has been a dramatic increase in the percentages of overweight and obese women of child-bearing age. In developed nations, obesity is mostly attributable to sedentary lifestyle habits and the ready availability of high-calorie food. Obesity was recognized as a risk factor in pregnancy more than 50 years ago. Since then, numerous retrospective, prospective, and case–control studies have demonstrated the association between maternal obesity and various pregnancy complications. Moreover, high fat diets and obesity induce systemic inflammation and oxidative stress (Djuric et al., 1991; Ramachenderan et al., 2008), two key factors associated with endothelial cell dysfunction (Kobayasi et al., 2010) and pregnancy complications.

The maternal diet, and therefore the nutrient supply to the developing oocyte, embryo or fetus, influences development and supports the high rates of cellular proliferation and DNA replication that take place during fetal life (Maloney and Rees, 2005). Diet is a key factor in determining genomic stability as it affects all relevant developmental pathways, i.e., activation/detoxification of chemicals preventing DNA oxidation, DNA repair, apoptosis, and DNA synthesis (Fenech, 2001). There is increasing evidence indicating that DNA damage, in the absence of overt exposure to exogenous chemicals, is a marker of nutritional deficiency (Fenech, 2007; Fenech et al., 2005). Micronutrient deficiency, in particular folate and vitamin B_{12}, can cause DNA damage of the same magnitude, if not greater, than exogenous chemicals such as carcinogens (Crott et al., 2001; Cruz Suarez et al., 2001; Fenech, 2003; Fenech and Ferguson, 2001; Fenech et al., 1998).

The role of antioxidants in preventing DNA damage caused by oxidative stress is well known and their nutritional adequacy is important in pregnancy (Ebisch et al., 2007; Fenech, 2005). Therefore, one may think the obvious solution to oxidative stress conditions is to exogenously provide antioxidants. However, despite cell culture and animal models of human disease demonstrating that antioxidant supplementation reduces ROS, antioxidant trials in humans have generally not modified oxidative damage or prevented disease (Halliwell, 2011). Current evidence supports the use of systemic antioxidants for the management of selected cases of male infertility (Showell et al., 2011), but there a few randomised controlled trials investigating antioxidants in female infertility and they lack power because of small patient numbers. Moreover, in 2008, a cochrane review found no evidence that vitamin E and vitamin C reduce the risk of preeclampsia (Rumbold et al., 2008). Overall, there is a lack of consensus on the type and dosage of antioxidants to be used and at what time point supplements should be given in pregnancy, henc clinical evidence of the benefits of antioxidant supple mentation is ambiguous. Furthermore, antioxidants ma not demonstrate a significant oxidative stress reductio in humans because of interactions with factors associate with obesity, hyperglycemia, and overall dietary intak (Halliwell, 2011). Cellular homeostasis is an extremel delicate process and the detection of oxidative stress at bio logical sites is essential to elucidate mechanisms of activit and develop antioxidant intervention strategies (Barzila and Yamamoto, 2004).

3.3. Toxins

The adverse effects of smoking and alcohol on birth out comes have been well documented and growing evidenc indicates that exposure to either can delay conception an cause pregnancy complications (de Assis et al., 2009; Kh et al., 2009). Cigarette smoke contains a number of RO and metabolism of ethanol generates ROS through the elec tron transport chain (Ruder et al., 2009). Both have bee shown to increase DNA damage (de Assis et al., 2009 Ishikawa et al., 2007; Tsui et al., 2008). A meta-analysi reported an odds ratio of 1.60 for infertility in femal smokers compared with nonsmokers, with evidence of dose-dependent relationship with the number of cigarette smoked (Augood et al., 1998). In addition, male smoker have elevated sperm DNA damage (Ji et al., 1997). Envi ronmental exposure to pollutants has also become a hug issue for human health. Currently, human biomonitorin is becoming one of the main priorities of the Europea Union. Both European and American Health Authoritie have stressed the importance of paying special attentio to pollution levels in susceptible populations and, mor specifically, in pregnant women and children (Aragone et al., 2008).

3.4. Physical activity

A substantial proportion of women stop exercising afte they discover they are pregnant, but women should b encouraged to maintain physical activity during pregnancy while being aware of the limitations (Melzer et al., 2010 Vladutiu et al., 2010). As stated throughout this revie abnormal placental development, predisposing mater nal constitutional factors, oxidative stress, inflammation and genetic susceptibility, including damaged DNA, a contribute to the development of adverse pregnancy out comes. Physical conditioning and regular prenatal exercis are believed to stimulate placental growth and vascular ity, reduce oxidative stress, and exercise-induced reversa of maternal endothelial dysfunction (Weissgerber et al 2006). Furthermore, maintaining physical fitness prevent maternal obesity and is thought to produce positive mater nal effects, including shorter labor, fewer reproductiv complications, and faster recovery after delivery (Ma et al., 2010; Stutzman et al., 2010; Weissgerber et al 2006). It is stated that exercise in early and mid-pregnanc stimulates placental growth, while the relative amoun of exercise in late pregnancy determines its effect o late fetal growth (Clapp, 2006). Controlled randomize

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clinical trials examining the effects of prenatal exercise on markers of inflammation, oxidative stress, endothelial dysfunction, placental dysfunction, and DNA damage are needed.

4. Conclusions

There is convincing evidence that the establishment of a chronic inflammatory response, together with the presence of a local oxidative environment, could play an important role in the etiology and the progression of several pregnancy complications (Iborra et al., 2005). Modern sedentary lifestyles, including exposure to toxins and genetic polymorphisms, that predispose individuals to increased inflammation and oxidative stress, ultimately lead to elevated DNA damage.

Increased DNA damage can have an impact on oocytes, spermatozoa, and/or the developing embryo leading to infertility, miscarriage, and birth defects. In addition, if conception takes place abnormal placental development caused by altered trophoblast invasion and angiogenesis may occur if cells experience abnormal DNA damage rates, given that increased DNA damage often results in altered gene expression, cell cycle delay, reduced nuclear division rate, and cell death (Fenech, 2005). Aside from damaged gametes it is plausible that maternal systemic inflammation, oxidative stress, and DNA damage in pregnancy may be common fundamental abnormalities associated with pregnancy complications because genomic instability may alter cellular phenotypes and possibly reduce the proliferative potential of cells, leading to pregnancy complications associated with defective placentation. Furthermore, defective placentation leads to placental hypoxia and reperfusion injury due to ischemia. As a result, ROS triggers the release of cytokines, causing endothelial cell dysfunction, which also plays an important role in the development of pregnancy complications (Malek et al., 2001).

There is a great need for large prospective pregnancy studies, including lifestyle, dietary, and medical history assessment with the collection of biological samples prior to conception with endpoints of time-to-pregnancy, early pregnancy loss, and late-gestation maternal and fetal health. These studies should be designed with uniform DNA damage evaluation techniques, such as the gold standard CBMN cytome assay, with similar outcomes so that results can be pooled and easily compared. To date, most studies have focused on the relationship between maternal and fetal DNA damage or sperm DNA damage in association with infertility. Future studies must include both the mother and father in relation to pregnancy outcome. These studies may provide DNA damage thresholds enabling the prediction of pregnancy complications and possible interventions and prevention strategies. It is well known that optimal nutrition, a healthy BMI, smoking cessation, and restriction of alcohol and caffeine, in addition to other lifestyle modifications can reduce DNA damage. In turn, this reduction in DNA damage will provide couples with a greater chance of a natural conception and a healthy pregnancy.

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