An estimated 44.5 million adults in the USA smoke cigarettes, and tobacco use is the leading preventable cause of death in that country. Cigarette smoking during pregnancy continues to be a significant public health concern. Despite decreases in the percentage of women who smoked during pregnancy in the 1990s, the Centres for Disease Control and Prevention reported that 11.4% of mothers who gave birth during 2002 smoked. A South African study reported that 39% of pregnant women smoked, with considerable variation between racial groups.

It is known that smoking in pregnancy is associated with a number of adverse outcomes, including low birth weight, abruptio placentae, miscarriage, premature delivery and an increase in perinatal mortality. In addition, smoking affects the gametes and ovarian function, which can impair fertility, as well as having more long-lasting effects such as an earlier onset of menopause. It is also an important co-factor in the genesis of cervical cancer, one of the major health concerns in women in South Africa. This review discusses the effects of cigarette smoking on reproductive health issues.

**Exposure**

Cigarette smoke contains over a thousand different compounds, including carbon monoxide, nicotine, polycyclic aromatic hydrocarbons (PAHs), nitroso compounds, aromatic amines, protein pyrolosates and trace elements such as cadmium and nickel. Two major mutagenic compounds are nitrosamines and PAHs. The two
compounds responsible for most of the harmful effects in pregnancy are nicotine and carbon monoxide.

Nicotine readily crosses the placenta and has been measured in amniotic fluid and foetal blood in concentrations exceeding those in the mother. It has also been found in the breast milk of smoking mothers, as well as those exposed to passive smoking. While nicotine has a short half-life of 1–2 hours, its metabolite, cotinine, has a half-life of 15–20 hours and can thus be used as a marker of exposure to cigarette smoking. A number of mechanisms have been postulated to account for the harmful effects in pregnancy. Carbon monoxide binds to haemoglobin with a higher affinity than oxygen, thus displacing it. The formation of carboxyhaemoglobin decreases oxygen-carrying capacity to the placenta, with impaired oxygen delivery to the foetus and resultant hypoxia. In addition, changes in the utero-placental circulation and in foeto-placental blood flow are related to the vasoconstrictive effects of nicotine.

Potent tobacco-related carcinogens also cross the placenta and have even been identified in the urine of infants born to smokers. In addition, tobacco smoke induces placental and foetal enzyme systems capable of bio-activation of pro-carcinogens to carcinogens and mutagenic products. Chemicals in tobacco smoke can therefore exert direct toxic effects on the placental and foetal cells.

**FERTILITY**

Several studies have suggested that smoking has a negative effect on fertility in both men and women. A meta-analysis of 13 studies of natural conception demonstrated a longer time to conception and a lower live birth rate in smokers. These effects appear to be age- and dose-related. Smoking one pack per day and starting to smoke before the age of 18 years were further associated with an increased risk of infertility.

Reproductive medicine technologies have allowed an opportunity for study of the effects of smoking on gametes. In men, reduced fertility rates are found in smokers. Smoking affects semen quality with sperm concentration on average 13% lower in smokers than in non-smokers. Sperm function tests assessing the fertilisation potential of sperm have also shown the detrimental effect of smoking, which was worse in heavy smokers. In addition, tobacco smoke can cause DNA damage or chromosomal damage in sperm and oocytes. Because ejaculated sperm has minimal repair capacity, damaged DNA is potentially transmitted to the embryo. A 3.7-fold increase in concentrations of these smoking-related abnormalities was found in embryos of smokers, suggesting transmission of modified DNA from parental smoking. Parental transmission of altered DNA may compromise embryonic development in utero, resulting in failed implantation, early pregnancy loss or disturbances in postnatal development.

In a case control population study of 642 individuals of a Chinese community where female smoking is discouraged, paternal smoking in the preconception period was associated with an increased risk of childhood cancer within the first 5 years of life. It can be postulated that transmission of damaged genetic material in spermatozoa of fathers who smoke may have significant implications.

From studies on assisted reproduction, it appears that, in women smokers, fewer oocytes are retrieved at ovum pick-up following controlled ovarian hyperstimulation, and the number of embryos that develop is also decreased. Furthermore, women who smoked in their treatment cycle had a 50% reduction in implantation rate and ongoing pregnancy rate, compared with women who had never smoked. Women who stopped smoking before their treatment cycle had the same pregnancy rates as non-smokers, suggesting some reversible effects.

Smoking also has effects on fallopian tube function. In Rhesus monkeys, nicotine exposure resulted in altered tone and contractility of the fallopian tubes. There was also inhibition of the cilia, with decreased oocyte pick-up rate. This was thought to be related to the potassium cyanide component of tobacco smoke. These factors increase the rate of ectopic pregnancies. Smoking appears to be protective against fibroids, endometriosis and endometrial cancer, but impairs implantation. Protection against endometrial carcinoma may be due to the effects of benzopyrene, which inhibits endometrial cell proliferation and adhesion to adjacent cells. It may be postulated that this mechanism interferes with trophoblast invasion and thus with implantation.

**MISCARRIAGE**

Cigarette smoking is considered to be a risk factor for spontaneous miscarriages, with the relative risk increased by a third. A number of mechanisms have been postulated:

- **Corpus luteum insufficiency.** Nicotine has a direct inhibitory effect on ovarian granulosa cell aromatase activity in vitro. A decrease in oestradiol production was found in women smokers undergoing ovarian stimulation. This inhibition may affect granulosa luteal cell function, resulting in corpus luteum insufficiency as one of the mechanisms for early pregnancy loss.
- **The vasoconstrictive effects of nicotine result in decreased uterine and placental blood flow with subsequent miscarriage.**
- **Impaired implantation may occur and this has been discussed above.**
- **There is increasing evidence that constituents of tobacco have the potential to alter trophoblast gene expression by down-modulation of positive regulators and up-modulation of negative regulators of trophoblast function.**
- **Smoking-induced hypoxia may be a factor in altered trophoblast differentiation.**

Some studies have shown stronger associations with late versus early miscarriages, perhaps reflecting the second mechanism. There have been some suggestions of an association between maternal smoking and foetal structural abnormalities. While a meta-analysis demonstrated a small but significant association between
smoking during the first trimester and cleft palate in the child, there is insufficient evidence to associate smoking with an increase in foetal abnormalities.

**PREGNANCY COMPLICATIONS**

**Low birth weight**

There is a well-documented increase in the incidence of low birth weight, defined as birth weight less than 2 500 g, in women who smoke. While many co-existing factors such as low income, poor diet, low socioeconomic status and drug abuse may be confounding variables, numerous studies have shown an average reduction in birth weight in smoking mothers of 200 g. This appeared to be related to the number of cigarettes smoked. When light smokers were compared with non-smokers, the odds ratio for low birth weight was 1.89 in one study, whereas when heavy smokers were compared with non-smokers, the odds ratio was 3.03.

Babies of smokers had less muscle mass and more fat than babies of non-smokers, suggesting growth restriction as the reason for the increase in low-birth-weight babies. Maternal cigarette smoking is associated with evidence of chronically increased resistance in the uterine, umbilical and foetal middle cerebral vessels. The vasoconstrictive effects as well as the effects on oxygenation of carboxyhaemoglobin are the likely mechanisms for the decreased birth weight. The critical period during which smoking exerts its deleterious effect is not clear. It is, however, known that mothers who stop smoking during the third trimester have babies with comparable weights to non-smokers.

It is important to note that maternal self-reporting of the number of cigarettes smoked does not always correlate with exposure as measured by cotinine levels. The changes in vascular resistance and in low birth weight have been confirmed in studies which measured cotinine levels as an indicator of exposure. Cotinine levels may be increased in women exposed to passive as well as active smoking, and the effects are similar.

While growth restriction is increased in babies of mothers who smoke, there also appears to be an increased incidence of preterm labour. A French study of 864 very preterm births found that smokers were more likely than non-smokers to give birth to a very preterm infant. Heavy smoking reduced the risk of preterm birth due to pre-eclampsia, but light, moderate and heavy smoking all increased the risk of preterm birth due to all other mechanisms.

**Placental problems**

Both placental abruption and placenta previa are increased in mothers who smoke. Alterations in trophoblast invasion may be responsible for the increased rate of abruption, with a reported odds ratio of 1.6. The increase in abruptio placenta was borne out in a South African study, where abruption occurred in 15% of smokers compared with 10% of non-smokers. Abruptio placenta and preterm labour are two of the main contributors to perinatal mortality in this country. The increase in placenta previa may be explained by an enlargement of the placenta as a compensatory mechanism for hypoxia.

**Perinatal mortality**

There is a 33% increase in perinatal mortality (after 20 weeks’ gestation) and neonatal mortality (in the first 28 days of life) in smoking women. This increase occurs independently of the decrease in birth weight. Factors contributing to the increase in perinatal mortality include an increase in antepartum haemorrhage, preterm delivery and sudden infant death syndrome (SIDS). Babies whose mothers smoke before and after birth are 3 – 4 times more likely to die from SIDS. Babies exposed to ‘second-hand’ smoke after birth have double the risk of SIDS.

**Intelectual function and childhood illnesses**

A wide range of cognitive and behavioural problems such as attention deficit hyperactivity disorder (ADHD) have been identified in children of mothers who smoke during pregnancy. While it is difficult to exclude all confounding variables, case-controlled studies have continued to show intellectual impairment as well as an increase in unexplained mental retardation after controlling for a wide range of variables.

A worrying association is an increase in the incidence of childhood cancers in the children of women who smoked during pregnancy. This increased risk applies to all cancers, as well as acute lymphocytic leukaemia and lymphoma. It is known that tobacco smoke contains many carcinogens which may be transferred in utero. The evidence of transfer of damaged genetic material from fathers who smoke may also be contributory, as discussed above.

**OTHER REPRODUCTIVE HEALTH RISKS**

**Early age at menopause**

It is well accepted that menopause occurs 1 – 1.5 years earlier in current smokers compared with women who have never smoked. Cigarette smoke and nicotine cause both acute and chronic inhibition of steroidogenic function and oestrogen synthesis. Smoking also appears to affect steroid hormone metabolism with increased catechol oestrogen formation. A number of ovarian toxins such as cadmium and PAHs are present in tobacco smoke and all of these may account for the earlier age of menopause in smokers.

**Cervical cancer**

The cervical mucus of smokers contains constituents of cigarette smoke, including the nitrosamine NNK, and smoking is associated with a decrease in the number of cervical Langerhans’ cells which mediate local immune responses in the genital tract. These may contribute to the fact that smoking is a co-factor in the development of cervical cancer, a major women’s health problem in South Africa and throughout the world. The effects of smoking on the immune system may increase the risk of HIV transmission, but this requires further study.

**CONCLUSIONS**

Cigarette smoking has wide-ranging effects on a variety of organs related to
IN A NUTSHELL

Nicotine and carbon monoxide are the substances in cigarette smoke that are responsible for most of the adverse effects in pregnancy.

Smoking in pregnancy is associated with an increase in miscarriage, low birth weight babies, abruptio placentae, placenta praevia and perinatal mortality.

Women who smoke have an earlier onset of menopause when compared with non-smoking women.

Smoking impairs fertility in both men and women via its effect on gametes and ovarian function.

Smoking is an important co-factor in the development of cervical cancer.

A wide range of cognitive and behavioural problems such as attention deficit hyperactivity disorder (ADHD) have been identified in children of mothers who smoke during pregnancy.

There is an association between smoking in pregnancy and an increase in childhood cancers, such as leukaemia and lymphoma.

References: