Pregnancy smoking, child health and nutrition
Koshy, G.

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Chapter 1  General introduction and study objectives
Pregnancy smoking, child health and nutrition

Introduction

The research reported in this thesis was completed in Merseyside in Liverpool and Wallasey primary school children between 1991 and 2006. Four cross-sectional community child health surveys were conducted in 1991, 1993, 1998 and 2006 with a focus on respiratory health in children. In view of the high prevalence of cigarette smoking in the parents of children in this population, specific emphasis was given to factors related to parental smoking. In addition a related analysis using the Liverpool Women’s Hospital perinatal database was conducted.

Historical overview of Merseyside community respiratory surveys in primary school children

The Merseyside Respiratory Child Health Surveys were initially undertaken because of concerns over the effects of airborne dust pollution on asthma risk among children attending primary schools and living around the Bootle and Sefton Dock area of Liverpool. The Liverpool docks were well known as a route for importation of a range of commodities and importation of steam coal started on a large scale during the period from 1980 to 1990. The coal was unloaded and stockpiled in goods yards for variable amounts of time and transferred for transportation by road or train wagons. These dock activities resulted in air pollution from black dust which affected people living in and around the dock area.

Children attending primary schools adjacent to the Bootle dock area were first reported by school teachers in 1990 and 1991 to be experiencing frequent asthma episodes which required inhaler use. To investigate these complaints and determine the prevalence of respiratory morbidity in primary school children in the area exposed to airborne dust, a Steering Committee was established under the auspices of Liverpool Sefton Health Authority. The primary objective of the Committee was to establish if a public health problem of excess childhood respiratory symptoms occurred in this area, compared to other locations in Merseyside, not considered to be exposed to airborne coal dust, or other dock related airborne pollutants.

The parental concern over asthma risk in their children, and the need to determine if there was any significant association between asthma in children and the coal dust pollution in the dock area, led to completion of a respiratory health survey in 1991, among primary school children in Merseyside (Brabin et al, 1994; Kelly et al, 1995; Kelly et al, 1996). The main objectives were to determine whether school children in a specific locality, exposed to airborne coal dust pollution had an excess of respiratory symptoms compared to school children of the same age from non-dust exposed areas of Merseyside with comparable socio-economic status.

A link with airborne dust pollution was demonstrated (Milligan et al, 1998) and as a consequence further sequential surveys were planned in the same primary schools in order to monitor changes following the introduction of environmental interventions. These would also allow other health trends in children to be assessed through community surveillance. The environmental interventions included improved measures for handling/processing steam coal in the dock area, and re-construction of the Rimrose housing estate which was close to the
dock area. As a consequence of these activities, the changes in parent-reported childhood asthma prevalence in Merseyside have been assessed in these consecutive cross-sectional surveys undertaken in Liverpool and Wallasey primary schools in Merseyside in 1991, 1993, 1998 and 2006. The same survey methodology and school populations were used for each survey to allow standardisation of the assessment methodology. The 1993 survey aimed to determine the associations of environmental and host risk factors with respiratory symptoms in primary school children and included monitoring of asthma prevalence in children over a two year period (Milligan et al, 1998; Kelly et al, 1996). The 1998 survey involved on-going monitoring of childhood respiratory symptoms (Rizwan et al, 2004, Rizwan et al, 2007, Koshy et al 2010a, Koshy et al, 2010b, Koshy et al 2011a). These studies showed a significant rise in prevalence of reported doctor diagnosed asthma in children 5-11 years of 12.1% between 1991 and 1998. The most recent 2006 survey was conducted to assess if the trend for rising asthma prevalence to 1998 had continued. In the 1998 and 2006 surveys, specific questions were introduced in order to assess additional health associations with parental smoking, as the 1991 and 1993 surveys showed high household smoking prevalence estimates of 64.6 % and 60.0% respectively.

Rationale for the study

Although a significant minority of women do attempt to stop smoking during pregnancy, about half of those who are successful relapse within a month of giving birth (Polanska et al, 2008). There has been a national decrease in prevalence of smokers in England since 2008 following introduction of various smoking cessation programs and after new smoking ban laws came into effect in 2007 (West, 2008). Despite these interventions, the number of pregnant women who are exposed to cigarette smoke still remains high in the Merseyside area with a substantial proportion of heavy smokers. By encouraging smoking cessation during pregnancy, Health Authorities can save between three to six times the costs of pregnancy or peri-natal interventions related to complications due to cigarette smoking. (Buck et al, 1997).

Studies on the prevalence of pregnancy smoking and health outcomes in UK have mostly been limited to the assessment of a single health outcome, for example birthweight and/or fetal growth restriction. As pregnancy smoking has several effects on childhood health it is important to assess these child health outcomes within the same population. This was the primary aim of the present analysis which utilised the datasets from four school based community child health surveys conducted in Merseyside undertaken in 1991, 1993, 1998 and 2006. Concurrent hospital data was also available from the Liverpool Women’s hospital perinatal database for which parental smoking exposures, as well as birth outcomes, were recorded for the period between 1998 and 2003. A better understanding of mechanisms underlying associations of child health with smoking exposure in pregnancy should provide insights into preventive strategies for improving child health. In this thesis the primary child health related outcomes assessed in relation to parental cigarette smoking were: asthma, obesity, overweight, short stature, ADHD, low birthweight, pre-term birth, intra uterine growth restriction and the fetal sex ratio.

Smoking in pregnancy

Smoking during pregnancy is a common problem in industrialised countries and has detrimental effects for the mother as well as the fetus (Defranza et al, 2004). It increases the
risk for intrauterine growth restriction, pre-term birth (Dewan et al, 2003; Moore & Zacharo, 2000; Nabet et al, 2005) and subsequent health problems in childhood including hyperactivity, behavioural disorders and poor school performance (Batstra et al, 2003). Pregnancy smoking has also been associated with an increased risk of sudden infant death syndrome and is reported to increase subsequent risk for diabetes, obesity, criminal behaviour and substance abuse developing in adulthood (Brennan et al 2002). Several of these factors could also be linked to an individual’s socio-economic status (Humensky, 2010). Studies on maternal smoking and subsequent child growth have shown greater weight gains across differing growth periods for children of mothers who smoked during pregnancy (Andres & Day, 2000). Maternal smoking during pregnancy has also been reported to contribute to development of obesity in children later in life independent of fetal growth (Toschke et al, 2003; Power, 2002).

Smoking during pregnancy remains a major health problem as there are more than one billion individuals in the world using tobacco products (Defranza et al, 2004). It has been estimated that about 24% of men and women smoke in the United Kingdom with heavy smokers mostly belonging to the age group of 20 to 34 years (National UK Smoking Statistics, 2005) which for women covers the child bearing years. Smoking prevalence is high in the North West of England with as many as 1 in 3 (32%) women smoking during pregnancy (National UK smoking statistics, 2007). A previous analysis of data from the Liverpool Women’s Hospital between 1998 and 2003 on adolescent pregnancy smoking and birth outcomes showed that there was marked fall in birthweight from 36 weeks of gestation in babies of mothers who smoked during their pregnancy (Delpisheh et al, 2006). There are about 700,000 births annually in the UK which equates to 245,000 infants annually exposed in-utero to cigarette smoke (National UK birth statistics, 2007).

**Toxicology of tobacco smoke**

Tobacco smoke contains more than 4700 harmful and chemical toxins, which are inhaled and absorbed into the body. Cigarette smoke may be divided into two categories—main-stream smoke and side-stream smoke. Main-stream smoke is the smoke created when the smoker draws on the cigarette and inhales, and side-stream smoke is the smoke created as the cigarette smoulders while not being inhaled. Side-stream smoke is more toxic and harmful as it contains larger quantities of organic chemical compounds. Nicotine is the most important constituent of tobacco smoke which quickly spreads throughout the body after absorption and it is the addictive drug, which increases the nicotine receptors in the brain making the smoking habit irreversible.

**Environmental tobacco smoke exposure among children**

Environmental tobacco smoke (ETS) is also known as second hand smoke or passive smoking. Exposure to ETS at home still continues to be one of the major health risks for children around the world (Boyaci et al, 2006). ETS contains carcinogens and toxic agents, which have more serious adverse effects on children than adults (Cobanoglu et al, 2007). ETS is associated with increased risk of lower respiratory tract infections, middle ear effusion, increased episodes and severity of asthma, reduced levels of pulmonary function in children, (Chen et al, 1998), and development of dental caries and behavioural problems (Weitzman et al, 1992). Parental smoking is the main source for children’s ETS exposure which occurs mainly at home (Jarvis et al, 2000; Jordaan et al, 1999). Measuring ETS is a central feature of
clinical and epidemiological studies with children’s exposure often assessed through parental estimates (Boyaci et al, 2006). The best marker for ETS exposure is cotinine in biological fluids.

**Childhood asthma**

Childhood asthma is a disease with major public health importance in developed countries. Childhood asthma is one of the important causes of impaired quality of life, hospital admission and increased mortality across a wide spectrum of age, socio-economic status and geographical locations (Ross et al, 2007). The UK has one of the highest prevalence estimates for hospital admission or mortality from asthma (Gupta et al, 2006; WHO, 2006). The prevalence of childhood wheeze varies greatly between 15% to 30% in the UK (Kaur et al, 1998), and of these children the proportion with asthma ranges between 30% - 70%. A third of those affected by asthma experience restriction of activities or absenteeism from school. There is evidence that the prevalence of asthma has increased nationally in the UK and locally in Merseyside during the decade of the 1990s (Rizwan et al, 2004). At the national level, and to a lesser extent sub-national level, there are geographic variations in prevalence. The causes of these variations are unclear. It is known that genetic factors predispose to asthma and other atopic disorders, but migrant studies indicate that the reasons for regional variations are likely to be environmental rather than genetic (Rizwan et al, 2004). An environmental factor might act either by inducing the asthmatic tendency in a genetically susceptible individual, or by inducing attacks in individuals who have become asthmatic (Delpisheh et al, 2006). There is evidence that factors associated with a modern lifestyle and environment (e.g. diet and air pollution) are important.

Prevalence of childhood asthma may vary over time and between studies due to changes in diagnostic labelling, clinical practice, or variation in study methodologies, all of which could affect the magnitude and interpretation of secular trends (Rizwan et al, 2004). There is evidence that the prevalence of asthma has increased significantly in the school age population over the past 25-30 years in the UK nationally, and also locally in Merseyside (Ninan & Rusell, 1992). The increase in asthma prevalence in childhood, especially in westernized countries, is sufficiently large as to become a major public health problem and with associated high costs to society in terms of health care (Graham, 2006). Recent reductions in prevalence may relate to altered environmental exposures, as well as improved diagnostic criteria and management (Claudia et al, 2006).

Despite considerable research on the causes and treatment of this condition, there has been relatively little attention given to the growing problem of asthma in pregnancy. Asthma is a common pre-existing medical disorder encountered in pregnancy (Clark et al, 2007). It affects 3.7% to 8.4% of pregnant women (Luskin, 1999), with about one third experiencing worsening of symptoms (Schwartz,1988). Since 1972, when the Norwegian birth registry data first reported the adverse prenatal outcomes of maternal asthma, several studies have been carried out to investigate maternal asthma outcomes. Demissie et al (2001) reported an association of pregnancy in asthmatic mothers with increased risk of prenatal adverse outcomes, and having other health impacts on mothers, including obstetric complications (Gamrah & Refaat, 2005), and adverse neonatal outcomes including transient tachypnoea of birth (Wen et al, 2001). Asthma in the mother can increase the likelihood of low birth weight (LBW), pre-term delivery and perinatal mortality, compared to these risks in babies of non-asthmatic women (Bracken et al, 2003). The risk of maternal and fetal hypoxia are also
increased, especially when maternal asthma is poorly controlled and this could potentially affect placental function and cause impaired fetal growth (Clifton et al, 2002). Risk factors for increased severity during pregnancy include viral infections, lack of prenatal care and inappropriate use of inhaled steroids (Murphy et al, 2006). Strict control of maternal asthma during pregnancy is essential to reduce the risk of these adverse maternal and fetal outcomes.

Children born to parents who smoke are at increased risk of developing respiratory complications compared with children of non-smokers (Gilliland et al, 2001), and prevalence was higher when both parents smoked (Kay et al, 1995). By inheritance of asthma susceptibility through epi-genetic mechanisms, it is possible that through altered DNA methylation patterns in fetal oocytes, tobacco products may affect both the immune function and xenobiotic detoxification mechanisms in offspring resulting in increased susceptibility to asthma affecting one generation to the next (Kay et al, 1995). There are many studies showing a link between maternal smoking during pregnancy and childhood predisposition to respiratory disorders including detrimental effects on childhood lung function (Cunningham et al, 1994), increased childhood asthma (Jaakkola & Gissler, 2004; Delpisheh et al, 2008) and wheeze (Rizwan et al, 2004). In an analysis of cross-sectional data from the 1993 Liverpool child health survey maternal smoking during pregnancy was an independent risk factor associated with pre-term delivery predisposing the child to the development of subsequent asthma (Kelly et al, 1995). There is substantial evidence from other studies and a meta-analysis of 17 studies showed that maternal smoking in pregnancy leads to sizeable adverse effects on neonatal lung function increasing the risk of infant respiratory disorders and childhood asthma (Jaakkola & Gissler, 2004; De Franza et al, 2004). Children are more susceptible to environmental exposure because their bronchial tubes are smaller and their immune systems are less developed making them more likely to develop respiratory illness, if exposed to cigarette smoke. They also breath faster taking in more harmful chemicals per kg body weight than adults. A dose-response relationship between maternal smoking during pregnancy and infant respiratory function including asthma has been reported (Wright et al, 1991).

**Childhood obesity**

Childhood obesity is a challenging multi-factorial problem. It’s escalating prevalence is alarming across the globe for all age groups especially among urban populations. Obesity in childhood is a risk factor for obesity in adulthood and up to 80% of obese children become obese adults. Childhood obesity is a new challenge in both the developed and developing world. However, the data on prevalence in many populations in children and adolescence are inadequate because initially there was no agreed cut-off for the measurement of obesity in childhood. Pediatric overweight is a major problem because its childhood onset increases the overall length of exposure to the detrimental effects of overweight, accelerating the onset of chronic disease, with adverse effects on children’s physical, psychological, and social development (Michael & Mamun, 2006).

Defining overweight and obesity in children is influenced by the fact that weight varies with height during child growth. Therefore unlike in adults, age specific BMI reference values are required throughout childhood (Canoy & Buchan, 2007). Most health care providers agree that children whose BMI (wt/l²) exceeds the age–gender specific 95th percentile are obese. High BMI correlates with excess body fat in all age groups and for males and females both genders (Nelson, 2004).
An association between maternal smoking during pregnancy and offspring obesity has been reported (Von Kries et al, 2002; Toschke et al, 2003). The effect of intrauterine tobacco exposure on childhood obesity may depend largely on cigarette smoking during the first trimester, whereas the additional impact of smoking throughout pregnancy might be influenced by confounding due to socio-demographic factors. Women should be encouraged to quit smoking prior to conception (Toschke et al, 2003). A dose-dependent association between childhood overweight / obesity and maternal smoking during pregnancy has been observed that could not be explained by a wide range of confounders suggesting that intrauterine exposure to inhaled smoke products, rather than lifestyle factors associated with maternal smoking, may have been responsible for this finding (Von Kries et al, 2002).

Attention deficit hyperactivity disorder

There has been increase in the number of behavioural problems including attention deficit hyperactivity disorder (ADHD), psychological problems and conduct disorders being reported in children of mothers who smoked during their pregnancy period (Maughan et al, 2001). Maternal pregnancy smoking has been associated with increased risk of childhood ADHD, which in turn could increase the risk of substance abuse (Neuman et al, 2007). Danish researchers, who examined the association between pregnancy smoking and ADHD in 170 children with behavioural problems and more than 3700 children matched by age, sex and date of birth, reported that pregnant women who were smokers were twice as likely to give birth to a child with ADHD compared to non-smokers (Linnet et al, 2003). However, this study did not consider other risk factors for ADHD such as environmental factors, lower socio-economic status, or a family history of mental disorder.

Possible mechanisms underlying the association of pregnancy smoking with ADHD could relate to a direct effect of toxins and their metabolites on the fetus, or compromise of maternal - fetal blood flow caused by prenatal smoking thus reducing the amount of oxygen to the fetus resulting in reduced neuronal development of various regions of hippocampus with alteration of brain structure (Plessen et al, 2006).

Fetal sex ratio

There has been a significant decline in the number of males born compared with females in several developed countries over the past two decades (Parazzini et al, 1998). It has been suggested that chronic exposure to toxic substances in the environment may be responsible for this change in the gender ratio. The exact mechanism and causal factors are unclear, but parental smoking habits might be contributory because of parallel changes in smoking prevalence. In particular peri-conceptional smoking could be a contributing factor. It has been reported that the offspring gender ratio (male: female) was lower, when either one or both parents smoked more than 20 cigarettes per day, compared with couples in which neither of the parents smoked (p < 0·0001), (Misao et al, 2002). Mackenzie et al (2005) reported that parents who smoked both before and around the time of conception were more likely to have female babies. Although, Belloni et al (2001) reported that there was no clear relationship between the risk of giving birth to a male child and the number of cigarettes smoked per day. Whether smoking influences the ratio still remains controversial and findings in different studies may relate to geographic and genetic differences as well as smoking exposure risk.
Pregnancy smoking and birth outcomes

Smoking in pregnancy is associated with decreased mean birth weight and increased risk of low birth weight (LBW) mainly through intrauterine growth restriction (IUGR) (Figuera et al, 2008). A Swedish study reported that the fetal effects of maternal smoking were primarily noted in the last trimester of pregnancy. The combination of intrauterine hypoxia and impaired placental blood flow which may occur secondary to pregnancy smoking, is likely to cause fetal growth restriction (Assmussen, 1980).

In developed countries maternal smoking has been identified as the single largest modifiable risk factor for IUGR. Van der Meulen et al (2002) reported that babies of mothers who smoked were on average 160 gms lighter at birth than babies of non-smokers. A direct dose-response association between the number of cigarettes smoked and the risk of IUGR has been reported (Horta et al, 1997). In the same study it was shown that smoking in pregnancy was associated with doubling of the risk of IUGR, irrespective of the presence or absence of LBW or pre-term birth, suggesting that IUGR was the key factor mediating the effect of smoking on birth weight (Horta et al, 1997). It has been shown that not all women who smoke cigarettes during pregnancy have low birth weight babies, which may relate to heterogeneity in maternal genetic polymorphisms, (Wang et al, 2002), implicating a gene-environment mechanism. Genetic polymorphisms of nicotine metabolism have been studied previously in the Liverpool population and CYP1A1 and GSTT1 variants were associated with fetal growth restriction in mothers who smoked during pregnancy (Delpisheh et al, 2009). The genetic control of the conversion of toxic metabolites of tobacco smoke to less damaging substances is important for maternal and fetal health.

Study objectives

Primary objective

To assess health and nutrition among primary school children in Merseyside in relation to pregnancy smoking.

Secondary objectives

1. To determine childhood asthma prevalence and its association with pre-term birth or fetal growth restriction among mothers with asthma and who smoked during pregnancy.

2. To assess the dose-response association between pregnancy cigarette smoke exposure, childhood stature, overweight and obesity.

3. To determine the association between pregnancy smoking and childhood attention deficit hyperactivity disorder (ADHD).

4. To determine the association between pregnancy smoking and the fetal sex ratio.
5. To assess the trends in prevalence of childhood and parental asthma in Merseyside between 1991 and 2006, and in relation to smoking prevalence.

6. To assess factors related to parental compliance in completion of child health community questionnaires.

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