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Maternal smoking and blood pressure in 7·5 to 8 year old offspring

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Abstract

Reduced fetal growth in babies born preterm may be associated with reduced later blood pressure, but in children born at term, higher blood pressure. It was hypothesised, therefore, that maternal smoking in pregnancy, associated with reduced fetal growth, programmes later blood pressure differentially according to length of gestation. Six hundred and eighteen children born preterm and now aged 7·5 to 8 years were studied prospectively. Systolic blood pressure in children from smoking compared with non-smoking mothers was significantly *lower* in those born before 33 weeks' gestation and significantly *higher* in those born at 33 or more weeks. Within the range 0–40 cigarettes per day until delivery (after adjusting for potentially confounding factors, including social class and current weight) each 10 was associated with a 1·5 mm Hg fall and 2·9 mm Hg rise in pressure for children born below or above 33 weeks' gestation respectively. Similar though smaller differences were seen in diastolic pressure. These data support our hypothesis that later effects of insults impairing fetal growth are gestation dependent, and provide the first evidence that maternal smoking may have long term consequences for blood pressure in children.

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Blood pressure is higher in adults and children who were of low birth weight, had a large placenta, or a large placenta relative to birth weight.[1–4] One recognised cause of an increased placental to fetal weight ratio is maternal smoking,[5] but the few retrospective studies conducted have failed to show any clear influence of maternal smoking in pregnancy on the child's later blood pressure.[2 3]

Recently we examined data from a large prospectively studied cohort of 7·5 to 8 year old children who weighed under 1850 g at birth and found that in those born at less than 34 weeks' gestation blood pressure paradoxically *decreased* with lower size for gestation.[6] We speculated, therefore, that there may be a 'watershed' during gestation: thus up to 33 weeks' gestation fetal growth retardation is associated with lower blood pressure,[6] but if a growth retarded fetus remains in utero during later pregnancy, high blood pressure may be programmed.[1–4] It seemed possible to us that the previous failure of investigators to detect any relationship between maternal smoking in pregnancy and blood pressure in the offspring may have been because possible gestational age related effects were not taken into account. We have investigated, therefore, the relationship between maternal smoking and later blood pressure in our cohort of 7·5 to 8 year old children with gestational ages ranging from 25 weeks to near term and whether there is a watershed in this relationship at around 33 weeks' gestation.

Methods

Infants weighing under 1850 g, from five centres, were enrolled into trials of preterm infant feeding within 48 hours of birth. Extensive social, antenatal, and neonatal data were recorded by trained research nurses.[7] Size for gestation was calculated as birthweight ratio (birth weight divided by mean birth weight for sex and gestation). Mothers were asked how many cigarettes per day they were currently smoking when they booked at their maternity hospital, generally at around 12 weeks' gestation and they were asked again, after delivery, how many cigarettes per day they had smoked from booking until delivery.

Children were seen and their blood pressure measured (by GL, CLP, and RM) when they were aged between 7·5 and 8 years. In most cases (74%) an 'accutor' (Datascope Ltd) was used, but during a period when two of these were not available to us a standard sphygmomanometer was used. Blood pressure was measured three times and the mean of the last two values was calculated.

Data were analysed using Student's t test, χ^2, and linear regression.

Results

Maternal smoking history and blood pressure measurements were available for 618 subjects. Mean gestational age was 31·3 weeks (minimum 25, maximum 39) and mean birth weight was 1412 g (663, 1847).

Mothers of 257 (42%) children said they were smokers at antenatal booking; only 22 of these gave up smoking after booking. The median number of cigarettes smoked per day was 15 (range 1–60) at booking and 10 (range 1–40) during the rest of gestation. Children of mothers who smoked were significantly less likely to be from a non-manual social class group (social class 1, 2, or 3 non-manual, 21% v 43%, $p<0·00001$ by χ^2 and less likely to be

Table 1 Demographic characteristics and current weight of subjects according to whether mother was smoking at the time of antenatal booking; values are mean (SE) unless otherwise stated

	All children		*Gestation <33 weeks*		*Gestation ≥33 weeks*	
	Non-smoking (n=361)	*Smoking (n=257)*	*Non-smoking (n=247)*	*Smoking (n=175)*	*Non-smoking (n=114)*	*Smoking (n=82)*
No (%) of boys	162 (45)	133 (52)	118 (48)	90 (51)	44 (39)	43 (52)
No (%) social class non-manual	155 (43)	54 (21)***	109 (44)	38 (22)***	46 (40)	16 (20)**
Birth weight (g)	1419 (15)	1402 (19)	1338 (18)	1304 (23)	1594 (19)	1612 (21)
Gestation (weeks)	31·3 (0·1)	31·0 (0·2)	30·0 (0·1)	29·6 (0·1)†	34·2 (0·1)	34·9 (0·2)‡
Birthweight ratio	0·83 (0·01)	0·83 (0·01)	0·91 (0·01)	0·93 (0·01)	0·67 (0·01)	0·63 (0·01)†
No (%) from multiple pregnancy	100 (28)	46 (18)**	60 (24)	29 (17)	40 (35)	17 (21)*
Current weight (kg)	22·9 (0·2)	22·8 (0·3)	23·3 (0·3)	22·8 (0·4)	22·0 (0·3)	22·7 (0·5)

For comparisons between smoking and non-smoking mothers: ***p<0·0001, **p<0·005, *p<0·03 by χ^2; †p<0·02 and ‡p<0·003 by *t* test.

from a multiple pregnancy (18% *v* 28%, p<0·005) than those of non-smokers, but there was no significant difference in sex distribution or mean birth weight, gestation, birthweight ratio, or current weight at the time of blood pressure measurement. Table 1 also shows data for subjects categorised according to whether they were born before 33 weeks or later in gestation. Although there was no overall difference in gestational age or birthweight ratio between children of smoking compared with non-smoking mothers, children born to smokers had significantly shorter mean gestation in the group born before 33 weeks whereas in the group born at 33 weeks or later maternal smoking was associated with longer mean gestation and smaller mean birthweight ratio.

The lower mean gestation of children born before 33 weeks to smokers, compared with non-smokers, may relate to the known association between smoking and premature birth. Before 33 weeks there was no evidence that maternal smoking was associated with fetal growth retardation, whereas later in gestation, children of smoking mothers were born with a significantly lower mean birthweight ratio (a measure of weight for gestation) than those of non-smokers. This, together with the 1850 g cut off used in this study, explains the higher mean gestational age of children born to smokers later in gestation.

Data in table 1, described above, are based on maternal smoking up to the time of antenatal booking. Values based on maternal smoking up to delivery were very similar.

Overall, there was no difference in systolic or diastolic pressure between children of smokers versus non-smokers (table 2A). Further analyses, however, showed that the association between smoking and blood pressure was influenced by gestational age, with a watershed at 33 weeks. In the group born before 33 weeks' gestation, children of smoking mothers had significantly lower systolic and diastolic pressures than those with non-smoking mothers (table 2B), whereas at 33 or more weeks of gestation the relationship was reversed, with significantly higher mean systolic pressure in children whose mothers had smoked compared with non-smoking mothers (the difference in diastolic pressure was not significant, table 2C). Thus maternal smoking led to lower mean systolic pressure in 7·5 to 8 year old children born before 33 weeks' gestation but higher pressure if the fetus had remained in utero for longer.

From regression analyses, we found that the influence of maternal smoking on later blood pressure increased with the number of cigarettes smoked per day even after adjustment for current weight, exact age at measurement, instrument used, size for gestation (as

Table 2 Influence of maternal smoking in pregnancy on blood pressure of their 7·5 to 8 year old children; mean (SE) pressure in mm Hg

	Smoking history until booking			*Smoking history until delivery*		
Maternal smoking	*No*	*Systolic*	*Diastolic*	*No*	*Systolic*	*Diastolic*
(A) All children						
Non-smoking	361	100·1 (0·5)	61·1 (0·4)	383	99·9 (0·5)	61·0 (0·4)
Smoking (cigarettes/day)						
1–10	119	99·7 (1·0)	60·6 (0·7)	138	99·9 (0·9)	60·5 (0·7)
11+	138	99·5 (0·8)	59·7 (0·6)	97	99·8 (1·0)	60·1 (0·7)
95% CI for difference between smokers and non-smokers		−2·0 to 1·2	−2·1 to 0·3		1·7 to −1·5	−1·7 to 0·7
(B) Gestation <33 weeks						
Non-smoking	247	101·0 (0·6)	61·6 (0·5)	262	100·9 (0·6)	61·5 (0·5)
Smoking (cigarettes/day)						
1–10	82	99·6 (1·1)	60·9 (0·9)	94	99·7 (1·0)	60·5 (0·8)
11+	93	97·9 (0·9)	58·9 (0·6)	66	97·4 (1·1)	59·0 (0·7)
95% CI for difference between smokers and non-smokers		−4·1 to −0·4,	−3·1 to −0·2		−3·9 to −0·2	−2·9 to 0
p Value by *t* test		<0·02	<0·03		<0·03	<0·05
(C) Gestation ≥33 weeks						
Non-smoking	114	98·0 (0·8)	60·0 (0·6)	121	97·7 (0·8)	59·8 (0·6)
Smoking (cigarettes/day)						
1–10	37	100·1 (2·1)	60·0 (1·3)	44	100·6 (1·8)	60·5 (1·0)
11+	45	102·9 (1·6)	61·6 (1·2)	31	105·0 (1·8)	62·4 (1·6)
95% CI for difference between smokers and non-smokers		6·5 to 0·7,	3·0 to −1·2		7·6 to 1·8	3·6 to −0·6
p Value by *t* test		<0·01			<0·002	

CI=confidence interval.

*Table 3 Relationship between the number of cigarettes smoked/day by the mother until booking (range 0—60) and until delivery (0–40) and the child's later blood pressure, from regression analyses**

	Change in blood pressure as mm Hg/ 10 cigarettes smoked/ day (from regression coefficient)*	*95% CI for difference*	*p Value*
Gestation <33 weeks			
Up to booking			
Systolic	−1·2	−0·2 to −2·4	<0·02
Diastolic	−1·4	−0·6 to −2·1	<0·001
Up to delivery			
Systolic	−1·5	−0·4 to −2·7	<0·02
Diastolic	−1·7	−0·8 to −2·7	<0·001
Gestation ≥33 weeks			
Up to booking			
Systolic	1·9	0·3 to 3·6	<0·05
Diastolic	0·6	−0·6 to 1·8	
Up to delivery			
Systolic	2·9	1·0 to 4·8	<0·003
Diastolic	0·9	−0·5 to 2·2	

CI=confidence interval.
*Adjusting for exact age and current weight when measured, instrument used, birthweight ratio (size for gestation), whether from singleton or multiple pregnancy and social class.

birthweight ratio, a continuous variable, or above or below the 10th centile), whether from singleton or multiple pregnancy and social class. Among children born before 33 weeks' gestation, for example, from the regression coefficient both systolic and diastolic pressures fell significantly by 1·5 and 1·8 mm Hg respectively per 10 cigarettes smoked up to delivery whereas in children born at 33 or more weeks there was a rise of 2·9 mm Hg in systolic pressure for each 10 cigarettes smoked until delivery (table 3). The only other factor significantly associated with later blood pressure (apart from instrument used) was current weight. From the regression coefficients, systolic pressure rose by 0·6 mm Hg and diastolic by 0·3 mm Hg for each 1 kg increase in weight, in both gestation groups. Social class, multiple birth, and age at measurement had very small and inconsistent influences on blood pressure. A trend to higher blood pressure with increasing size for gestation below 33 weeks (similar to that described in our previous paper[6]) persisted, together with a trend to lower pressure with increasing size for gestation at or above 33 weeks, though these trends did not reach statistical significance.

In order to determine whether the relationship between smoking and later blood pressure was significantly different between the two gestation groups, regression models were constructed for the whole cohort including the factors above and an interaction term for smoking and gestational age. Whether this was derived from gestation categorised into two groups as described above, and maternal smoking as smoker or non-smoker, or from gestational age and smoking treated as continuous variables, the interaction term was significantly associated with both systolic and diastolic pressures. For example, with gestation categorised as <33 weeks versus ≥33 weeks and maternal smoking as the number of cigarettes per day up to delivery, the t value for the interaction between gestation and smoking on systolic pressure was 3·7 ($p<0·0001$) and for diastolic pressure 3·0 ($p<0·003$).

We considered the possibility that height or weight at 7·5 to 8 years might be different in children of smokers from those of non-smokers and influence the relationship between smoking and blood pressure. There was, however, little difference (see table 1 for weight) and inclusion of both of these factors in the regression models above did not diminish the association between smoking and blood pressure or the significance of the interaction between smoking and gestational age.

It could be argued that as only children weighing under 1850 g were enrolled in this study most (94%) born at or more than 33 weeks had weights under the 10th centile, whereas those born before 33 weeks had significantly higher weights for gestation and that this may account for the intergroup differences. However, even when only those 288 children born small for gestational age (with weights below the 10th centile) were included in analyses (not shown here), systolic blood pressure in those with smoking mothers was lower if they were born before 33 weeks and higher if they were born later in gestation, compared with children of non-smokers.

The number of mothers who stopped smoking after booking (n=22) was too small to permit separate analyses for this group. Exclusion of their children, or exclusion of neurologically abnormal children from analyses did not alter any of the findings above.

Discussion

Our data on 7·5 to 8 year old children born weighing under 1850 g have shown that maternal smoking in pregnancy is associated with lower blood pressure in those children born before 33 weeks' gestation and higher blood pressure in those born in the last two months of gestation. The strongest relationship was with systolic blood pressure and was found even after adjustment for a range of possible confounding factors, including current weight.

The contrast between our data from children born before 34 weeks' gestation on size at birth and later blood pressure[6] and that from population studies had led us to hypothesise that there may be a watershed during in utero life, before which poor fetal growth is associated with *lower* later blood pressure and after which with *higher* later blood pressure. We were unable to investigate this hypothesis because children in our study (weighing under 1850 g) born after 34 weeks were all small for gestational age. In this study we had specifically set out to test the hypothesis that there is a watershed gestational age at around 33 weeks in terms of the effects of maternal smoking on later blood pressure. Our data strongly supported this hypothesis. The term watershed here is justified by our finding of a highly significant 'interaction' between gestation and maternal smoking – that is, a *significantly* different, indeed opposite, effect of maternal smoking on later systolic and diastolic blood pressure in children born above and below 33 weeks. Even without taking any particular gestation as a cut off value, there was a highly significant interaction ($p<0·0005$) between maternal smoking and gestation influencing later blood pressure when both factors were

treated as continuous variables. This provides compelling evidence that the effects of maternal smoking on the later blood pressure of the offspring are gestation dependent.

In view of our findings in children born after 33 weeks or more of gestation, it is perhaps surprising that other investigators have failed to find any association between maternal smoking and later blood pressure in children born at term. In the study of Whincup *et al* mothers were asked to fill in a questionnaire (including information on their smoking during pregnancy) on the same day as their 5–7 year old child's blood pressure was measured.[3] In the study of Law *et al* mothers were asked about smoking history by the research nurse measuring blood pressure in their 4 year old children.[2] It is widely believed that women tend to under report their smoking when questioned and it is possible that data are inaccurate in these studies and in ours. Our data were, however, collected during and again immediately after pregnancy. Furthermore, any inaccuracy in our study is likely to be the same in both gestation groups and it is unlikely that the difference between the groups could be accounted for in this way.

Perhaps a more likely explanation, however, for the difference between our findings and those of previous investigators is that the children born at 33 or more weeks of gestation in our study all had birth weights near or below the 10th centile (as discussed above). As growth retardation is itself a risk factor for raised blood pressure in infants born around term it is possible that maternal smoking is especially deleterious in this group. We were unable to explore this hypothesis further because so few children born at or after 33 weeks had birth weights above the 10th centile. Our hypothesis could, however, be further tested by a comparison of the influence of maternal smoking on blood pressure in children born growth retarded compared with those normally grown at term.

From our statistical model we would predict that a 7·5 to 8 year old child born weighing under 1850 g at birth at 33 or more weeks' gestation and whose mother smoked 30 cigarettes per day during pregnancy would have a mean systolic pressure 8·7 mm Hg higher than in a child whose mother did not smoke. Indeed raw data on the children of mothers who smoked 20–40 cigarettes per day showed that they had a mean systolic pressure of 108·9 mm Hg, nearly 11 mm Hg higher than in children of non-smokers (mean 98·0 mm Hg). This heavy maternal smoking in pregnancy was, in children in this birth weight and gestation range, associated with around a 1 SD rise in later blood pressure; 1 SD reflecting around 20% of the population variance in blood pressure. The magnitude of this relationship is greater than that previously reported between birth weight and blood pressure later in childhood.[1–4]

Our data showing a reduction in later blood pressure in children born more than seven weeks preterm to smoking mothers should not be interpreted as supporting smoking in pregnancy. Smoking increases the risk of preterm delivery, which is associated with a higher risk of adverse neurodevelopmental outcome. In any case, most pregnancies continue beyond 33 weeks, when we found maternal smoking was associated with higher later blood pressure in the child.

Further work is needed to explore the mechanisms whereby maternal smoking could 'programme' later blood pressure. It is well recognised that maternal smoking is associated with lower social class and hence poorer quality of diet and it could be argued that smoking influences later blood pressure indirectly, perhaps because of associated anaemia or by affecting fetal growth. We found, however, that the significant influence of maternal smoking on the child's later blood pressure was independent of size for gestation and Godfrey *et al* found that smoking significantly influenced placental to fetal weight ratio, independently of maternal anaemia.[5]

Smoking has been shown to have a wide variety of influences on placental structure, endocrine secretion, metabolism, and gene expression.[8–19] It is possible that smoking induced changes in the placenta or direct effects of smoking on the fetal circulation might influence the development or 'setting' of blood pressure homoeostasis. Further studies are also required to explore whether there is a watershed during gestation for the influence of other intrauterine factors on later blood pressure, as this would have important implications for the timing of interventions that might reduce the risk of hypertension in adult life.

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BERPS

A pair of scientists in America and France have studied babies' event related potentials (ERPs) in an attempt to increase understanding of response to phonetic contrasts in infancy (Ghislaine Dehaene-Lambertz and Stanislas Dehaene, *Nature* 1994; **370:** 292–5). It is known from behavioural studies that young babies have 'universal representation'. That is, they are able to distinguish phonetic contrasts used in all languages, not only the language they will speak. This ability is lost in adults; for instance, Japanese babies can distinguish between 'r' and 'l' whereas Japanese adults cannot (Anne Christophe and John Morton, *Nature* 1994; **370:** 250–1).

Dehaene-Lambertz and Dehaene studied 3 month old babies and recorded evoked potentials over a wide area of cortex using spoken syllables as the stimulus. The syllables were presented in runs of five in which either all were the same (standard, for example ba, ba, ba, ba, ba) or the fifth was different (deviant, ba, ba, ba, ba, ga). Each syllable produced two early peaks on the ERP recording. Peak one occurred at about 220 msec, attenuated after the first syllable presentation and did not recover with the deviant syllable. This peak was generated in the temporal lobes. Peak 2, at about 390 msec also decreased in amplitude after the first stimulus but this peak increased back to its original amplitude with the deviant syllable. Peak 2 also appeared to come from the temporal lobes but from loci different from those of peak 1. Deviant, but not standard, syllables also produced a late negative trough at 700 to 1000 msec coming from the frontal lobes. These experiments show not only that the brains of young infants can distinguish between different phonemes but that they can do it quickly (within 0·4 seconds) and at sites within both temporal lobes. Which, if either, temporal lobe is dominant in this respect was not demonstrable from this study.

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