SMOKING IN PREGNANCY

Barbara G. Brennan, MD, FRCSC,

Associate Professor,
Department of Obstetrics and Gynaecology,
McMaster University

ABSTRACT

Cigarette smoking is common in pregnancy. Smoking is associated with lower birth weights in a dose-dependent manner. There are more abruptions and higher perinatal mortality rates. There also seems to be a slight increase in spontaneous abortions. Although there is a small increase in preterm delivery rates this involves a shortening of the gestation by only one to two days and probably is not clinically significant. Women should be questioned about their use of cigarettes and encouraged to stop as early as possible in the pregnancy.

RESUME

Pendant la grossesse, les femmes fument fréquemment la cigarette. Le tabagisme est associé à des poids de naissance plus faibles et liés à la dose. Les décollements sont alors plus nombreux, et les taux de mortalité périnatale sont plus élevés. Il semble aussi y avoir un léger accroissement des avortements spontanés. Même si l'augmentation des taux d'accouchement avant terme est légère, cela suppose une réduction de la durée de gestation, d'un ou deux jours seulement, ce qui n'est sans doute pas cliniquement significatif. Il faudrait interroger les femmes au sujet de leur consommation de cigarettes et les encourager à cesser de fumer le plus tôt possible pendant la grossesse.

J SOC OBSTET GYNAECOL CAN 1997;19:1405-1410

KEY WORDS

Cigarette smoking, complications during pregnancy.

Received on April 30th, 1996. Revised and accepted on May 28th, 1996.

INTRODUCTION

The prevalence of cigarette smoking during pregnancy is approximately 20 to 30 percent.[1] There is a reasonable amount of Canadian data to support this statement. In 1983, a survey of Ottawa women revealed that approximately 37 percent smoked prior to pregnancy.[2] A follow up to this study reported a decrease to 26 percent over the subsequent decade mostly due to a reduction in the proportion of women smoking before pregnancy.[3] Similar proportions have been described in Nova Scotia.[4]

At the request of Health and Welfare Canada, a review of the effects of smoking during pregnancy was conducted.[5] A medline search was conducted using the key words "low birth weight, gestational age, preterm labour, birth defects, and spontaneous abortion." All papers using these words with smoking in the title or as a MESH heading were obtained. The search encompassed the years 1966 to the present. In order to decrease the numbers of articles, only English language papers were studied. Due to the large number of papers, the discussion in this article will be limited to key papers. The conclusions will be those based on the exhaustive review of the literature. Canadian studies will be highlighted.

The literature on smoking is difficult to assess. Many articles have multiple end-points. In addition, there are often several confounding variables which could affect

the outcome. In the variables which are controlled for, there is a lack of consistency. Most of the studies use survey or interview information to assess the use of cigarettes, and smoking is quantified in different ways. Many of the older studies do not present their data in familiar ways. In the original review, therefore, some data sets had to be re-analysed. It is not appropriate to combine studies for statistical analysis. Most of the studies do not use any biochemical validation of smoking behaviour. From the studies that do, it is estimated that 30 to 40 percent of women who report being non-smokers have significant levels of tobacco metabolites in their blood[6] so they are either not truthful or have been exposed to high levels of second-hand smoke. This would tend to minimize any difference between apparent smokers and non-smokers.

This paper will review briefly the effects of cigarette smoking on various pregnancy outcomes.

SPONTANEOUS ABORTIONS

Over 100,000 women have been surveyed regarding pregnancy losses. No studies looking at miscarriage rates used any biochemical confirmation of smoking. Unfortunately, even different gestations have been used to define miscarriage. In the only prospective study,[7] there was a dose-dependent increase in first and second trimester losses which was only significant for second trimester losses in women smoking more that two packs per day. There were more miscarriages in smokers who used alcohol compared to non-drinkers. Armstrong *et al.* reported the outcomes of 47,146 pregnancies in Montreal from 1982 to 1984.[8] They found a slight increase in spontaneous abortions (defined as losses up to 27 weeks gestation). This was dose-dependent with significant confidence intervals, and odds ratios of 1.2 and 1.68 for moderate and heavy smoking, respectively. These authors have been contacted but have been unwilling or unable to provide data for the more standard gestation of less than 20 weeks. We would expect that the group from 20 to 27 weeks would be a small proportion of the total and probably would not alter the results. Although these authors controlled for many confounders, they did not control for the effect of alcohol use.[9] Two case-controlled studies[10] have shown similar effects.

Although these studies are all flawed methodologically, there is a similar estimate of the magnitude of the smoking effect. This would give an odds ratio in the range of 1.2. The effect is probably only significant for those smoking more than one pack per day. There is a suggestion that there may be a combined effect of alcohol and smoking.

CONGENITAL ANOMALIES

There has been only one prospective study examining the effect of smoking on the incidence of birth defects.[11] Women enrolled for prenatal care in California clinics completed a questionnaire regarding their smoking habits. The associations which were identified were then looked for in the data from the Collaborative Perinatal Project. In an analysis of these 53,512 pregnancies, there was no increase in anomalies in smoking mothers. Haemangiomas were less frequent in offspring of smokers. Specifically the odds ratio for cleft lip and palate was 1.1.

Two retrospective studies have been conducted. One of these was quite small and no other factors were controlled for in the analysis, so although a slight increase in birth defects was found in light of the remainder of the information, this should be discarded.[12] Malloy *et al.* reported on over 288,000 pregnancies.[13] Combined anomalies in smokers were not increased, even in heavy smokers (OR .98 [.92–1.05]). There was also no increase in specific anomalies.

Three case-control studies were all very small and failed to document a significant increase in birth defects.[14-16]

Overall, more than 320,000 pregnancies including 20,000 resulting in fetal anomalies have been studied from the point of view of smoking. There was no increase in birth defects .

PRETERM DELIVERY

Many studies defined low birth weight as less than 2,500 grams and then proceeded to study the frequency of this event. However, this really involves two clinical questions: 1) is there an increased risk of preterm delivery? 2) is there an increased risk of intra-uterine growth restriction?

The largest study was a retrospective survey of women delivering singletons in Montreal from 1982 to 1984.[17] There was a total of 51,512 pregnancies, but several were excluded from the analysis of effect on gestation because of the presence of factors known to increase the risk of prematurity (i.e. multiple gestation, hypertension, bleeding). The authors were left with a

total of 40,445 pregnancies. Smoking information was obtained from the history. At all levels of smoking there was a small but significant increase in preterm deliveries. The odds ratio was 1.22 at less than 10 cigarettes, 1.43 at 11 to 19, and 1.33 at greater than 20 cigarettes per day. There was no clear dose relationship. All confidence intervals excluded one. This may appear quite dramatic at first glance, however, when one looks at the gestation effect, the mean shortening of pregnancy with smoking is 0.2 weeks or one to two days. Although this may be statistically significant, it is not clinically significant. Measures of neonatal morbidity are not included.

Wen *et al.* also conducted a retrospective survey of 15,539 births.[18] Smoking information was based on the history obtained at the first prenatal visit and was not quantified but was classified simply as "ever" or "never" use of cigarettes during the pregnancy before the first prenatal visit. Multiple logistic regression was done adjusting for race, parity, maternal age, and weight. There was a significant increase in preterm delivery rates especially in smokers aged 26 to 35 with an odds ratio of 1.4 (95% CI 1.0–2.4) at ages 31 to 35. When this was examined as gestational weeks rather than delivery before 37 weeks, the average decrease in gestation in smokers was about 0.5 weeks ($p<.05$).

A prospective cohort study looked specifically at the risks of smoking for adolescent pregnancies.[19] The authors only studied 775 teenage pregnancies. The odds ratio for preterm birth among smokers was .72 (95%CI 0.4–1.3). The differences in gestation discussed above are all quite small, so it may be that with such a reduced sample size the authors were unable to find this statistically significant.

There is one small case-control study in which there was no increase in preterm delivery rates.[20]

SUMMARY

The two largest studies are remarkably similar although they are both retrospective. There does appear to be a slight shortening of the gestation in smokers. The magnitude of this effect is less than one gestational week. Although statistically significant, there have been no studies examining the morbidity related to this, and one would expect such measures to show little effect of such a slight shortening of the pregnancy.

BIRTH WEIGHT

When considering the effect on birth weight, there are several different approaches: to compare the birth weights in grams, to compare percentages of infants less than a specific weight (usually 2,500 grams), or less than a specific percentile. The percentiles chosen range from three to ten. Most studies do not include morbidity measures.

The 51,512 pregnancies studied by McDonald *et al.* are considered in this paper under a number of different topics as there were multiple endpoints.[17] Women with factors that were known to affect birth weight were excluded from their analysis. This left 40,445 pregnancies. At all levels of smoking there was an increase in the proportion of babies less than the fifth percentile for gestational age. The odds ratio when less than 10 cigarettes per day were smoked was 1.97. This rose to 2.58 at 10 to 19 cigarettes and 3.19 when greater than 20 cigarettes per day were smoked. This indicates a dose related effect. All confidence intervals excluded unity. This is a large study, using Canadian data and well-controlled for confounding factors so these results suggest a significant effect on fetal growth. In the heaviest smokers, the average effect on birth weight was a decrement of 150 grams.

Meyer *et al.*, also reporting Canadian data, looked at the numbers of births less than 2,500 grams to smokers and non-smokers.[21] The adjusted rates for birth weights less than 2,500 grams rose from 49 per 1,000 births in non-smokers to 76 in women smoking less than one pack per day and 114 per 1,000 births in women smoking more than one pack per day.

In another retrospective survey, the frequency of birth weights less than the tenth percentile was compared in women who stated that they "never" versus "ever" smoked.[18] There was a significant difference in the numbers of infants less than the tenth percentile at all maternal ages. The odds ratios varied slightly but averaged around 2.3 at maternal ages between 20 to 35 with confidence limits that did not include unity. There was a much greater effect at a maternal age of more than 35, with an odds ratio of 5.1. The greatest birth weight difference was 251 grams. Without quantifying the amount smoked it is difficult to know if there is an age factor or simply if older women smoked more.

Similar effects on birth weight have been described by a number of authors in prospective,[22-24] retrospective,[25,26] and case-control studies.[27,28]

The studies using biochemical confirmation of smoking were all non-North American. Cotinine is the major metabolite of nicotine and has a half-life of approximately 24 hours. The fetal cotinine level is approximately 0.9 times that of maternal serum.[29] Haddow *et al.* measured cotinine in 1,211 women having alpha-feto-protein levels measured at 16 weeks gestation, and studied the birth weights of their infants.[30] The cotinine level was more closely related to the birth weight than the estimate of the amount smoked. At the highest level of cotinine, the birth weight was reduced by 441 grams. It is interesting that the cotinine level at 16 weeks was still reflective of the effect of smoking on birth weight. The relationship of cotinine was studied further using maternal and umbilical venous samples of mother-infant pairs.[6] The birth weight difference between "exposed" and "unexposed" was 185 grams. There was a dose relationship between birth weight decrement with increasing cotinine level, and the authors calculated that for every one microgram per litre of cotinine there was a lowering of the birth weight by 1.29 grams.

Thiocyanate is derived from hydrogen cyanide found in tobacco smoke and has a half-life of two weeks. Fetal levels are 0.8 that of maternal levels.[31] Thiocyanate has also been measured,[32] but a dose relationship was not examined. It was used as a way to verify the history of smoking.

Other non-North American studies of birth weight are numerous and will not be discussed.

In summary, although studies are quite different in design and how smoking is quantitated, they are all consistent in demonstrating an effect on birth weight. This effect is dose-related and perhaps more profound in women over 35 years. If one wishes to make a more accurate assessment of the birth weight effect, then to measure serum cotinine seems reasonable. One would expect a decrement of approximately 1.3 grams for every microgram of cotinine. The dose effect seems to be somewhere between 10 to 20 grams per cigarette if a reliable history can be obtained. If smoking is stopped before the third trimester, the birth weight is comparable to non-smokers (comparing proportions less than the tenth percentile). Cessation during the first or second trimester has a beneficial effect on birth weight.[33] When smoking began during the second or third trimester, the reduction in birth weight is similar to that seen when the women smoked throughout pregnancy. It has been estimated that 20 percent of small for gestational age infants (less than 2,500 grams) at term are secondary to smoking.

OTHER COMPLICATIONS

There is an increase in abruptions in smokers.[34] This effect seems to be greater when the smoking is of long duration. Women who stopped smoking in the first trimester had a lower rate of abruption. The increase also seems to be dose-related. This information comes from the Ontario Perinatal Mortality Survey 1960 to 1961.[21] The estimated rates of placental abruptions were 16/1,000,20/1,000, and 27/1,000 live births in non-smokers, less than and greater than one pack per day, respectively. It is estimated that from 15 to 38 percent of abruptions are attributable to smoking.[21,35] A study of placental pathology has shown more syncytiotrophoblast necrosis in smokers,[36] lending some biological support to the clinical information.

This increase in abruptions is also associated with a statistically significant increase in perinatal deaths.[34] There is also an increase in placenta praevia in smokers.[21,37] For placenta praevia, there is increased perinatal mortality in smokers compared to non-smokers.[34] The odds ratio for stillbirth in smokers has been estimated at 1.4.[38] When placental complications and intra-uterine growth restriction are excluded, the relationship with smoking disappears. An alteration of the Doppler velocity waveform has been demonstrated within minutes of smoking, and this has been interpreted to represent a degree of hypoxia.[39] Abruptions in smokers are not due to maternal hypertension. No increase in hypertension rates in smokers has been demonstrated and in fact, the evidence suggests a decrease in gestational hypertension and pre-eclampsia.[22,28] This seems to be dose dependent, with women who smoke more having the lowest incidence. Again there are some methological flaws and not all levels are significant, but the trend is consistent.

CONCLUSION

Smoking has effects during each trimester of a pregnancy. There is reasonable evidence to support a lowering of the birth weight in a dose-related manner, an increase in placental complications, and subsequent perinatal death. There seems to be a slight increase in miscarriage rates which is probably more pronounced in women over 35 years and those who concurrently use alcohol. The slight effect on gestational length is

probably not clinically significant. All the above effects, however, stress that smoking is still a serious risk factor in pregnancy with consequences for the health care system. In these days of trying to contain costs to the health care system it is extremely important that attention be focused on how to encourage women to modify their behaviour in order to improve outcome. There is certainly some indication that a reduction or cessation of smoking early in the pregnancy can lessen some of these risks. Pregnancy is a time when women are motivated to change their habits, and approximately 50 percent of smokers reduce or stop during pregnancy.[1] However, the more a woman smokes, the less likely she is to quit. Smoking cessation programmes should be aimed at all groups, but teenagers, heavy smokers, older women, and alcohol users should be targetted specifically as they are at greater risk.

REFERENCES

1. Fried PA. Prenatal exposure to tobacco and marijuana: effects during pregnancy, infancy and early childhood. Clin Obstet Gynecol 1993; 36(2):319-37.
2. Stewart PJ, Dunkley GC. Smoking and health care patterns among pregnant women. Can Med Assoc J 1985; 133:989-94.
3. Stewart PJ, Potter J, Dulberg C, Niday P, Nimrod C, Tawagi G. Change in smoking prevalence among pregnant women 1982-93. Can J Public Health 1995; 86(1):37-41.
4. Dodds L. Prevalence of smoking among pregnant women in Nova Scotia from 1988 to 1992. Can Med Assoc J 1995; 152(2):185-90.
5. Hughes EG, Brennan BG. Effects of Active and Passive Smoking on Fertility and Pregnancy. In: Health and Welfare Canada (Ed). Tobacco Related Health Impacts in Canada. Ottawa: Environment Health Directorate Health Canada, 1995:
6. Bardy AH, Lillsunde P, Kataja JM, Koskela P, Pikkarainen J, Hiilesmaa VK. Objectively measured tobacco exposure during pregnancy: neontal effects and relation to maternal smoking. Br J Obstet Gynaecol 1993; 100:721-6.
7. Harlap S, Shiono PH. Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. Lancet 1980; July 26:173-6.
8. Armstrong BG, McDonald AD, Sloan M. Cigarette, alcohol, and coffee consumption and spontaneous abortion. Am J Public Health 1992; 82(1):85-7.
9. Kline J, Stein MA, Susser M, Warburton D. Smoking: a risk factor for spontaneous abortion. N Engl J Med 1977; 297(15):793-6.
10. Windham GC, Swan SH, Fenster L. Parental cigarette smoking and the risk of spontaneous abortion. Am J Epidemiol 1992; 135(12):1394-1403 (abstract).
11. Shiono PH, Klebanoff MA, Berendes HW. Congenital malformations and maternal smoking during pregnancy. Teratology 1986; 34:65-71.
12. Himmelberger DU, Brown BW, Cohen EN. Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. Am J Epidemiol 1978; 108:470-9.
13. Malloy MH, Kleinman JC, Bakewell JM, Schramm WF, Land GH. Maternal smoking during pregnancy: no association with congenital malformations in Missouri 1980-83. Am J Public Health 1989; 79(9):1243-6 (abstract).
14. Khoury MJ, Weinstein A, Panny S, *et al.* Maternal cigarette smoking and oral clefts: a population-based study. Am J Public Health 1987; 77(5):623-5.
15. Werler MM, Mitchell AA, Shapiro S. Demographic, reproductive, medical and environmental factors in relation to gastroschisis. Teratology 1991; 45:353-60.
16. Van Den Eeden SK, Karagas MR, Daling JR, Vaughan TL. A case-control study of maternal smoking and congenital malformations. Paediatr Perinat Epidemiol 1990; 4:147-55.
17. McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and prematurity. Am J Public Health 1992; 82(1):87-90.
18. Wen SW, Goldenberg RL, Cutter GR, *et al.* Smoking, maternal age, fetal growth, and gestational age at delivery. Am J Obstet Gynecol 1990; 162(1):53-8 (abstract).
19. Scholl TO, Salmon RW, Miller LK. Smoking and adolescent pregnancy outcome. J Adolescent Health Care 1986; 7:390-4(abstract).
20. de Haas I, Harlow BL, Cramer DW, Frigoletto FD. Spontaneous preterm birth: a case-control study. Am J Obstet Gynecol 1991; 165:1290-6.
21. Meyer MB, Jonas BS, Tonascia JA. Perinatal events associated with maternal smoking during pregnancy. Am J Epidemiol 1976; 103(5):464-76.
22. Hoff C, Wertelecki W, Blackburn WR, Mendenhall H, Wiseman H, Stumpe A. Trend associations of smoking with maternal, fetal, and neonatal morbidity. Obstet Gynecol 1986; 68(3):317-21.
23. Cliver SP, Goldenberg RL, Cutter GR, *et al.* The relationships among psychosocial profile, maternal size, and smoking in predicting fetal growth retardation. Obstet Gynecol 1992; 80(2):262-7.
24. Abrams B, Newman V. Small-for-gestational-age birth: maternal predictors and comparison with risk factors of spontaneous preterm delivery in the same cohort. Am J Obstet Gynecol 1991; 164(3):785-90.
25. Mitchell MC, Lerner E. Factors that influence the outcome of pregnancy in middle-class women. J Am Dietetic Assoc 1987; 87(6):731-5.
26. Arbuckle TE, Sherman GJ. Comparison of the risk factors for pre-term delivery and intrauterine growth retardation. Paediatr Perinat Epidemiol 1989; 3:115-29.

27. Callan NA, Witter FR. Intrauterine growth retardation: characteristics, risk factors and gestational age. Int J Gynaecol Obstet 1990; 33:215-20.
28. Marcoux S, Brisson J, Fabia J. The effect of cigarette smoking on the risk of preeclampsia and gestational hypertension. Am J Epidemiol 1989; 130(5):950-7.
29. Donnenfeld AE, Pulkkinen A, Palomaki GE, Knight GJ, Haddow JE. Simultaneous fetal and maternal cotinine levels in pregnant women smokers. Am J Obstet Gynecol 1993; March:781-2.
30. Haddow JE, Knight GJ, Palomaki GE, Kloza EM, Wald NJ. Cigarette consumption and serum cotinine in relation to birthweight. Br J Obstet Gynaecol 1987; 94:678-81.
31. Jensen OH, Foss OP. Smoking in pregnancy. Acta Obstet Gynecol Scand 1981; 60:177-81.
32. Brooke OG, Anderson HR, Bland JM, Peacock JL, Stewart CM. Effects on birth weight of smoking, alcohol, caffeine, socioeconomic factors, and psychosocial stress. Br Med J 1989; 298:795-801.
33. Lieberman E, Gremy I, Lang JM, Cohen AP. Low birthweight at term and the timing of fetal exposure to maternal smoking. Am J Public Health 1994; 84(7):1127-31.
34. Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. Obstet Gynecol 1980; 55(6):701-4.
35. Voigt LF, Hollenbach KA, Krohn MA, Daling JR, Hickok DE. The relationship of abruptio placentae with maternal smoking and small for gestational age infants. Obstet Gynecol 1990; 75(5):771-4.
36. Jauniaux E, Burton GJ. The effect of smoking in pregnancy on early placental morphology. Obstet Gynecol 1992; 79(5):645-8.
37. Zhang J, Fried DB. Relationship of maternal smoking during pregnancy to placenta previa. Am J Prevent Med 1992; 8(5):278-82.
38. Raymond EG, Cnattingius S, Kiely JL. Effects of maternal age, parity, and smoking on the risk of stillbirth. Br J Obstet Gynaecol 1994; 101:310-6 (abstract).
39. Bruner JP, Forouzan I. Smoking and bucally administered nicotine: acute effect on uterine and umbilical artery Doppler flow velocity waveforms. J Reprod Med 1991; 36(6):435-40.