an epidemiologic study. *Alcoholism (NY)* 1980; 4: 135–145
9. OUELLETTE EM, ROSETT HL, ROSMAN NP, WEINER L: Adverse effects on offspring of maternal alcohol abuse during pregnancy. *N Engl J Med* 1977; 297: 528–530
10. LITTLE RE: Moderate alcohol use during pregnancy and decreased infant birth weight. *Am J Public Health* 1977; 67: 1154–1156
11. KAMINSKI N, RUMEAU-ROUQUETTE C, SCHWARZ D: Consommation d'alcool chez les femmes enceintes et issue de la grossesse. *Rev Epidemiol Med Sante Publique* 1976; 24: 27–40
12. HARLAP S, SHIONO PH: Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. *Lancet* 1980; 2: 173–176
13. KLINE J, SHROUT P, STEIN Z, SUSSER M, WARBURTON D: Drinking during pregnancy and spontaneous abortions. Ibid: 176–180
14. ROSETT HL: A clinical perspective on the fetal alcohol syndrome. *Alcoholism (NY)* 1980; 4: 119–122
15. MORRISON AB, MAYKUT MO: Potential adverse effects on maternal alcohol ingestion on the developing fetus and their sequelae in the infant and child. *Can Med Assoc J* 1979; 120: 826–828

Alcohol and abnormal outcomes of pregnancy

ROBERT J. SOKOL, MD

Heavy alcohol consumption by the mother during pregnancy has long been suspected of being a risk factor for abnormalities in the fetus or infant. Only during the last decade have these assumptions been supported by scientific studies. A clustering of fetal defects observed in some cases has been labelled the fetal alcohol syndrome. The syndrome involves prenatal and postnatal growth retardation, central nervous system involvement and craniofacial abnormalities, some of which are characteristic of the syndrome. Fetal alcohol syndrome is relatively rare, affecting from 1 in 300 to 1 in 2000 infants; approximately 450 cases have been reported since the syndrome was identified. Despite this rarity, however, heavy alcohol consumption is an important risk factor during pregnancy. A review of the current literature indicates that in animals alcohol in high doses is embryotoxic and teratogenic, that heavy drinking is not uncommon before and during pregnancy and that the fetal alcohol syndrome and other effects on the fetus associated with alcohol abuse appear with significant frequency among mothers who drink heavily. Heavy alcohol consumption is a perinatal risk factor that not only can be detected by the physician, but also can be reduced in concerned, cooperative patients. Thus, awareness of this problem gives health care personnel an opportunity to help in the prevention of abnormal outcomes of pregnancy.

Une forte consommation d'alcool chez la mère durant la grossesse a longtemps été soupconné de présenter un risque d'anomalie pour le foetus ou le nouveau-né. Ce n'est qu'au cours de la dernière décennie que cette hypothèse a pu être confirmée par des études scientifiques et qu'on a pu apposer, dans quelques cas, le vocable de syndrome alcoolique foetal à un ensemble d'anomalies foetales. Ce syndrome comprend un retard de croissance prénatal et postnatal, une atteinte du système nerveux central et des anomalies craniofaciales dont certains sont caractéristiques du syndrome. Le syndrome alcoolique foetal est relativement rare, sa fréquence chez le nouveau-né étant comprise entre 1 sur 300 et 1 sur 2000 enfants; environ 450 cas ont été signalés depuis que le syndrome a été identifié. Toutefois, en dépit de cette rareté, une forte consommation d'alcool constitue un important facteur de risque durant la grossesse. Une revue de la littérature actuelle révèle que l'alcool à forte dose est embryotoxique et tératogène chez l'animal, qu'une forte consommation d'alcool avant et durant la grossesse n'est pas rare et que le syndrome alcoolique foetal et d'autres effets sur le foetus reliés à l'abus de l'alcool apparaissent avec une fréquence appréciable parmi les mères ayant des problèmes d'alcoolisme. Une forte consommation d'alcool est un risque périnatal qui non seulement peut être détecté par le médecin, mais aussi peut être réduit chez les patientes coopératives et soucieuses de leur responsabilité. La connaissance de ce problème offre donc aux professionnels de la santé la possibilité d'aider à prévenir certaines anomalies de la grossesse.

Members of the scientific community and the public are becoming increasingly aware that there is a relation between heavy drinking habits in the mother and adverse outcomes in the fetus and infant. The purpose of this paper is to provide a survey of the problem of heavy consumption of alcohol by pregnant women. I will focus on the highlights of the relevant scientific and clinical evidence, and consider the implications of this evidence for health care planning for women of childbearing age, by first reviewing the long history of the recognition of this problem and the retrospective studies in humans that indicate that there is a fetal alcohol syndrome. I will then describe the syndrome, giving an example, and present the accepted criteria for making this diagnosis. Because fetal alcohol syndrome is a relatively rare complication of pregnancy, I will attempt to answer the question as to why heavy alcohol consumption is an important risk factor during pregnancy by describing some animal studies (in which many confounding variables were controlled) indicating that alcohol may adversely affect the fetus, and I will briefly discuss the incidence of problem drinking in women. Finally, I will review some of the

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results from prospective studies of alcohol abuse during pregnancy in humans.

Historical background

A relation between heavy alcohol consumption in pregnancy and the birth of abnormal offspring has been suspected since antiquity. The Carthaginians proscribed drinking on the wedding night, apparently on the grounds that the conceptus might be abnormal. Aristotle was of the opinion that drunken women often gave birth to abnormal children.[1] This "clinical suspicion" continued through the centuries, but was highlighted during the gin epidemic that occurred in England between 1720 and 1750. Taxes were removed from gin at that time, making it inexpensive, and alcohol abuse became a major public health problem. A famous print by William Hogarth, entitled "Gin Lane",* clearly points out some of the excesses observed at that time — a baby is dropped to the ground by a drunken mother, an alcoholic is buried, there is squabbling and crime. The problem became so severe that the Royal College of Physicians requested Parliament to reinstate the tax on alcoholic beverages to protect the public health, including that of mothers and infants.

Through the 19th century there were intermittent reports suggesting that parental alcoholism was associated with the birth of defective children. At the beginning of the 20th century Nicloux[2] reported that alcohol crossed the placenta, and in 1916 Stockard and Papanicolaou reported that the intake of alcohol by pregnant guinea pigs was associated with a decrease in the number and birthweight of viable offspring and an increase in postnatal mortality.[1] Disagreement concerning the adverse effects of alcohol on reproduction persisted, however, among investigators using animal models.

During the early part of the 20th century alcohol abuse became an important social issue, and the scientific studies on its association with birth defects were often interpreted as supporting one point of view or another. The beginning of prohibition in the United States in 1920 marked the start of a considerable decrease in scientific activity concerned with alcohol and pregnancy. Only sporadic reports can be found in the world literature over the next 50 years.[3]

The fetal alcohol syndrome

Recognition

From the perspective of the early 1980s a very important study was published in France in 1968, although it received little attention at the time. Lemoine and colleagues[4] reported on 127 offspring of 69 French families in which there was chronic alcoholism. Of these children 25 had malformations, including abnormal facies, heart anomalies and limb deformities. Delays in psychomotor and language development were noted among the 127 children; their average intelligence quotient was approximately 70.

In 1970 a paper from Seattle highlighted the observation that infants of women with chronic alcoholism failed to thrive,[5] but it was 3 more years before the papers that aroused international interest were published.[6,7] In the first of these articles 11 children of women with chronic alcoholism were reported to show growth retardation, craniofacial, limb and cardiac defects, and developmental delays.[6] The most important contribution of the second article was the use of the term "fetal alcohol syndrome";[7] this term and the concepts it entails focused interest on important questions for scientific research and public policy.

Description

Approximately 450 documented cases of fetal alcohol syndrome have now been reported in the world literature. Features of the syndrome described in these reports include the following:

- Prenatal and postnatal growth retardation.
- Evidence of central nervous system dysfunction, including physiologic depression, hypotonia, irritability and jitteriness, mental retardation, poor coordination and hyperactivity during childhood.
- Craniofacial abnormalities, such as microcephaly, short palpebral fissures, ptosis, strabismus and epicanthal folds. Of particular importance is midfacial hypoplasia, evidenced by a hypoplastic philtrum, a thin upper lip and a short, upturned nose.
- A number of associated features, including defects in major organ systems, such as abnormalities of the eyes, ears and mouth; heart murmurs, particularly those associated with septal defects; genitourinary anomalies; hemangiomas; and musculoskeletal anomalies, such as hernias.

Clarren and Smith[8] have described the principal and associated abnormalities observed in children with the fetal alcohol syndrome, and indicated how frequently these features occur. The fetal alcohol study group of the Research Society on Alcoholism has proposed a set of minimum criteria for identifying the syndrome in order to simplify, clarify and standardize the diagnosis (Table I).[9] If an individual child does not show at least one feature in each of the three areas of growth, central nervous system function and cranio-

Table I—Minimum criteria for diagnosing the fetal alcohol syndrome, as recommended by the fetal alcohol study group of the Research Society on Alcoholism[9]

Area	Manifestations
Growth	Prenatal or postnatal growth retardation or both: weight, length or head circumference, or any combination of these, less than the 10th percentile for gestational age
Central nervous system function	Signs of neurologic abnormality, developmental delay or intellectual impairment
Craniofacial appearance	Characteristic abnormalities (at least two of these): Microcephaly – head circumference less than the third percentile Microphthalmia or short palpebral fissures or both Poorly developed philtrum, thin upper lip and flattening of maxillary area

*See the cover of the May 1, 1981 issue of the Journal.

facial appearance, a diagnosis of "suspected fetal alcohol effects" has been suggested.[8]

An illustration (Fig. 1) and description of an affected infant may help health care workers visualize some of the abnormalities associated with the fetal alcohol syndrome. The infant's mother was a 30-year-old black woman who had had 10 pregnancies and given birth to 9 children, several of whom had had a low birthweight. She had chronic hypertension and had been admitted to hospital for pneumonia and pancreatitis before the birth of this infant. Her long history of psychosocial dysfunction included a diagnosis of chronic alcoholism, and she admitted to drinking approximately 1 qt (946 ml) of beer a day. Intrauterine growth retardation was suspected during this pregnancy. At 35 weeks' gestation the patient entered labour; a cesarean section was performed because of fetal distress. The 1550-g female infant had Apgar scores of 6 and 8 at 1 and 5 minutes respectively. Her weight, length and head circumference were all less than the third percentile for infants of the same gestational age. In addition to this evidence of intrauterine growth retardation, she showed 10 features associated with the fetal alcohol syndrome. She was jittery in the nursery and had diastasis recti abdominis. Her palpebral fissures were short, and there was evidence of midfacial hypoplasia. The infant's nose had a broad, deep bridge and was short and upturned, giving the impression of a long, flattened philtrum. The vermilion border of the upper lip was distinctly thin. The ears appeared to be posteriorly rotated, and the infant was hirsute. She was given hyperalimentation to induce weight gain, treated with phototherapy for hyperbilirubinemia and discharged after 1 month. Her neurobehavioural development was to be followed closely.

This infant was diagnosed as having the fetal alcohol syndrome by a developmental pediatrician who was unaware of the maternal history as part of a prospective study of the syndrome at Cleveland Metropolitan General Hospital. This case provides an excellent example of some of the abnormalities that may be observed.

Why heavy alcohol consumption is an important risk factor during pregnancy

As only about 450 cases of the fetal alcohol syndrome have been reported, the importance of heavy alcohol consumption as a risk factor during pregnancy can be questioned even though the syndrome may be considerably under-reported. There are, however, at least three reasons why the heavy alcohol consumption problem is important.

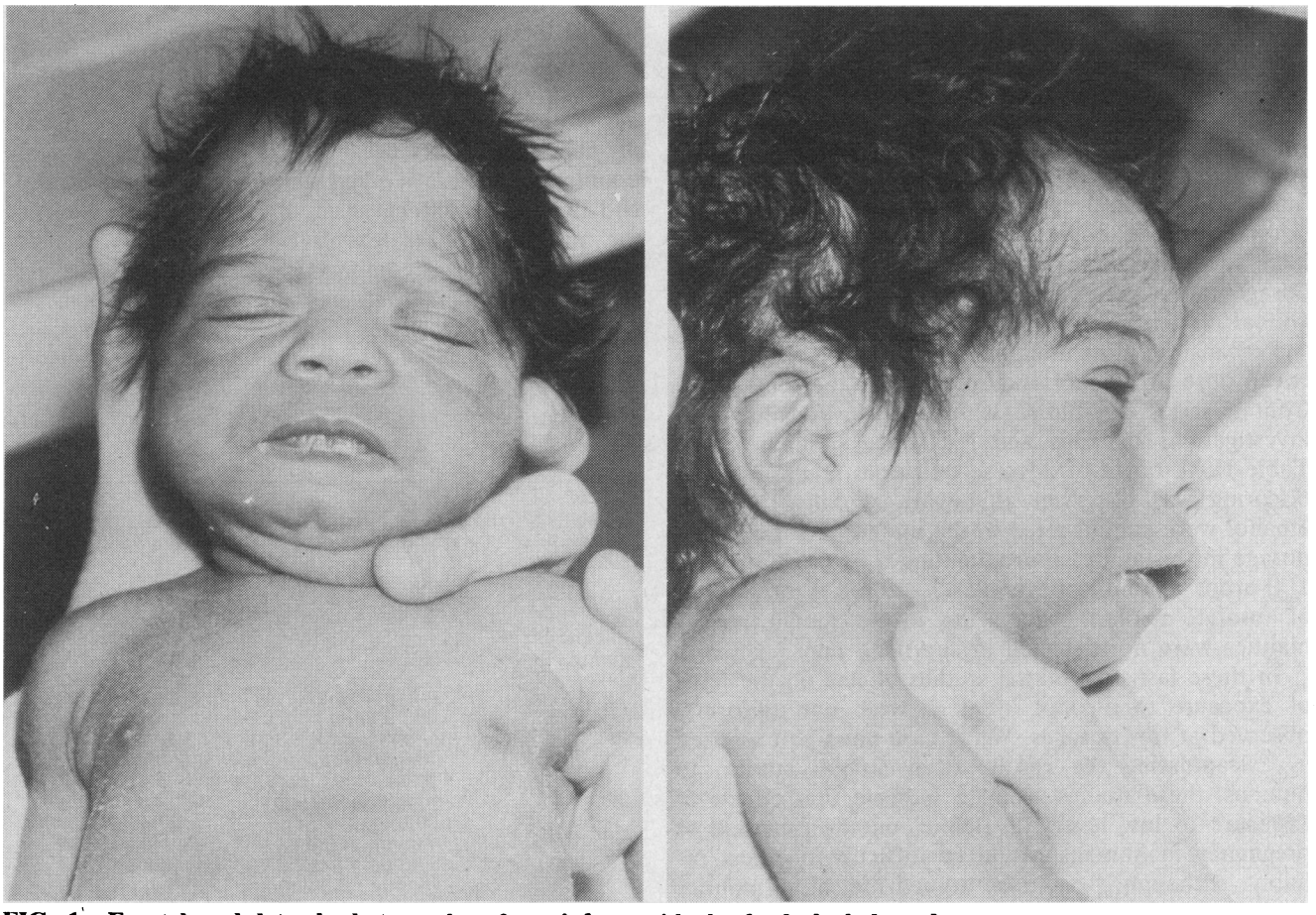

FIG. 1—Frontal and lateral photographs of an infant with the fetal alcohol syndrome.

- Animal studies indicate that exposing the fetus to alcohol can produce malformations, as well as a range of other abnormal outcomes of pregnancy.
- Heavy drinking is relatively common in women of childbearing age.
- A range of abnormal outcomes (possible fetal alcohol effects) has frequently been observed in pregnancies complicated by a heavy intake of alcohol by the mother.

Animal studies

It is extremely difficult to separate the effects of multiple covarying risk factors, such as differences in age and parity, other drug use, cigarette use and nutrition, in studies of alcohol use during pregnancy in humans.[10] In animal models such possibly confounding variables can be controlled. Numerous investigative groups have used several species, including the mouse, rat, beagle, swine and monkey, to study this problem. Three key studies can be cited as examples.

Brown and colleagues[11] have reported on a study of the 24-hour in vitro culture of rat embryos. Compared with unexposed controls, embryos exposed to 150 or 300 mg of ethanol per 100 ml of culture medium demonstrated decreases in crown to rump and head length, as well as in the total cell count. Retardation in development for the stage of gestation was also observed in the exposed embryos. These results suggest a relatively direct effect of alcohol or its metabolites, such as acetaldehyde, or both, on fetal development.

Randall and associates[12] administered alcohol orally to mice that were on a vitamin-fortified liquid diet and compared these animals and their pregnancy outcomes with a group of controls fed the same diet. These investigators documented dose-related effects of exposure of the fetus to alcohol on prenatal mortality and on the frequency of malformations — of the heart, limbs, kidneys and eyes in particular. (The renal abnormalities first observed in this animal model were later identified in affected human infants.) At low dosages no effects on the fetus were observed in this animal model.

Perhaps the most interesting data on the relation between dose of alcohol and response in the fetus come from a series of studies with beagles. Results from investigations by Ellis and Pick[13] are summarized in Table II. A range of adverse outcomes in the fetus or offspring was observed after various daily doses of ethanol were administered to the mother. At the lowest dosage in this study, approximating 6 oz (150 ml) of a 100-proof alcoholic beverage (3 oz [68 g or 85 ml] of absolute alcohol) twice a day in the human, abnormalities were not detected in surviving pups.

In these last two animal studies effects on the fetus of exposure to alcohol in utero were not uniformly observed at low dosages. While care must be exercised in extrapolating the results from animal studies to humans, these studies seem to indicate that effects of exposure to low levels of alcohol on the outcome of pregnancy in humans would be difficult to detect reliably. Although it could be argued that abnormalities might be present but are not easily detected, it is equally reasonable to argue from the animal data that any effects of low dosages of alcohol on human infants might be small and clinically insignificant or, indeed, nonexistent. Thus, animal studies support the concept of a range of adverse outcomes in the fetus or infant that are attributable to exposure to high doses of alcohol. This should not be confused with an assertion that adverse effects are attributable to a full range of levels of alcohol consumption, including low doses. In my opinion these available animal studies do not support a contention that light intake of alcohol during pregnancy will have an adverse effect. However, human habits in drinking alcohol are very complex and not easily reproduced in animal studies. The question of the degree of risk associated with different levels of consumption of alcohol in humans is an important issue when considering how to counsel patients as well as how to formulate public policy. The article by Rosett and Weiner and that by Little and Streissguth in this issue of *CMAJ* will address this from another perspective.

Drinking by women

It has been estimated that approximately 18 million individuals in the United States are heavy drinkers, and there is evidence that the rate of heavy drinking among women is rapidly rising and approaching that seen in men.[3] It has even been suggested that heavy drinking by women may, in the future, exceed that seen in men. Finally, women of childbearing age may be over-represented among heavy users of alcohol relative to their proportion in the general population.[3]

A number of studies have directly addressed the issue of drinking by pregnant women. Estimates of the proportion of women who drink heavily during pregnancy range from 2% to 13%, depending on the population sample studied, the definition of "heavy" and the study methods used. By comparison, many of the maternal risk factors that perinatologists consider important, such as diabetes mellitus, chronic hypertension and adverse outcomes of previous pregnancies, are present in less than 5% of cases. Phenylketonuria and congenital hypothyroidism, for which we routinely screen infants, are extremely rare. Because heavy alcohol consumption is relatively common in pregnant

Table II—Relation of dose of ethanol administered intragastrically to female beagles during pregnancy to the effect on the fetus or offspring[13]

Daily dose of ethanol (g/kg body weight)	Effect
5.7	Fertilization and implantation, but no fetal differentiation
4.7	Spontaneous abortion
4.2	Viable offspring with severe intrauterine growth retardation and malformations
3.6	Intrauterine growth retardation but no anomalies
3.0	Intrauterine growth retardation but no anomalies
2.4	More stillbirths, but viable offspring not growth-retarded

women, and because alcohol readily crosses the placenta,[2] a comparatively large number of fetuses may be exposed to high levels of alcohol in utero.

Adverse sequelae of heavy alcohol consumption in humans during pregnancy

The frequency of adverse sequelae in human pregnancies may best be observed by prospective cohort studies. This method allows researchers to directly estimate the relative risks for adverse outcomes of pregnancy in the presence and absence of a specific risk factor.[10] In 1976 Kaminski and associates[14] reported the results of a cohort study of 9236 pregnancies in France, contrasting the outcome when the mother drank more than 1.5 oz (34 g or 43 ml) of absolute alcohol with that when the mother drank less or none. Controlling for confounding variables, these investigators found in their study group a significantly higher incidence of premature placental separation, stillbirth and low birthweight of the infants. They did not identify any increase in the proportion of preterm deliveries or fetal anomalies.

A similar prospective cohort study at Cleveland Metropolitan General Hospital was based on the medical records of 12 127 pregnant women consecutively delivered during a 52-month period. My associates and I found that health care personnel had identified 204 women (1.7%) as having a pregnancy complicated by maternal alcohol abuse.[15] A profile of these patients' concomitant risk factors and their pregnancy outcomes indicated that they tended to be older, to already have several children and to not be married at the time they delivered. Their obstetric histories were marked by a disproportionate number of previous spontaneous abortions, low birthweight of their infants and fetal anomalies. They were more likely to smoke cigarettes and abuse other drugs. During labour their risks of infection and premature placental separation were increased, though no significant differences in placental characteristics were identified between the women who abused alcohol and those who did not.

Although we did not detect any increase in perinatal mortality, the fetal alcohol syndrome was identified in 2.5% of the pregnancies complicated by alcohol abuse.[15] For the total population of pregnant women the fetal alcohol syndrome was observed in 0.04% or 1 in 2425 pregnancies.

We also found other adverse outcomes of pregnancy to occur more frequently when the mother abused alcohol. For example, a significant increase in the proportion of infants with congenital anomalies (38%, compared with a maximum expected rate of 10%) was identified in association with alcohol abuse. These anomalies included abnormalities of the oral cavity and genitourinary system, hip dislocations, heart murmurs, hernias and birthmarks. Extrapolating to the entire population of pregnant women and using an alcohol abuse rate of 17 per 1000 pregnancies shows that the 17 pregnancies complicated by alcohol abuse would be expected to produce 6.4 infants with anomalies and the 983 other pregnancies would be expected to produce 98.3 affected infants, for an approximate total of 105. If none of the 1000 pregnancies had been complicated by alcohol, 100 infants would be expected to have anomalies. This leads to the conclusion that of 1000 pregnant women, those who abuse alcohol produce five infants with anomalies, a 5% increase above the basal rate.

Infants born to Cleveland mothers who abused alcohol were more likely to suffer other adverse effects as well. Their birthweights were significantly lower, by an average of approximately 190 g. This was accounted for by an increased frequency of intrauterine growth retardation — 2.7-fold overall. Preterm delivery was not more common, but the risk of intrauterine growth retardation was estimated to be increased 2.4 times by alcohol abuse alone, 1.8 times by smoking alone and 3.9 times by these risks together; this confirms Kaminski and associates' previous findings.[14] Fetal distress during labour and neonatal depression were also more common outcomes of pregnancy in women who abused alcohol.

Estimates from this and other studies of the risk ratios and incidence rates for various adverse sequelae in the fetus or infant associated with heavy alcohol consumption by the pregnant woman are shown in Table III. It is clear that the adverse outcomes associated with heavy drinking in pregnancy are not rare and that the fetal alcohol syndrome represents only a small proportion of the observed abnormalities.

Conclusion

Heavy alcohol consumption in pregnancy is an important public health problem. Because it is a perinatal risk that can be detected by health care personnel and that is potentially avoidable, there is a clear opportunity for introducing preventive measures that can improve the outcome of pregnancy.

The conclusion that heavy alcohol consumption is a common problem in pregnancy has important implications for the practising clinician. We should be screening our pregnant patients for alcohol problems. Unfortunately, there are no simple biochemical markers for problem drinking.[16] Moreover, because individuals tend to deny to themselves and to others that they have this problem,[17] obtaining an accurate estimate of the amount a pregnant woman drinks may be difficult. Results from the prospective study conducted by myself and my colleagues in Cleveland suggest that clin-

Table III—Estimates of the risk for adverse effects in the fetus or infant associated with heavy alcohol consumption by the mother during pregnancy (uncorrected for concomitant risk factors)

Outcome	Risk ratio	Incidence (%)
Spontaneous abortion	2	30
Fetal alcohol syndrome	–	2.5
Congenital anomalies	4	40
Low birthweight	2	25
Intrauterine growth retardation	2.5	10
Neonatal depression	1.5	20
Any abnormality	–	50

icians caring for pregnant women may miss as many as three out of four cases.[18] We have reported a method, based on our clinical experience, that clinicians may use to obtain a more reliable history.[19] Our experience indicates that clinicians who were certain that none of their patients had a drinking problem were surprised by the amount of heavy drinking they were able to detect once they began obtaining the history in an appropriate way.

It must be kept in mind that the risks described in this review relate specifically to heavy alcohol consumption. The fact that a range of adverse consequences can be associated with high doses of alcohol should not lead to an assumption that such consequences are associated with a range in the amount of alcohol consumed. There is persistent marked disagreement in the literature concerning the effects of "moderate" or "infrequent" drinking on the fetus. Data have been presented that have been interpreted by the investigators as indicating an increased risk for low birthweight,[20] abnormal neurobehavioural development[21] and spontaneous abortion[22,23] with limited alcohol intake during human pregnancy. However, interpreting the published data[9,24,25] conservatively, one can argue that these risks are limited to less than 5% of pregnant patients — those who consume alcohol heavily — and that over 95% of patients do not appear to be at risk.

In my opinion the question of any effect in human pregnancy of alcohol consumption that is less than heavy remains open. Physicians should critically evaluate the evidence in deciding what advice to give their patients. There is little doubt, however, that the fetus or infant of the patient whose alcohol intake is heavy is at increased risk.

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References

1. WARNER RH, ROSETT HL: The effects of drinking on offspring. An historical survey of the American and British literature. *J Stud Alcohol* 1975; 36: 1395–1420
2. NICLOUX M: Passage de l'alcool ingéré de la mère au foetus et passage de l'alcool ingéré dans le lait, en particulier chez la femme. *Obstétrique* 1900; 5: 97–132
3. ABEL EL: Fetal alcohol syndrome: behavioral teratology. *Psychol Bull* 1980; 87: 29–30
4. LEMOINE P, HARONSSEAU H, BORTERYU JP, MENUET JC: Les enfants de parents alcooliques: anomalies observées à propos de 127 cas. *Ouest Med* 1968; 25: 477–482
5. ULLELAND C, WENNBERG RP, IGO RP, SMITH NJ: The offspring of alcoholic mothers (abstr). *Pediatr Res* 1970; 4: 474
6. JONES KL, SMITH DW, ULLELAND CN, STREISSGUTH AP: Pattern of malformation in offspring of chronic alcoholic mothers. *Lancet* 1973; 1: 1267–1271
7. JONES KL, SMITH DW: Recognition of the fetal alcohol syndrome in early infancy. *Lancet* 1973; 2: 999–1001
8. CLARREN SK, SMITH DW: The fetal alcohol syndrome. *N Engl J Med* 1978; 298: 1063–1067
9. ROSETT HL: A clinical perspective on the fetal alcohol syndrome. *Alcoholism (NY)* 1980; 4: 119–122
10. SOKOL RJ: Alcohol-in-pregnancy: clinical research problems. *Neurobehav Toxicol* 1980; 2: 157–165
11. BROWN NA, GOULDING EH, FABRO S: Ethanol embryo toxicity: direct effect on mammalian embryos in vitro. *Science* 1979; 206: 573–575
12. RANDALL CL, TAYLOR WJ, WALKER DW: Ethanol-induced malformations in mice. *Alcoholism (NY)* 1977; 1: 219–224
13. ELLIS FW, PICK JR: An animal model of fetal alcohol syndrome in beagles. *Alcoholism (NY)* 1980; 4: 123–134
14. KAMINSKI M, RUMEAU-ROUQUETTE C, SCHWARTZ D: Consommation d'alcool chez les femmes enceintes et issue de la grossesse. *Rev Epidemiol Med Sante Publique* 1976; 24: 27–40
15. SOKOL RJ, MILLER SI, REED G: Alcohol abuse during pregnancy: an epidemiologic study. *Alcoholism (NY)* 1980; 4: 135–145
16. HOLT S, SKINNER HA, ISRAEL Y: Early identification of alcohol abuse: 2. Clinical and laboratory indicators. *Can Med Assoc J* 1981; 124: 1279–1299
17. MILLER SI, COLLINS G, SOKOL RJ, MARTIER S: Coping with alcohol abuse and alcoholism during pregnancy. In AHMED P (ed): *Coping with Pregnancy* (in press)
18. SOKOL RJ, MILLER SI, DEBANNE S, GOLDEN N, COLLINS G, KAPLAN J, MARTIER S: The Cleveland NIAAA prospective alcohol-in-pregnancy study: the first year. *Neurobehav Toxicol Teratol* (in press)
19. SOKOL RJ, MILLER SI, MARTIER S: Identifying the alcohol-abusing obstetric/gynecologic patient: a practical approach. *Alcohol Health Res World* 1980; 4: 36–40
20. LITTLE RE: Moderate alcohol use during pregnancy and decreased infant birthweight. *Am J Public Health* 1977; 67: 1154–1156
21. STREISSGUTH AP, BARR HM, MARTIN DC, HERMAN CS: Effects of maternal alcohol, nicotine, and caffeine use during pregnancy on infant mental and motor development at eight months. *Alcoholism (NY)* 1980; 4: 152–164
22. HARLAP S, SHIONO PH: Alcohol, smoking, and incidence of spontaneous abortions in the first and second trimester. *Lancet* 1980; 2: 173–176
23. KLINE J, SHROUT P, STEIN Z, SUSSER M, WARBURTON D: Drinking during pregnancy and spontaneous abortions. Ibid: 176–180
24. SOKOL RJ: Alcohol and spontaneous abortion (C). Ibid: 1079
25. Idem: A biological perspective on substance use in pregnancy: alcohol as a paradigm for possible effects on the offspring. Presented at "Biological Vulnerabilities and Psychosocial Factors in 'Infants at Risk' for Developmental Dysfunction", conference sponsored by the institute of medicine, National Academy of Sciences, Washington, Aug 28–29, 1980

Determination of absolute alcohol content

All alcoholic beverages contain a volume or weight of alcohol dissolved in a larger volume of fluid. For example, on average, beer contains 5% alcohol by volume; the remaining 95% is water and other ingredients. Similarly, whisky containing 40% alcohol by volume also contains 60% nonalcoholic matter. When one drinks a bottle of beer it is logical to ask "How much pure or 100% alcohol did I get from the drink?" because it is only pure 100% alcohol that acts on the body pharmacologically. Another term for pure 100% alcohol is absolute alcohol. The amount of absolute alcohol in any type of alcoholic beverage is calculated by multiplying the percentage of alcohol in the beverage by the total volume.