The Fetal Alcohol Syndrome

Part two of a two-part article

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Summary
In part 2 the metabolism of alcohol is described, especially in relation to pregnancy; literature is critically reviewed with special emphasis on the problems facing the general practitioner.

KEYWORDS: Fetal Alcohol Syndrome; Fetal Growth Retardation; Physicians, Family; Alcoholism; Social Problems.

Curriculum Vitae

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PHYSIOLOGY
The rate of alcohol metabolism is little influenced by bodily and external factors9. The first step is the removal of hydrogen, an oxidation process, which is catalyzed by the zinc-containing enzyme, alcohol dehydrogenase. Alcohol is thereby reduced to acetaldehyde. The second step is the oxidation of acetaldehyde, catalyzed by the N A D-dependent dehydrogenase to acetic acid. This oxidation process is so rapid that the level of acetaldehyde in the human body normally does not become notably elevated during
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The oxidation of alcohol. These reactions take place in the liver and upper gastro-intestinal tract. The fetal liver does not contain the enzyme alcohol dehydrogenase.\textsuperscript{19}

The rate-limiting step in the overall oxidation of alcohol to carbon dioxide and water is the oxidation of alcohol to acetaldehyde by alcohol dehydrogenase.

During pregnancy\textsuperscript{20} there is usually a delay in gastric emptying time and decreased intestinal motility. It is therefore expected that pregnant women will have lower peak alcohol levels, but these are sustained longer due to delayed absorption. Alcohol is distributed at a diffusion equilibrium according to the water content of the various body compartments. Alcohol readily crosses the placenta and reaches concentrations in the placenta equivalent to those in the maternal circulation.

The pregnant uterus and fetus add considerably to the distribution of alcohol due to an approximated water increase of six litres in all compartments.

The effects of alcohol will vary with changes in the water concentration during pregnancy. In early pregnancy the fetal water concentration is high, in advancing pregnancy, maternal water retention increases.

Fetal blood alcohol concentration falls at only half the rate of the maternal concentration. By comparing the elimination of alcohol in adults, small-for-dates and preterm infants, it can be computed that the fetus develops its own alcohol metabolism only after maturation of liver enzymes, which occurs during the second half of pregnancy. It must be assumed that the fetus is at much greater risk for alcohol effects during the first half of pregnancy.

The mechanism whereby alcohol produces FAS is at present largely unknown, although many potential factors can be postulated\textsuperscript{11}. Alcohol abuse has been associated with an increased incidence of chromosomal alterations\textsuperscript{18}. At least some parts of the syndrome may result from acquired chromosomal damage, possibly due to interference with the structure and function of the microtubular system of the adult liver\textsuperscript{19}. Direct toxicity from alcohol\textsuperscript{17} and from acetaldehyde\textsuperscript{12,13} are postulated. Endocrine disorders\textsuperscript{12} and disturbance of prostaglandin and essential fatty acid metabolism\textsuperscript{20} are also thought to be involved in the pathogenesis.

ALCOHOL AND PREGNANCY

Animal studies seem to confirm the teratogenic effects of alcohol, the studies do not, however, present any consistent patterns and actual advances in knowledge concerning the FAS, based on animal models, have been a little disappointing\textsuperscript{21,22,23,24,25,26,27,28,29,30}.

For practical purposes a history of chronic maternal alcohol use throughout the first trimester of pregnancy, pre- and post-natal growth retardation, characteristic facial features or central nervous system dysfunction are ample criteria for a diagnosis of the FAS. The mother need not, however, be an alcoholic to make the diagnosis.

FAS is an expression of child abuse in utero.

**CLINICAL FEATURES:**

**Growth:**

Pre-natal growth deficiency for weight, length and head circumference is frequent. The most noticeable feature is shortening of length in relation to weight, in contradiction to other cases of intra-uterine growth retardation, where weight is usually much more reduced than length.\textsuperscript{21} There is seldom any catch-up growth post-natally; in fact, the children tend to become underweight for height during infancy and childhood, with diminished adipose tissue\textsuperscript{1}. Thus they may be misdiagnosed as "failure to thrive" of post-natal onset. This retarded post-natal physical development has been shown by Tze\textsuperscript{20} not to be due to a growth hormone deficiency. Majewski\textsuperscript{20} recently reviewed 108 cases of FAS and found some catch-up growth for height, but none for head size.

Little\textsuperscript{21} supports the view that intra-uterine growth retardation is associated with lower doses of alcohol consumption. It was also found that two drinks a day (one drink is the equivalent of one whisky, one beer or one medium glass of wine) caused an average weight decrease of 60-160 gm at birth, compared to expected weight\textsuperscript{22}. These findings correlate with those of Silva\textsuperscript{30} who found that the prenatal effects of ethanol were significantly greater among neonates born to mothers who were heavy drinkers. A dose-response curve is emerging.

**Facial dysmorphia:** (See Fig 3)

The faces often have a distinctive appearance. The palpebral fissures tend to be short, possibly because the eye size is small. Jones et al\textsuperscript{21} measured the length of the palpebral fissure and found that it was below 1,9 cm, the normal for a full-term infant.

**The fetus is at much greater risk for alcohol effects during the first half of pregnancy.**

The nose may be small and short, with a low nasal bridge and redundant inner canthal skin folds. The short nose may give the philtral region the appearance of being long. The philtrum tends to be smooth and as a result the upper lip may lack its usual indentation bow.
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The vermilion of the upper lip may be thin. The maxillae tend to be small or hypoplastic. Micrognathia may be present. Microcephaly is a fairly constant feature, reflecting deficient brain growth. Hirsutism may be noticeable at birth but usually recedes post-natally.

Central Nervous System and its Dysfunction:
Mental retardation is one of the most common and serious problems of the FAS. Of all known causes of mental retardation in children, the FAS appears to be the third most prevalent — after Down’s Syndrome and neural tube defects. Of these, the FAS is the only definite preventable cause and a neural tube defect has been described in association with FAS. Although not all persons affected are retarded, of 126 patients described with specific mention of standardized testing of performance 85% (107) scored more than two standard deviations below the mean.

In a study by Stressguth et al involving 20 patients with the FAS, the average IQ was 65, ranging from 16 to 105. In general, the more phenotypically involved patients had the lower IQ scores. Darby et al reported the mean IQ score of eight children with FAS as 76 (range 40-107). The ages varied from 14 months to 6% years. These children were followed from birth or within the first eight months of life.

Lewis and Boylan and also Fox et al showed that small amounts of alcohol during pregnancy can depress fetal breathing and central nervous system arousal. Evidence is growing that moderate alcohol intake may affect the fetus and that brain damage may occur even when outward signs of the FAS are not evident.

Pre-natal alcohol exposure and minimal brain dysfunction have been linked. A correlation has been found between parental alcoholism, learning disabilities and hyperactivity in children. Shaywitz et al described two preschool children with a similar pattern of verbal and behavioural dysfunctions, characterized by marked hypervigilence, distractability and cognitive confusion which manifested as anxiety and behavioural disorganisation. Delayed language acquisition and impaired modulation of attention were especially marked.

Morbid neuroanatomical studies have shown gross brain malformations, including interruption in neuronal and glial migrations, cerebellar dysplasias, microcephaly and hydrocephalus.

Neurological abnormalities include irritability, jitteriness, lethargy, poor sucking, tremors, increased muscle tone, hyperacusis, spontaneous seizures and abdominal distension. These abnormalities may persist as permanent tremor and fine motor inco-ordination, presenting permanent brain damage.

Alcohol withdrawal effects after birth have been described and include irritability, tremulousness and transient seizures. The withdrawal phenomenon, when present, is usually not a serious problem.

Slavney et al described a case of FAS where the patient developed schizophrenia. This is a very important observation, in view of animal studies which showed alterations in neurochemicals in pre-natally alcohol-exposed fetuses. In recent years attention has been focussed largely on biological factors in the aetiology and pathogenesis of schizophrenia. In several cases of chronic paranoid schizophrenia the norpinephrine levels in certain limbic areas of the brain, have been significantly increased.

There are a multiplicity of associated defects in FAS occurring in 1-50% of cases. These are varied: ophthalamic lesions, cardiovascular, genito-urinary, skeletal and other systems.

Differential Diagnosis
There is no single feature of the FAS that is pathognomonic, although the features reported form a phenotypically recognizable continuum. The diagnosis is often missed in a fetal alcohol syndrome patient with a major malformation, because there is a tendency to focus on the major malformation rather than on the total pattern of malformation, which includes growth retardation and mental deficiency.

The most common misdiagnoses include:
De Lange Syndrome, Noonan Syndrome, Williams Syndrome and others like: Dubowitz syndrome, The Fetal hydantoin syndrome, Phenylketonuria, Disulfiram (antabuse) malformations, Diabetes and The Di George syndrome.

The FAS is "ruining a child's brains before birth".

There is seldom any catch-up growth of the retarded fetus post-natally.

EPIDEMIOLOGICAL SURVEYS
The FAS is now recognized as a major public health problem, which Beattie described as the incurable hangover. The risk of a serious problem in the offspring of chronic alcoholic women has been estimated to be in the range of 30-50%

Important studies to take note of are the Boston City Hospital Study, the Seattle Study, and the Göteborg Study in Sweden. The Göteborg Study is an academically acceptable study that showed clearly the risk of a fetal alcohol lesion/effect as 1:300, of whom half had the complete FAS.

Other reported studies include those by Kaminski, Sokol et al and the Loma Linda University Study.
Mental retardation is one of the most common and serious problems of FAS.

Two well-documented series by Kline et al and Harlap and Shiono suggest an abortifacient effect of alcohol consumption. More recently, Vitez et al described a semiquantitative score system for epidemiologic studies.

Although all the cited reports have certain shortcomings and fall short of establishing a causal association between heavy drinking in pregnancy and the full FAS, the consistent findings of association between heavy in utero alcohol exposure and other unfavorable pregnancy outcomes, can be accepted as proof for clinical purposes. This does not obviate the need for systematic study based on epidemiological principles.

IMPLICATIONS FOR THE FAMILY AND SOCIETY
IMPACT OF FEMALE ALCOHOLISM:
The problems of alcoholism in women are special and unique and cannot be understood by extrapolating from studies of male alcoholics.

In the study of Morrissy and Schuckit, it was found that 90% of their alcoholic women were married, of which 78% were parents. The average age at which alcohol was perceived as a problem was 33 years and the average age for the first medical diagnosis of physical harm from alcoholism was 34 years, which is clearly within the childbearing years.

To detect the female alcoholic is very difficult. Johnson and Garzon noted some recurring characteristics among alcoholic women. These include the following:

(i) The presence of an alcoholic father. The mother is dominant and emotionally distant and the father is weak and passive;
(ii) The patient is constantly burdened by an inability to satisfy her mother;
(iii) The loss of one or both parents before the age of 16 years, rendering them especially vulnerable to loss, fear of loss and other forms of emotional deprivation;
(iv) The patient is often the first or last born in the family;
(v) An alarming feature is reports that alcoholic women say they would like to have 4.15 children on average, whereas control groups say 2.94;
(vi) These patients are more prone to severe depressions — the mother of the child cited in Case 4, committed suicide in an acute depressive state.

The diagnosis of FAS is often missed when the focus is on the major malformation rather than on the total pattern of malformation.

Doctors providing antenatal care should take note of some of the maternal characteristics of the FAS, as described by Pirog et al. These alcoholic mothers have a poor obstetric history such as one of premature labour or abortions and attend few or no antenatal clinics. A high percentage abandon their babies.

When a woman is suspected of being an alcoholic, the doctor should engage in conversation about her drinking. The best indicator for successful treatment is if the woman’s life is intact — if she retains her work and if her family is together.

The possibility of termination of the pregnancy should be raised early, to give the patients time to think about the seriousness of the issue. Preferably the father should participate in the matter. A team approach can be useful, but the discussions must be straightforward and honest.

The medico-legal liability must also be considered. A case has been quoted in New Jersey in which the doctor was found to be at fault after the delivery of a FAS infant. This doctor had not known that FAS was a possibility, but the judgement was made that he should have known that the mother was an alcoholic and that delivery of a FAS infant was a possibility. Thus doctors must warn and advise patients adequately of the risk of bearing an abnormal child.

Sociologically, the FAS is an expression of child abuse.
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in utero, the ultimate in the "Battered Child Syndrome" — ruining children's brains before birth.14

FAMILY DYNAMICS:
If a child with the FAS or fetal alcohol effects is born, dreams are shattered. This leads to mourning or grieving and intense guilt feelings that lead to a crisis in the family.

Kenneth Moses134, a clinical psychologist described the grieving process experienced by parents as being similar to the stages described by Kübler-Ross145.

Alcoholic women want 4 or more children — other women only want 2 to 3!

CONCLUSIONS
The FAS is the biggest preventable public health hazard136 known in the Western World, although one can assume a similar incidence in the underdeveloped and Third World countries, partially due to ignorance and the drinking of traditional home brews. The question "What must become of an infant who is conceived in Gin?" asked by Fielding17, more than 200 years ago, is still pertinent.

Public awareness must be increased and all patients must be warned about the untoward outcomes of pregnancies with alcohol. Particular attention should be given to "hidden" forms of alcohol, which is frequently found in patent medicines and cough syrups.18 Chasnoff et al115 described an infant with fetal alcohol effects born to a mother who abused cough syrup.

Patients should be warned about the hidden forms of alcohol found in patent medicines and cough syrups.

Clinicians must promote the principle of mothering from conception as opposed to mothering from birth.4 Perhaps attention should be focussed on a new concept, "mothering from menarche", as the effects of alcohol or acetaldehyde on the ovum are still largely unknown.

When faced with an unusual clinical problem in a child, the question "Is this child's problem secondary to alcohol exposure in utero?" should be asked.

The family physician, general practitioner or primary clinician will have to face the FAS in its multitude of forms first. The detection of the overt alcoholic, antenatal and labour ward problems, post-natal difficulties, the detection of congenital abnormalities, the presentation of failure to thrive, the management of behavioural problems, the support of the affected family and maintaining social perspectives — all these present the ultimate challenge: THE FETAL ALCOHOL SYNDROME.

"Behold, thou shalt conceive, and bear a son, and now drink no wine or strong drink . . . " (Judges 13:7)

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Mothering from conception, not mothering from birth!
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