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How strong is the evidence for using blood biomarkers alone to screen for alcohol consumption during pregnancy? A systematic review

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ABSTRACT

Accurate and early identification of women at risk from alcohol consumption during pregnancy allows education and support programmes to be targeted at those most in need. We aimed to conduct a systematic review to compare the efficacy of blood analysis and maternal self-report in detecting at risk women during pregnancy. This review investigated diagnostic accuracy. We searched four databases (Medline, Embase, Psychinfo and CINAHL) for relevant articles and conducted hand searches of recent issues of key journals in the field. No restriction was placed on inclusion in terms of publication date or language. Studies were deemed eligible if they were original research and included a direct comparison of the results of blood biomarker analysis and self-reported alcohol use for the detection of alcohol consumption in pregnant women. Quality appraisal of included studies was conducted using the QUADAS II tool. Eight studies met the inclusion criteria. Gamma-glutamyltransferase (GGT) was investigated in five studies, mean corpuscular volume (MCV) and phosphatidylethanol (PEth) in three studies and carbohydrate deficient transferrin (CDT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and whole blood associated acetaldehyde assay (WBAA) were each investigated in two studies. Although all of the studies were rated of good methodological quality, none of the biomarkers had both high sensitivity and specificity when compared to self-report. There was some evidence that a combination of biomarkers, or combining biomarkers with self-report, increases accuracy. In summary, the blood biomarkers examined were of limited use in screening for low and moderate alcohol consumption in pregnancy when compared to self-report. However, certain biomarkers, such and CDT and PEth may complement self-report and help improve the accuracy of diagnosis.

Introduction

Fetal Alcohol Spectrum Disorder (FASD) is a range of disorders present at birth resulting from alcohol exposure in pregnancy [1,2]. Alcohol is teratogenic (i.e. a substance which can interfere with the normal development of the embryo or fetus) and, as such, for women who consume alcohol in pregnancy there is an increased risk that their baby may present with FASD [3]. FASD is a leading, preventable cause of developmental delay in high-income countries [4]. FASD children usually present with damage to the brain and central nervous system which cause lifelong intellectual and developmental disabilities. This can have a number of negative impacts on the person with FASD, including attention deficits, poor social skills, hyperactivity, reduced coordination and slower cognitive processing speeds, with deficits in receptive language and verbal working memory [5]. Executive functioning difficulties are demonstrated with poor organisational and planning skills, and the inability to learn from consequences [6,7]. Physical disabilities of FASD can affect any organ or system in the body and symptoms may include cardiac, renal, ocular and auditory defects [6]. Babies born in the severest 10% of FASD can be diagnosed with Fetal Alcohol Syndrome (FAS), which, in addition to the impacts listed above, is associated with facial dysmorphologies, smaller birth weight and a range of mental health disorders in later life [1,2]. Consequently, FASD constitutes a significant public health issue, impacting on health and social care resources, as well as the education and justice systems [5,7].

Reports of the prevalence of FASD vary widely depending on the setting. Prevalence figures from 11.1 to 33.5 per 1000 have been reported in the United States [6,8]. The highest reported prevalence of FASD is 63.9–207.5 per 1000, from a South Africa study [9,10].

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Variations in prevalence rates are likely to be attributable to differences in maternal drinking behaviour, degrees of public awareness, differences in the diagnostic criteria, assessment techniques used, methods of surveillance, and varying sample/population demographics [7]. However, generally the most significant challenge in obtaining reliable data on prevalence is the need for a maternal history of alcohol use in pregnancy to allow diagnosis.

Screening for alcohol use in pregnancy

In the UK, and many other countries, screening, based on self-report, followed by in-depth interview of those who screen positive, is widely used as a means of identifying those at risk and is seen by many as a 'gold standard' [5]. Self-report avoids many, although not all, of the ethical problems associated with more invasive screening methods. However, self-report can be unreliable and may be biased by social desirability responses dependant on the patient-clinician interaction and perceived stigma around alcohol use in pregnancy [11,12]. For some women the situation is complicated by confusion regarding what is a 'safe' amount of alcohol to consume in pregnancy and difficulty in judging how much alcohol they have consumed [3,13–16].

Nevertheless, given the potential profound impact of the physical and psychological problems which are caused by FASD, it is essential that women drinking alcohol in pregnancy are identified and offered support as early in pregnancy as possible [17]. The use of simple screening questionnaires is inexpensive, non-invasive, relatively quick to administer and requires no specialist equipment [18,19]. Tools such as TWEAK, CAGE, T-ACE, AUDIT and AUDIT-C are widely used in clinical practice, and their relative merits have been reviewed [20,21]. AUDIT-C, T-ACE and TWEAK are cited as the most valid tools for identifying drinking in BMA guidance and in a systematic review by Burns et al., and are recommended by the UK Department of Health [19,20]. In the United States, the National Institute of Alcohol Abuse and Alcoholism (NIAA) also advocate simple screening questionnaires, such as the T-ACE, as worthwhile preventive measures [22]. Despite the limitations of self-report, in the absence of a valid alternative, it remains the most suitable method for identifying women who drink alcohol in pregnancy.

Biomarkers for alcohol use in pregnancy

Over the last 10–15 years, there has been a growing interest in the identification of novel biomarkers for alcohol consumption in pregnancy in samples of maternal blood, urine and hair and post-partum meconium [14]. Such biomarkers offer the prospect of an objective and quantitative method for identifying women who consume alcohol in pregnancy. Analysis of meconium samples has been of particular interest, given the possibility that it can provide information regarding alcohol use across a substantial portion of the ante-natal period [23]. Although meconium testing may be useful as an aid to the diagnosis of FASD, a simple, inexpensive and accurate method is needed that can detect alcohol exposure in the early stages of pregnancy. This would allow women who may be drinking, or are at risk of drinking, during pregnancy to be offered early help and support, and thus prevent further harm to the fetus. Biomarkers in blood may offer a useful compromise between the identification of exposure over the long-term offered by meconium, hair and nail analysis, but which involve complicated and expensive analytical techniques, and the much shorter half-life of biomarkers from urine analysis. Unlike other tissue sample types, alcohol biomarkers in blood samples taken during the first

Table 1
Summary information for biomarkers used.

Name	Description	Period after alcohol consumption during which a positive result may be recorded	Strengths	Weaknesses
Gamma-Glutamyltransferase (GGT), Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)	Liver enzymes	Elevated 1–3 weeks after last exposure	Able to measure relatively recent changes in alcohol consumption patterns and may be a good marker for drinking in early pregnancy and before the pregnancy was confirmed. [21].	Not increased by binge drinking. May be elevated by other forms of liver damage, including non-alcoholic fatty liver disease. Sensitivity and specificity are thought to be low, limiting clinical utility. [21]
Mean Corpuscular Volume (MCV)	Average red blood cell volume	Elevated after 1–3 months of heavy alcohol consumption	Greater specificity than GGT, AST and ALT. [21,14].	MCV is naturally elevated in mid- to late stage pregnancy, limiting specificity. Elevated MCV levels are only produced after sustained and regular excessive drinking. [14] Therefore, MCV has limited value as a single marker. [21].
Carbohydrate Deficient Transferrin (CDT)	CDT is synthesised and secreted in the liver and acts as a carrier for iron in the blood.	Elevated 1–3 weeks after sustained exposure	Thought to have higher specificity, but lower sensitivity than GGT or MCV. Able to detect binge drinking and sustained exposure. Commercial assays for clinical use available. [21,39].	Will not detect low/moderate drinkers. Total transferrin increases naturally during pregnancy, so CDT is taken as a percentage of total transferrin, the validity of this approach requires further investigation. [21] Historical studies may be affected by methodology and lack of suitable common standard material. [39]
Whole Blood Associated Acetaldehyde Assay (WBAA)	Acetaldehyde is the main product of oxidative ethanol metabolism.	Can be detected one month after alcohol consumption	Acetaldehyde-protein adducts (APAs) have a longer half-life than free acetaldehyde and remain high in blood for approximately a month after alcohol intake. Thought to have high sensitivity and specificity. [28]	Potential to produce false-positives due to the formation of acetaldehyde in blood after sample collection. [28]
Phosphatidylethanol (PEth)	A group of ethanol-derived phospholipids, formed in the presence of ethanol	Can be 2–3 weeks after sustained alcohol consumption	Sensitive indicator of heavy alcohol use. May be a good marker for drinking in early pregnancy and before the pregnancy was confirmed. [40,41]	Will not detect low/moderate drinkers. There is no suitable calibration material to standardise assays between different methods. PEth may be unstable unless frozen. [40,41].