Phosphatidylethanol is a promising tool for screening alcohol consumption during pregnancy

Häkkinen, Margareeta; Arponen, Anne; Jylhä, Antti; Sulin, Kati; Gunnar, Teemu

2024

John Wiley and Sons Inc.

http://hdl.handle.net/10138/585134

Häkkinen, M, Arponen, A, Jylhä, A, Sulin, K & Gunnar, T 2024, 'Phosphatidylethanol is a promising tool for screening alcohol consumption during pregnancy', Alcohol, Clinical and Experimental Research, vol. 48, no. 10, pp. 1892-1897. https://doi.org/10.1111/acer.15418

Received: 30 April 2024 | Accepted: 19 July 2024

DOI: 10.1111/acer.15418

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

RESEARCH ARTICLE

Phosphatidylethanol is a promising tool for screening alcohol consumption during pregnancy

Margareeta Häkkinen[1,2,3] | Anne Arponen[1] | Antti Jylhä[1] | Kati Sulin[4] | Teemu Gunnar[1]

[1]Department of Government Services, Finnish Institute for Health and Welfare, Helsinki, Finland

[2]Department of Psychiatry, University of Helsinki, Helsinki, Finland

[3]Addiction Hospital, A-Clinic Ltd, Järvenpää, Finland

[4]Finnish Red Cross Blood Service, Vantaa, Finland

Correspondence
Margareeta Häkkinen, Department of Government Services, Finnish Institute for Health and Welfare, P.O. Box 30, 00271 Helsinki, Finland.
Email: margareeta.hakkinen@thl.fi

Funding information
The Finnish Ministry of Social Affairs and Health

Abstract

Background: Prenatal alcohol exposure (PAE) is one of the leading causes of preventable developmental disabilities. A lack of objective screening methods results in an under-recognition of the phenomenon. Phosphatidylethanol (PEth) is a specific ethanol biomarker that reveals alcohol intake up to several weeks after alcohol use. So far, PEth has mostly been a tool for detecting moderate and heavy drinking. With lower PEth cut-offs, revealing even minor prenatal alcohol consumption is possible. We aimed to find out if a sensitive method for PEth analysis would give additional information about PAE and to assess the cut-off value for a positive alcohol result in prenatal screening.

Methods: The study was an observational study of 3000 anonymous blood samples collected from the Helsinki University Hospital Diagnostic Center between June and September 2023. The Finnish Red Cross Blood Service received the samples originally for blood group typing and antibody screening as part of the prenatal blood screening program. We developed a sensitive PEth 16:0/18:1 analysis method using ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC–MS/MS) equipment after liquid–liquid extraction of PEth from whole blood. The lower limit of quantification was 1 ng/mL.

Results: PEth was ≥2 ng/mL in 5.2% of the cases, ≥8 ng/mL in 2.0%, and ≥20 ng/mL in 1.0%. The detection time of PEth can be several weeks, especially with low PEth concentrations and after heavy alcohol consumption. It remained unknown whether the positive PEth tests resulted from drinking deliberately during pregnancy or before pregnancy recognition.

Conclusions: We suggest adding PEth 16:0/18:1 to a routine prenatal blood screening program with a cut-off of 2 ng/mL—and in positive cases, clinical evaluation and retesting in 2–4 weeks. In clinical settings, information on gestational week and alcohol consumption before pregnancy is relevant and needs to be considered when interpreting low PEth concentrations.

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

KEYWORDS
alcohol drinking, alcohol-related disorders, biomarkers, fetal alcohol spectrum disorders, prenatal care

INTRODUCTION

Alcohol consumption during pregnancy can cause serious, lifelong harm to a developing fetus and child. The World Health Organization (WHO) classifies prenatal alcohol exposure among alcohol's most dramatic manifestations of harm to persons other than the persons who are drinking (World Health Organization, 2023). WHO recommends that healthcare providers ask all pregnant women about their use of alcohol as early as possible and at every prenatal care visit (World Health Organization, 2016).

Traditionally, prenatal alcohol use screening has been based on self-reporting, such as the AUDIT (Alcohol Use Disorders Identification Test) questionnaire. Based on an anonymous online questionnaire for pregnant women and mothers with children less than 1 year old in 11 European countries from October 2011 to February 2012, the proportion of alcohol use during pregnancy was 15.8%. Of the 572 Finnish responders, 14.0% reported alcohol consumption after awareness of pregnancy, but the amounts were mostly small. Of the 79 responders who reported drinking, 78.5% had consumed 1–2 units during pregnancy, 19.0% 1–4 units per month, 1.3% 1–2 units per week, and 1.3% ≥1–2 units per week (Mårdby et al., 2017). In a Finnish questionnaire on 21,472 pregnancies, the proportion of prenatal alcohol use was 4.5% (Voutilainen et al., 2022). In 26% of the pregnancies, the women reported stopping alcohol use only after pregnancy recognition (Voutilainen et al., 2022). Most drinking occurred once a month or less often (Voutilainen et al., 2022). According to the latest national query in Finland in 2020, 1.9% of the 8938 responders reported alcohol use at least once after they knew they were pregnant (Finnish Institute for Health and Welfare, 2020), whereas the same figure in 2017 was 7% (Klemetti et al., 2018). In the Satakunta region of southwest Finland in 2019, 55% of the 217 pregnant women reported to have quit using alcohol only after they learned they were pregnant (Lehtinen & Ekblad, 2023). A meta-analysis reported even higher proportions of alcohol use during pregnancy worldwide: 25% in Europe and 10% worldwide (Popova et al., 2017).

Prenatal alcohol exposure (PAE) has been estimated to be at least four times more common than self-reports in questionnaires by pregnant women (Lange et al., 2014). Nowadays, we have better ways to screen prenatal alcohol consumption than just questionnaires and conversations. Measuring alcohol biomarkers, such as fatty acid ethyl esters, ethyl glucuronide, and ethyl sulfate in meconium may help to detect alcohol use in late pregnancy (e.g., Bager et al., 2017). To utilize early interventions, however, we need screening methods suitable for early pregnancy. Phosphatidylethanol (PEth) is a specific biomarker of ethanol use. PEth is an abnormal phospholipid that is formed in the cell membranes of red blood cells by the action of phospholipase D only in the presence of ethanol (Varga et al., 1998). PEth is measurable in pregnant people in different phases of pregnancy (Bager et al., 2017; Baldwin et al., 2020; Breunis et al., 2021; Finanger et al., 2021; Hasken et al., 2023; Kwak et al., 2014) or in newborns indicating alcohol exposure in late pregnancy (Baldwin et al., 2020; Henderson et al., 2023; Stevens et al., 2020). Finanger et al. utilized PEth in investigating the prevalence of early PAE in a general population of pregnant women whose PEth was analyzed from blood samples collected for Rhesus typing and antibody screening (Finanger et al., 2021).

Recognizing prenatal alcohol consumption as early as possible is important to prevent FASD (fetal alcohol spectrum disorders) and other alcohol-related harm to the fetus and the pregnant person. Despite the inevitable benefits of PEth in screening alcohol consumption in early pregnancy, there is no consensus on the cut-off for PEth for also revealing minor alcohol exposure (Franceschetto et al., 2022). We aimed to study even low PEth concentrations in real-world prenatal blood samples. Blood sampling as part of the routine prenatal health screening among other blood tests poses no extra risk for pregnant people or their fetuses, but revealing even minor PAE may lead to substantial health benefits. Our specific aims were the following:

- Develop a PEth screening method to detect even low alcohol consumption in anonymous blood samples collected from pregnant people
- Assess the prevalence of alcohol consumption during pregnancy in southern Finland
- Evaluate and suggest best possible practices in PEth laboratory diagnostics in a prenatal blood screening program.

MATERIALS AND METHODS

Finnish prenatal services

Finnish prenatal services are publicly funded and free of charge. According to the Finnish Medical Birth Register and primary care statistics, over 99% of pregnant people use prenatal services. Wellbeing service counties have been responsible for all healthcare in Finland (including prenatal care) since the beginning of 2023. Our data consist of 3000 anonymous whole blood samples from pregnant people living in seven wellbeing service counties in southern Finland: Central Uusimaa, Eastern Uusimaa, Kymenlaakso, South Karelia, Vantaa and Kerava, Western Uusimaa, and the city of Helsinki. In 2023, this area included 41 municipalities with 2.0 million inhabitants out of Finland's population of 5.6 million (Statistics Finland, 2024). In 2023, there were 17,300 live births in the study area and 43,400 in Finland (Statistics Finland, 2024).

In Finnish prenatal services, the first visit to a public health nurse is during gestational weeks 8–10. At the first visit, the nurse examines the pregnant person's health issues and lifestyle, including substance use, and the pregnant person receives a laboratory referral for blood tests. According to the national guidelines, all alcohol consumption during pregnancy is discouraged. The alcohol consumption screening tool is AUDIT—or the three first questions of AUDIT, which cover the last 12 months and mostly indicate some period before pregnancy. Those pregnant people receiving AUDIT scores ≥6 should be referred to hospital prenatal outpatient clinics for people with alcohol, drugs, or medication use (Finnish Institute for Health and Welfare, 2023). Those pregnant people with substance abuse are directed to substance use services along with prenatal healthcare and hospital outpatient monitoring.

The laboratory visit occurs after the first prenatal care visit at gestational weeks 8–12. The blood tests in the Finnish prenatal screening program include hemoglobin, blood group typing and blood group antibody screening, antibodies of HIV (human immunodeficiency virus), hepatitis B, and syphilis. Rhesus D (RhD)-negative pregnant people are also screened for blood group antibodies between gestational weeks 24 and 26 and during gestational week 36. The proportion of RhD-negative people is 12%. If an RhD-positive pregnant person has been given blood transfusions or the person's previous child has been treated for newborn jaundice, an additional sample is taken during gestational week 36.

Material

Prenatal blood samples were drawn according to the national prenatal screening program at local laboratories or prenatal care units and transported by mail or courier services to a Finnish Red Cross Blood Service laboratory from the areas mentioned above. The samples (3000 in total) taken between June and September 2023 were included without any preselection and separated for the study before ABO RhD blood group typing and blood group antibody screening. The anonymous whole blood sample aliquot 300 μL was collected in micro tubes on the day of arrival and frozen within 1 h to −70°C.

The aliquots were delivered to an analytical laboratory once a week and stored at +6°C until analysis. All samples were analyzed within 4 days after arriving at the laboratory. The remaining aliquots were destroyed after PEth analysis.

Analytical method

We analyzed PEth 16:0/18:1 with the validated ultra-high-performance liquid chromatography–tandem mass spectrometry (UHPLC–MS/MS) method. The method was also accredited according to ISO/IEC 17025. Extraction of PEth was done according to Skråstad et al. (2020). In short, 150 μL of sample was aliquoted in a 5 mL tube and 450 μL of 2-propanol containing internal standard PEth 16:0/18:1-d5. Samples were mixed and centrifuged (5 min, 2465 g), and 50 μL of supernatant was transferred to an autosampler vial. A total of 3 μL were injected in the UHPLC–MS/MS analysis. UHPLC–MS/MS analysis was performed by Agilent 1290 Infinity II UHPLC coupled to an Agilent 6475 tandem mass spectrometer. Chromatographic separation was done by a Waters Acquity UPLC® BEH C18 1.7 μm (2.1 × 75 mm) column using a mobile phase of A: 5 mM ammonium formate and B: 5 mM ammonium formate in acetonitrile. Gradient elution was used starting with 20% A with 80% B; the gradient was raised to 95% B during the first 60 s and kept for the next 2.3 min, then brought back to 80% B in 0.1 min, and kept for 1 min before the next injection. A flow rate of 0.5 mL/min was used and the runtime was 4.6 min. Detection and quantification of PEth 16:0/18:1 was done using the negative ionization mode. The lower limit of quantification (LLOQ) was 1 mg/mL, and the limit of detection (LOD) was 0.2 ng/mL. Mass transitions of *m/z* 701.7 > 255.2 were used for quantification and 701.7 > 281.3 as a qualifier. For internal standard 16:0/18:1-d5 706.7 > 255.2 transition was used. The calibration range was 1–400 ng/mL. The calibration curve had seven points across the range and $R^2 > 0.998$. Coefficient variants within the run were <3.9% ($n = 8$) and between runs <7.3% at two different concentration levels (20 and 180 ng/mL).

Ethical approvals

We received research permission from the wellbeing services counties of Central Uusimaa, Eastern Uusimaa, Kymenlaakso, South Karelia, Vantaa and Kerava, Western Uusimaa, and the city of Helsinki. The Research Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study (approval number HUS/14944/2022).

RESULTS

The proportion of all positive PEth samples during pregnancy was 8.4% (Table 1). The prevalence of alcohol consumption among pregnant people depends on the PEth cut-off. With a cut-off of 2 ng/mL, the prevalence would be 5.2% (Table 1).

TABLE 1 PEth (phosphatidylethanol) distribution of the 253 blood samples from pregnant people in which PEth was positive.

PEth 16:0/18:1 concentration (ng/mL)	*n*	%	Cumulative %
≥200	2	0.067	0.067
35–199	15	0.500	0.567
20.0–34.9	13	0.433	1.00
8.0–19.9	31	1.03	2.03
3.0–7.9	52	1.73	3.77
2.0–2.9	43	1.43	5.20
1.0–1.9	97	3.23	8.43

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH ISBRA

The median of the positive PEth concentrations was 2.7 ng/mL, the interquartile range was 1.5–6.6 ng/mL, the mean was 15 ng/mL, and the standard deviation was 68 ng/mL. The two highest PEth concentrations were 770 and 690 ng/mL, suggesting chronic excessive alcohol consumption during pregnancy.

DISCUSSION

We utilized a specific alcohol consumption biomarker, PEth, as a screening tool for alcohol use among Finnish pregnant people. Among the general population, PEth is a specific and sensitive method for screening alcohol use, especially in distinguishing moderate from excessive drinking. A consensus of PEth interpretations is that PEth below 20 ng/mL is compatible with abstinence or minimal alcohol consumption, and PEth above 200–210 ng/mL indicates chronic, excessive alcohol use (Luginbühl et al., 2022; Perilli et al., 2023). Still, a lack of consensus on the best cut-off for moderate but unhealthy drinking remains (Perilli et al., 2023). Lower cut-offs have been proposed for settings in which the consumption of small amounts of alcohol needs to be detectable (Aboutara et al., 2023). Among pregnant people, the use of PEth has been limited mainly by the absence of a globally agreed cut-off (Franceschetto et al., 2022). PEth studies detecting prenatal alcohol use have typically reported PEth cut-offs from 2 to 8 ng/mL (Franceschetto et al., 2022). Teetotalers have had PEth values below 0.001 μmol/L (0.7 ng/mL) (Nalesso et al., 2011).

Our LLOQ 1 ng/mL is analytically achievable with modern UHPLC–MS/MS equipment with very little or no risk of analytically false-positive results. Low PEth concentrations may, however, be difficult to interpret. It can take weeks or months before PEth falls below very low cut-offs after cessation of alcohol consumption. PEth studies among people with chronic heavy alcohol use and high PEth concentrations and cut-offs have reported half-lives of 4 days (Isaksson et al., 2011; Varga et al., 2000). Later, the reported half-lives of PEth 16:0/18:1 have been somewhat longer. Among heavy drinkers in alcohol detoxification, the median half-life was 6.1 days, ranging from 3.7 to 10.4 days (Helander et al., 2019). When comparing alcohol doses of 0.4 to 0.8 mg/kg, the higher alcohol dose tended to have a steeper decline of PEth over several days than the lower dose, with a median half-life of 7.8 ± 3.3 days (Hill-Kapturczak et al., 2018). The PEth half-life among social drinkers drinking for 5 days to a blood ethanol concentration of 1 g/kg ranged from 4.5 to 10.1 days in the first week and from 5.0 to 12.0 days in the second week (Gnann et al., 2012). A study reported a median PEth half-life of 7.9 days, and no evidence supported high PEth levels to be eliminated faster or slower than low levels, or vice versa (Van Uytfanghe et al., 2022).

The estimated prevalence of alcohol consumption among pregnant people also depends on the PEth cut-off. With the cut-off of 35 ng/mL used in routine Finnish PEth laboratory diagnostics, the proportion of positive samples in our study would have been only 0.6%, leaving most prenatal alcohol consumption unrevealed. This indicates that the present Finnish PEth cut-off is definitely too high for prenatal alcohol consumption screening. The Norwegian PEth study on early pregnancy with LLOQ 0.003 μmol/L (2.1 ng/mL) reported a positive PEth proportion of 1.4% (Finanger et al., 2021). Other countries have reported higher proportions of positive PEth results in early pregnancy. In the Netherlands, the total PEth concentration was based on the sum of PEth 16:0/18:1 with LLOQ 6.0 ng/mL, 16:0/18:2 with LLOQ 6.0 ng/mL, and 18:1/18:1 with LLOQ 3.0 ng/mL, leading to a positive early pregnancy PEth proportion of 5.3% (Breunis et al., 2021). In the United States, PEth 16:0/18:0 with LLOQ 8 ng/mL resulted in the respective proportion of 22/314 (7.0%) (Bracero et al., 2017). Our prevalence estimate of 5.2% with the cut-off of 2.0 ng/mL was higher than in Norway, although Finland and Norway have rather similar prenatal care programs and guidelines for alcohol abstinence, and the blood samples were collected almost similarly from the material originally collected for blood group antibody testing.

In Finland, the percentage of prenatal alcohol consumption based on self-reporting questionnaires has been estimated to be from 1.9% (Finnish Institute for Health and Welfare, 2020) to 14% (Popova et al., 2017). Questionnaires based on self-reporting usually underestimate prenatal alcohol consumption (Lange et al., 2014), but PEth results based on single prenatal blood tests cover only a short period of pregnancy. It is interesting, though, how close our prevalence estimates based on PEth screenings were to self-reported prenatal alcohol consumption studies. Our prevalence estimates with PEth cut-offs 2–3 ng/mL were close to the previous and largest Finnish self-reported prenatal alcohol consumption estimate of 4.5% (Voutilainen et al., 2022). In another study, as well, PEth with a cut-off of 2 ng/mL was closest to self-reports. When comparing PEth with the self-reported alcohol drinking proportion of 65% with a PEth cut-off of 2 ng/mL, 70% of the blood samples were positive, whereas with 8 ng/mL, the proportion of positive PEth samples was 56%, and with 20 ng/mL, 47% (Hasken et al., 2023).

A false-negative PEth result means PAE despite the negative PEth test. False negatives occurred in 0.3% of those women who reported prenatal alcohol consumption but had a negative PEth test with PEth isoform cut-offs of 3 to 6 ng/mL (Breunis et al., 2021). A higher, or more conservative, cut-off possibly leads to more false negatives than false positives. A false positive indicates alcohol consumption only before pregnancy despite the positive PEth test. A study analyzing the sum of PEth 16:0/16:0, 16:0/18:1, and 18:1/18:1 with the respective LLOQs of 1.5, 3.1, and 1.2 nmol/L (1.1, 2.2, and 0.8 ng/mL) found that 4.8% of those who reported being abstainers during pregnancy had a false-positive PEth result, but all of these people reported alcohol consumption close to conception (Kwak et al., 2014). Blood sampling occurred 3–4 weeks after the recruitment to participate in the study, but exact gestational weeks were not reported (Kwak et al., 2014).

We propose a PEth 16:0/18:1 cut-off of 2 ng/mL, which should lead to a careful check-up at the prenatal care unit. Because prenatal alcohol exposure is potentially very harmful to a fetus—yet treatable and avoidable when recognized—we consider false-negative PEth results more harmful than false positives. The false positives, both

indicating alcohol use before conception and other uncertain conditions, can be excluded with careful exploration of the situation and repeated PEth measurements within 2–4 weeks. Since the majority of the positive PEth values we detected were low and most of the prenatal alcohol consumption in Finland has been minimal and sporadic (Mårdby et al., 2017; Voutilainen et al., 2022), most of the low positive PEth values should fall below 2 ng/mL in the second PEth test. Even though the cut-off of 1 ng/mL was achievable, its interpretation would be challenging due to the long half-life of PEth, leading to excessively increased costs and the need for reperforming the screening in cases of positive PEth results.

Strengths and limitations

Our study was the first one in Finland to utilize a large sample of anonymous, prenatal blood samples to objectively study prenatal alcohol consumption. Anonymous sampling may allow for more reliable results since self-reporting markedly underreports PAE (Lange et al., 2014). PEth analyses are eligible at every phase of pregnancy, and blood samples for PEth screening can be drawn at the same time as other blood tests in the prenatal screening program. Performing PEth tests as part of routine blood sampling would be easy for both the pregnant person and the personnel at the prenatal care.

A limitation of our study was that we had no information on gestational weeks and AUDIT tests or other information on self-reported alcohol consumption. Since we analyzed the samples even with very low PEth cut-offs, a theoretical risk of contamination of alcohol by the use of skin disinfection during blood sampling remained. In a real-life prenatal screening program, this would be overcome with instructions to not use ethanol-containing disinfectants. However, for protecting the health of a fetus, a false positive is better than a false negative. Although some prenatal alcohol consumption studies cover several PEth isoforms, we studied only the PEth isoform 16:0/18:1 because it is the most prominent PEth isoform (Luginbühl et al., 2022), and if used in the prenatal screening program, only one PEth isoform was ideal in order to keep the procedure less complex. One limitation in detecting substance use, in general, is that PEth allows the detection of only one substance, and even with efficient screening of prenatal alcohol use, there still remains the need to assess the use of other substances harmful to a fetus.

CONCLUSIONS

To prevent alcohol-related harm to fetuses, early recognition of PAE is essential. There is no safe level of alcohol consumption during pregnancy. PEth screening with low cut-offs may help in recognizing prenatal alcohol consumption that otherwise would remain unidentified. We suggest a PEth 16:0/18:1 cut-off of 2 ng/mL among pregnant people. A positive PEth result should lead to a careful examination of the pregnant person's situation and a new PEth test within 2–4 weeks. PEth testing is applicable to all stages of pregnancy and easy to reperform in uncertain cases. We suggest that adding sensitive PEth testing to a prenatal blood screening program is worth considering.

AUTHOR CONTRIBUTIONS

MH and AA conceived and designed the study and were responsible for the project administration. AJ and TG designed and developed the laboratory analysis. KS designed the anonymized blood sample collection. MH wrote the first draft of the manuscript. All authors discussed the results, reviewed and edited the manuscript, and approved the final manuscript.

FUNDING INFORMATION

This research was part of a nationwide development project—Developing services for pregnant women and families with substance abuse 2021–2024. The Finnish Ministry of Social Affairs and Health funded and supervised the project, and the Finnish Institute for Health and Welfare was responsible for its coordination.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Margareeta Häkkinen https://orcid.org/0000-0001-6637-9103

REFERENCES

Aboutara, N., Jungen, H., Szewczyk, A., Müller, A. & Iwersen-Bergmann, S. (2023) PEth 16:0/18:1 and 16:0/18:2 after consumption of low doses of alcohol—a contribution to cutoff discussion. *Drug Testing and Analysis*, 15, 104–114.

Bager, H., Christensen, L.P., Husby, S. & Bjerregaard, L. (2017) Biomarkers for the detection of prenatal alcohol exposure: a review. *Alcoholism, Clinical and Experimental Research*, 41, 251–261.

Baldwin, A.E., Hayes, N., Ostrander, E., Magri, R., Sass, N., Mesquita, M.A. et al. (2020) Phosphatidylethanol (PEth) levels in post-partum women and their newborns in Uruguay and Brazil. *Alcoholism, Clinical and Experimental Research*, 44, 1292–1299.

Bracero, L.A., Maxwell, S., Nyanin, A., Seybold, D.J., White, A. & Broce, M. (2017) Improving screening for alcohol consumption during pregnancy with phosphatidylethanol. *Reproductive Toxicology*, 74, 104–107.

Breunis, L.J., Wassenaar, S., Sibbles, B.J., Aaldriks, A.A., Bijma, H.H., Steegers, E.A.P. et al. (2021) Objective assessment of alcohol consumption in early pregnancy using phosphatidylethanol: a cross-sectional study. *BMC Pregnancy and Childbirth*, 21, 342.

Finanger, T., Spigset, O., Gråwe, R.W., Andreassen, T.N., Løkken, T.N., Aamo, T.O. et al. (2021) Phosphatidylethanol as blood biomarker of alcohol consumption in early pregnancy: an observational study in 4,067 pregnant women. *Alcoholism, Clinical and Experimental Research*, 45, 886–892.

Finnish Institute for Health and Welfare. (2020) FinLapset-kyselytutkimus 2020, vauvaperheiden hyvinvointi, indikaattori: Synnyttänyt vanhempi käyttänyt alkoholia raskauden aikana. [FinLapset questionnaire survey 2020, wellbeing of families with infants, indicator:

the parent who gave birth had used alcohol during pregnancy]. Available from: https://sampo.thl.fi/pivot/prod/fi/lth/fl1bp/summary_vanhemmat3 [Accessed 31st August 2022].

Finnish Institute for Health and Welfare. (2023) Referral criteria for HAL outpatient clinics (drugs, alcohol, medications)—proposal by the Finnish Institute for Health and Welfare. https://urn.fi/URN:NBN:fi-fe20231219155589

Franceschetto, L., Perilli, M., Cinquetti, A., Giraudo, C., Gardi, M., Cecchetto, G. et al. (2022) Phosphatidylethanol in maternal or neonatal blood to detect alcohol exposure during pregnancy: a systematic review. *Life*, 12, 1528.

Gnann, H., Weinmann, W. & Thierauf, A. (2012) Formation of phosphatidylethanol and its subsequent elimination during an extensive drinking experiment over 5 days. *Alcoholism, Clinical and Experimental Research*, 36, 1507–1511.

Hasken, J.M., Marais, A.-S., de Vries, M.M., Kalberg, W.O., Buckley, D., Parry, C.D.H. et al. (2023) Assessing the sensitivity and specificity of phosphatidylethanol (PEth) cutoffs to identify alcohol exposed pregnancies. *Current Research in Toxicology*, 4, 100105.

Helander, A., Böttcher, M., Dahmen, N. & Beck, O. (2019) Elimination characteristics of the alcohol biomarker phosphatidylethanol (PEth) in blood during alcohol detoxification. *Alcohol and Alcoholism*, 54, 251–257.

Henderson, E.M.A., Tappin, D., Young, D., Favretto, D. & Mactier, H. (2023) Assessing maternal alcohol consumption in pregnancy: does phosphatidylethanol measured from day 5 newborn blood spot cards have any value? An observational, population-based study. *Archives of Disease in Childhood*, 108, 36–41.

Hill-Kapturczak, N., Dougherty, D.M., Roache, J.D., Karns-Wright, T.E. & Javors, M.A. (2018) Differences in the synthesis and elimination of Phosphatidylethanol 16:0/18:1 and 16:0/18:2 after acute doses of alcohol. *Alcoholism, Clinical and Experimental Research*, 42, 851–860.

Isaksson, A., Walther, L., Hansson, T., Andersson, A. & Alling, C. (2011) Phosphatidylethanol in blood (B-PEth): a marker for alcohol use and abuse. *Drug Testing and Analysis*, 3, 195–200.

Klemetti, R., Vuorenmaa, M., Ikonen, R., Hedman, L., Ruuska, T., Kivimäki, H. et al. (2018) *How are families with babies doing? Basic report of a pilot study on 3–4-month old babies and their families participating in the LTH survey. [Mitä vauvaperheille kuuluu? LTH-tutkimuksen 3–4-kuukautisten vauvojen ja heidän perheidensä pilottitutkimuksen perusraportti]*, Working Paper 18/2018. Helsinki: National Institute for Health and Welfare (THL). https://urn.fi/URN:ISBN:978-952-343-121-8

Kwak, H.-S., Han, J.-Y., Choi, J.-S., Ahn, H.-K., Ryu, H.-M., Chung, H.-J. et al. (2014) Characterization of phosphatidylethanol blood concentrations for screening alcohol consumption in early pregnancy. *Clinical Toxicology*, 52, 25–31.

Lange, S., Shield, K., Koren, G., Rehm, J. & Popova, S. (2014) A comparison of the prevalence of prenatal alcohol exposure obtained via maternal self-reports versus meconium testing: a systematic literature review and meta-analysis. *BMC Pregnancy and Childbirth*, 14, 127.

Lehtinen, E. & Ekblad, M. (2023) Alcohol consumption during the first weeks of pregnancy is still common. *Finnish Medical Journal*, 78, e36031.

Luginbühl, M., Wurst, F.M., Stöth, F., Weinmann, W., Stove, C.P. & Van Uytfanghe, K. (2022) Consensus for the use of the alcohol biomarker phosphatidylethanol (PEth) for the assessment of abstinence and alcohol consumption in clinical and forensic practice (2022 consensus of Basel). *Drug Testing and Analysis*, 14, 1800–1802.

Mårdby, A.-C., Lupattelli, A., Hensing, G. & Nordeng, H. (2017) Consumption of alcohol during pregnancy—a multinational European study. *Women and Birth*, 30, e207–e213.

Nalesso, A., Viel, G., Cecchetto, G., Mioni, D., Pessa, G., Favretto, D. et al. (2011) Quantitative profiling of phosphatidylethanol molecular species in human blood by liquid chromatography high resolution mass spectrometry. *Journal of Chromatography. A*, 1218, 8423–8431.

Perilli, M., Toselli, F., Franceschetto, L., Cinquetti, A., Ceretta, A., Cecchetto, G. et al. (2023) Phosphatidylethanol (PEth) in blood as a marker of unhealthy alcohol use: a systematic review with novel molecular insights. *International Journal of Molecular Sciences*, 24, 12175.

Popova, S., Lange, S., Probst, C., Gmel, G. & Rehm, J. (2017) Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *The Lancet Global Health*, 5, e290–e299.

Skråstad, R.B., Spigset, O., Aamo, T.O. & Andreassen, T.N. (2020) Stability of phosphatidylethanol 16:0/18:1 in freshly drawn, authentic samples from healthy volunteers. *Journal of Analytical Toxicology*, 45, 417–421. Available from: https://doi.org/10.1093/jat/bkaa082

Statistics Finland. (2024) *Official statistics of Finland (OSF): births 2023*. Helsinki: Statistics Finland. Available from: https://stat.fi/en/statistics/synt [Accessed 24th June 2024]

Stevens, S., Anstice, N., Cooper, A., Goodman, L., Rogers, J. & Wouldes, T.A. (2020) Multiple tools are needed for the detection of prenatal alcohol exposure: findings from a community antenatal setting. *Alcoholism, Clinical and Experimental Research*, 44, 1001–1011.

Van Uytfanghe, K., Heughebaert, L., Abatih, E. & Stove, C.P. (2022) Set-up of a population-based model to verify alcohol abstinence via monitoring of the direct alcohol marker phosphatidylethanol 16:0/18:1. *Addiction*, 117, 2108–2118.

Varga, A., Hansson, P., Johnson, G. & Alling, C. (2000) Normalization rate and cellular localization of phosphatidylethanol in whole blood from chronic alcoholics. *Clinica Chimica Acta*, 299, 141–150.

Varga, A., Hansson, P., Lundqvist, C. & Alling, C. (1998) Phosphatidylethanol in blood as a marker of ethanol consumption in healthy volunteers: comparison with other markers. *Alcoholism, Clinical and Experimental Research*, 22, 1832–1837.

Voutilainen, T., Rysä, J., Keski-Nisula, L. & Kärkkäinen, O. (2022) Self-reported alcohol consumption of pregnant women and their partners correlates both before and during pregnancy: a cohort study with 21,472 singleton pregnancies. *Alcoholism, Clinical and Experimental Research*, 46, 797–808.

World Health Organization. (2016) WHO recommendations on antenatal care for a positive pregnancy experience. https://iris.who.int/bitstream/handle/10665/250796/9789241549912-eng.pdf?sequence=1

World Health Organization. (2023) Global alcohol action plan 2022-2030. Action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority. https://www.drugsandalcohol.ie/34429/

How to cite this article: Häkkinen, M., Arponen, A., Jylhä, A., Sulin, K. & Gunnar, T. (2024) Phosphatidylethanol is a promising tool for screening alcohol consumption during pregnancy. *Alcohol: Clinical and Experimental Research*, 48, 1892–1897. Available from: https://doi.org/10.1111/acer.15418